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Androgen effects on body composition

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Abstract

Androgens are known to have a role in the body fat, muscle size, muscle performance and physical function differences seen between hypogonadal and eugonadal men. The results of investigations into effects of testosterone on body composition, fat metabolism and muscle anabolism are reviewed here. Testosterone dose–response relationships are presented in studies of the effects of physiologic and supraphysiologic doses with and without exercise in young hypogonadal men, older men with low testosterone levels and in chronic illness states.

Keywords: Androgen; Steroids; Testosterone; Muscle mass; Body fat; Athletic performance; Exercise; Hypogonadal; Eugonadal; Stacking

1. Introduction

The question of whether androgens increase muscle mass and improve muscle performance, physical function and athletic performance has been controversial for at least 60 years. Athletes and recreational body builders who abuse androgenic steroids fervently believe these compounds increase muscle mass and performance, and that higher doses of androgens produce greater effects on the muscle than do lower doses. Hence, they take large doses of multiple steroids simultaneously in a practice called *stacking*. On the other hand, until a few years ago, the academic community interpreted the available data to imply that only replacement doses of androgens in castrated males increased nitrogen retention, and that supraphysiologic doses of androgens did not provide any further increase in muscle mass and strength to eugonadal men. Considerable debate raged in the academic community for five decades on whether androgenic steroids had anabolic effects on muscle, due in part to the shortcomings of previous studies as cited in several reviews [1,2]. Many of the previous studies that examined the effects of androgenic steroids were neither blinded nor randomized. Some studies included competitive athletes, whose desire to win might have precluded compliance with a standardized diet and exercise regimen. Nutritional intake was not controlled in many of the studies, though changes in energy and protein intake might have had independent effects on nitrogen balance. Exercise stimulus was not standardized, and in some studies, the participants were allowed to exercise ad libitum. As a result, the effects of androgen administration could not be separated from the effects of resistance-exercise training. Most of the studies used relatively small doses of androgenic steroids. In contrast, athletes not only use much larger doses, they often stack multiple androgenic steroids simultaneously. Not surprisingly, the results of these studies were inconclusive.

Studies published in the last 6 years by a number of groups have now established that testosterone supplementation increases muscle mass and maximal voluntary strength [3–9]. In this review, we will examine the effects of androgenic steroids on body composition, fat metabolism, muscle anabolism and muscle strength in young hypogonadal men, in older men and in various chronic illness states.

2. Testosterone and body composition

2.1. Testosterone levels and fat-free mass

Low serum testosterone levels are associated with lower fat-free mass. Healthy, hypogonadal men have

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lower fat-free mass and higher fat mass when compared to age-matched eugonadal men [8,10]. Experimental suppression of serum testosterone levels by administration of a gonadotropin-releasing hormone (GnRH) agonist analogue in healthy young men is associated with a significant reduction in fat-free mass, an increase in fat mass and a decrease in fractional muscle protein synthesis [11]. The age-associated decline in serum testosterone levels correlates with decreased appendicular muscle mass and reduced lower extremity strength in Caucasian as well as African American men [12,13].

2.2. Physiologic replacement in healthy, young, hypogonadal men

Testosterone replacement was shown in early studies to increase nitrogen retention in castrated males of several animal species [14], as well as in eunuchoidal men, prepubescent boys and women [15]. Several recent studies have re-examined the effects of testosterone on body composition and muscle mass in hypogonadal men. These studies found that replacement doses of testosterone administered to young, healthy, androgen-deficient men increased fat-free mass, muscle size and maximal voluntary strength. The muscle accretion during testosterone treatment was associated with an increase in fractional muscle protein synthesis [5,16].

2.3. Supraphysiologic doses on body composition and muscle strength

Intense controversy persisted until recently with respect to the effects of supraphysiologic doses of androgenic steroids on body composition and muscle strength [1,2,17]. We conducted a placebo-controlled, double-blind, randomized clinical trial to separately assess the effects of supraphysiologic doses of testosterone and resistance exercise on fat-free mass, muscle size and strength [4]. Healthy men, 19–40 years of age, who were within 15% of their ideal body weight were randomly assigned to one of four groups: (1) placebo and no exercise, (2) testosterone and no exercise, (3) placebo plus exercise and (4) testosterone plus exercise. The men received 600-mg testosterone enanthate (TE) or placebo weekly for 10 weeks. Serum total and free testosterone levels, measured 7 days after each injection, increased fivefold above the baseline levels. Serum LH levels were markedly suppressed in the two testosterone-treated but not the placebo-treated groups, providing additional evidence of compliance. Men in the exercise groups underwent weight lifting exercises thrice weekly; the training stimulus was standardized based on the subjects' initial 1-repetition maximum (1-RM), and sessions were well supervised. Fat-free mass by underwater weighing, muscle size by magnetic resonance imaging (MRI), and muscle strength of the arms and legs in bench press and squat exercises were measured before and after 10 weeks of treatment.

The men given testosterone alone had greater gains in muscle size in the arm (mean [± SEM] change in triceps area 13.2 ± 3.3 vs $2.1 \pm 2.9\%$ of baseline cross-sectional area, $P < 0.05$) and leg (change in quadriceps area 6.5 ± 1.3 vs $-1.0 \pm 1.1\%$ of baseline cross-sectional area, $P < 0.05$) than men in the placebo alone group. Testosterone alone was also associated with greater gains in strength in bench press (increase 10 ± 4 vs $-1 \pm 2\%$ of baseline cross-sectional area, $P < 0.05$) and squat exercise capacity (increase 19 ± 6 vs $3 \pm 1\%$ of baseline cross-sectional area, $P < 0.05$) than placebo alone. Testosterone plus exercise produced greater increase in fat-free mass ($+9.5 \pm 1.0\%$) and muscle size ($+14.7 \pm 3.1\%$ in triceps area and $+14.1 \pm 1.3\%$ in quadriceps area) than either placebo alone or placebo plus exercise, and greater gains in muscle strength ($+24 \pm 3\%$ in bench press strength and $+39 \pm 4\%$ in squat exercise capacity) than either non-exercising group. Serum prostate-specific antigen (PSA) levels did not change during treatment and there were no prostate abnormalities detected on digital rectal examination during the 10-week treatment period. These results demonstrate that supraphysiologic doses of testosterone increase fat-free mass, muscle size and strength in healthy men, especially when combined with strength training.

TE was given at a dose of 3 mg/kg/week to healthy men 19–40 years of age in an open-label study that was not placebo controlled [18]. Muscle mass, estimated from creatinine excretion, increased by a mean of 20% and ^{40}K mass increased 12% after 12 weeks of testosterone treatment. In a separate study, a similar dose of TE given for 12 months to men with muscular dystrophy was associated with a 4.9 kg increase in lean body mass (approximately 10%) at 3 months; gains were maintained for 12 months [19].

Fat-free mass by dual energy X-ray absorptiometry (DXA) scan was examined in 13 nonathletic men treated with 200 mg TE weekly for 6 months during the course of a male contraceptive study [20]. This was an open-label study that included untreated controls. Testosterone treatment increased serum testosterone levels by 90% and was associated with a 9.6% increase in fat-free mass and a 16.2% decrease in fat mass.

Collectively these data demonstrate that when dietary intake and exercise stimulus are controlled, supraphysiologic doses of testosterone produce further increases in fat-free mass and strength in eugonadal men. Strength training may augment androgen effects on muscle.

2.4. Testosterone replacement in older men

Several studies have reported that increasing testosterone levels in older men with low testosterone to levels that are mid-normal for healthy young men is associated

with a significant increase in lean body mass and a reduction in fat mass [12,16,21–25]. Although testosterone supplementation is associated with greater gains in grip strength compared with placebo treatment, it remains unclear whether physiologic testosterone replacement can produce meaningful changes in muscle performance and physical function. In a recent study, testosterone treatment of men, 65 years of age or older, did not increase muscle strength or improve physical function, but these men were not uniformly hypogonadal and were unusually fit for their age [22]. In addition, their muscle strength was measured by a method (Biodex dynamometer) that did not produce a response even in frankly hypogonadal younger men treated with testosterone [9]. It is possible that testosterone might improve muscle strength and physical function in older men with clearly low testosterone levels. These studies also emphasize the need to use muscle function tests that are androgen-responsive, and to control for the confounding influence of the learning effect.

Although testosterone replacement in androgen-deficient men increases fat-free mass and maximal voluntary strength, we do not know if testosterone improves physical function. There are several reasons why previous studies of testosterone replacement in older men failed to demonstrate significant improvements in physical function. Many of these studies did not examine changes in physical function, and the few that did had methodological problems with its measurement. We believe a major reason for the failure to demonstrate improvements in physical function is that the measures used were relatively insensitive and ''threshold-dependent''. Widely used measures such as the 0.625 m stair climb, standing up from a chair, and the 20-m walk are tasks that require only a small fraction of an individual's maximal voluntary strength. In most healthy older men, baseline maximal voluntary strength is far higher than the threshold below which these measures would detect impairment. Given the low intensity of the tasks used to measure physical function, relatively healthy older men showed neither impairment in these threshold-dependent tasks at baseline nor improvement in their performance during testosterone administration. Because testosterone improves maximal voluntary leg strength, we postulate that it would improve threshold-independent measures of physical function and require near-maximal strength of critical muscle groups, such as the quadriceps.

Another confounding influence on the effects of anabolic interventions on muscle function is the learning effect. Subjects unfamiliar with weight lifting exercises often demonstrate improvements in measures of muscle performance due to increased familiarity with the exercise equipment and technique. Therefore, in efficacy trials of anabolic interventions, it is important to incorporate strategies to minimize the confounding influence of the learning effect. Because of the considerable test-to-test variability in tests of physical function, it is possible that previous studies [22,26] did not have adequate power to detect meaningful differences in measures of physical function between the placebo- and testosterone-treated groups.

3. Androgen supplementation in chronic illness

3.1. HIV infection

Several studies on the effects of androgen supplementation in HIV-infected men have been reported; however, many were not controlled clinical trials and most were of short duration, ranging from 12 to 24 weeks [27–34]. Several androgenic steroids have been studied in a limited fashion, including nandrolone decanoate, oxandrolone, oxymetholone, stanozolol, testosterone cypionate and TE.

Of the five placebo-controlled studies of testosterone replacement in HIV-infected men with weight loss, three demonstrated increases in fat-free mass [27,28,30] and two did not [31,32]. The three studies that showed gains in fat-free mass selected patients with low testosterone levels [27,28,30]. In a double-blind, placebo-controlled study, the effects of 200-mg testosterone cypionate given every 2 weeks for 3 months was examined in 40 HIV-seropositive patients with weight loss greater than 5% of usual body weight and CD4 cell counts less than 2×10^5/L [32]. Among the 35 patients who completed the first 3 months of the study, there was no significant difference between the effects of testosterone and placebo treatment on weight gain ($P = 0.27$); however, testosterone supplementation was associated with an improved overall sense of well-being ($P = 0.03$). Body composition was not assessed.

In a placebo-controlled, double-blind clinical trial, we examined the effects of physiological testosterone replacement by means of the nongenital patch [28]. Forty-one HIV-positive men with serum testosterone levels less than 400 ng/dl were randomly assigned to receive either two testosterone patches designed to release 5 mg testosterone over a 24-h period or two placebo patches nightly. Testosterone replacement was associated with a 1.34 kg increase in lean body mass ($P = 0.02$) as well as a significantly greater reduction in fat mass than that achieved with placebo treatment alone ($P = 0.04$). There were no significant changes in liver enzymes, plasma HIV-RNA copy number, and CD4 and CD8+ T-cell counts. Both placebo and testosterone treatment were associated with significant increases in muscle strength (P vs zero change 0.0011 and 0.0001 for placebo and testosterone groups, respectively). Because most of the participants in this study had not had prior weight lifting experience, we hypothesized that the apparent

increase in muscle strength in the placebo group reflected a learning effect. Most other studies in HIV-infected men have also failed to demonstrate significantly greater increases in muscle strength with testosterone supplementation than those associated with placebo.

Therefore, in a subsequent study we paid particular attention to having the subjects come back to the Exercise Laboratory on two or more occasions until they were familiar with the equipment and technique and stability of measurements had been achieved [27]. In this study we determined the effects of testosterone replacement, with or without a program of resistance exercise, on muscle strength and body composition in a placebo-controlled, double-blind, randomized clinical trial in HIV-infected men with serum testosterone less than 350 ng/dl and weight loss of 5% or more in the previous 6 months. Participants were randomly assigned to one of four groups: (1) placebo and no exercise, (2) testosterone and no exercise, (3) placebo plus exercise or (4) testosterone plus exercise [27]. Placebo or 100-mg TE were given IM weekly for 16 weeks. The exercise program was a thrice-weekly, progressive, supervised strength-training program. Effort-dependent muscle strength in five different exercises was measured using the 1-RM method. In the placebo only group, muscle strength did not change in any of the five exercises (−0.3 to −4.0%), indicating this strategy was effective in minimizing the influence of the learning effect. Men treated with testosterone alone, placebo plus exercise, or combined testosterone and exercise experienced significant increases in maximum voluntary muscle strength in the leg press (+22 to 30%), leg curls (+18 to 36%), bench press (+19 to 33%) and latissimus dorsi pulldowns (+17 to 33%) exercises. The gains in strength in all the exercises were greater in men receiving testosterone with or without exercise training compared with those receiving placebo alone. The change in leg press strength was correlated with change in muscle volume (Pearson correlation coefficient $r = 0.44$, $P = 0.003$) and change in fat-free mass (Pearson correlation coefficient $r = 0.55$, $P < 0.001$). We concluded that when the confounding influence of the learning effect is minimized and appropriate androgen-responsive measures of muscle strength are selected, testosterone replacement is associated with demonstrable increase in maximal voluntary strength in HIV-infected men with low testosterone levels.

Strength training also promotes gains in lean body mass and muscle strength [4,27]. Further, supraphysiologic doses of androgens augment the anabolic effects of resistance exercise on lean body mass and maximal voluntary strength [34,35].

The results from these studies suggest that testosterone can promote weight gain and increase lean body mass, as well as muscle strength, in HIV-infected men with low testosterone levels. We do not know, however, whether physiological androgen replacement can produce meaningful improvement in quality of life, utilization of health care resources or physical function in HIV-infected men. Emerging data indicate that testosterone does not affect HIV replication, but its effects on virus shedding in the genital tract are not known.

3.2. End-stage renal disease

There is a high frequency of low total and free testosterone levels, sexual dysfunction, infertility, delayed puberty and growth failure in patients with end-stage renal disease (ESRD) [36,37]. Fat-free mass is decreased and physical function is markedly impaired in men with ESRD who are receiving maintenance hemodialysis [38]. Androgen administration does not consistently improve sexual dysfunction in these patients [36,37]. Similarly, the effects of androgen treatment on growth and pubertal development in children with ESRD remain unclear [39,40]. Controlled clinical trials of nandrolone decanoate have reported increased hemoglobin levels with androgen treatment in men with ESRD who are on hemodialysis [38,41–43]. Prior to the advent of erythropoietin, testosterone was commonly used to treat anemia associated with ESRD. Testosterone increases red cell production by stimulating erythropoietin, augmenting erythropoietin action and by its direct action on stem cells. Further studies are needed to determine whether testosterone administration can reduce blood transfusion and erythropoietin requirements in patients with ESRD on hemodialysis.

3.3. Autoimmune disorders and COPD

Patients with autoimmune disorders, particularly those receiving glucocorticoids, often experience a reduction in circulating testosterone concentrations, muscle wasting and bone loss [44–46]. A replacement dose of testosterone esters (30 mg testosterone propionate, 60 mg, testosterone phenylprionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate, Sustanon, Organon, Inc. Oss, Netherlands) was given intramuscularly every month for 12 months to men receiving glucocorticoids in a placebo-controlled study [45]. Testosterone replacement was associated with a significantly greater increase in lean body mass ($P = 0.02$) and bone density ($P = 0.05$) than placebo.

Chronic obstructive pulmonary disease (COPD) is a debilitating disease for which there are few effective therapies. Muscle wasting and dysfunction are recognized as correctable causes of exercise intolerance in these patients. It has been speculated that low levels of anabolic hormones such as testosterone, growth hormone and insulin-like growth factor-I (IGF-I) may contribute to muscle atrophy and dysfunction [47]. Human growth hormone (hGH) increases nitrogen retention and lean body muscle in patients with COPD;

however, the effects of hGH on respiratory muscle strength and exercise tolerance remain to be established [48–50]. The effects of a low dose of nandrolone or placebo were studied in 217 men and women with COPD and modest increases in lean body mass and respiratory muscle strength were reported [51]. Recently, physiologic testosterone replacement was shown to increase fat-free mass, muscle size and muscle strength in men with COPD who have low testosterone levels [52].

4. Testosterone dose–response

Testosterone increases muscle mass and strength and regulates other physiologic processes. However, it is not known whether testosterone effects are dose-dependent, and whether dose requirements for maintaining various androgen-dependent processes are similar [53]. Androgen receptors in most tissues are either saturated or down-regulated at physiologic testosterone concentrations [1,54–56]. This has led to speculation that there might be two separate dose–response curves, one in hypogonadal range with maximal response at low normal testosterone concentrations, and a second in supraphysiologic range, representing a separate mechanism of action [1,27]. However, testosterone dose–response relationships have not been studied for a range of androgen-dependent functions in humans.

The effects of graded doses of testosterone on body composition, muscle size, strength, power, sexual and cognitive functions, PSA, plasma lipids, hemoglobin, and IGF-I levels were studied in 61 eugonadal men 18–35 years of age [57,58]. Subjects were randomized to one of five groups to receive monthly injections of a long-acting GnRH agonist to suppress endogenous testosterone secretion, and weekly injections of 25, 50, 125, 300 or 600 mg TE for 20 weeks. Energy and protein intake were standardized. The administration of GnRH agonist plus graded doses of testosterone resulted in mean nadir testosterone concentrations of 253, 306, 542, 1345, and 2370 ng/dl at the 25-, 50-, 125-, 300-, and 600 mg doses, respectively. Fat-free mass increased dose dependently in men receiving 125, 300 or 600 mg of testosterone weekly (change +3.4, 5.2 and 7.9 kg, respectively). As shown in Fig. 1, the changes in fat-free mass were highly dependent on testosterone dose ($P = 0.0001$) and were correlated with log testosterone concentrations (Pearson correlation coefficient $r = 0.73$, $P = 0.0001$). Changes in leg press strength (Fig. 2), leg power, thigh and quadriceps muscle volumes, hemoglobin and IGF-I were positively correlated with testosterone concentrations, while changes in fat mass and plasma high-density lipoprotein (HDL) cholesterol were negatively correlated. Sexual function, visual–spatial cognition, mood and PSA levels did not change significantly at any dose. These findings demonstrate that changes in circulating testosterone concentrations, induced by GnRH agonist and testosterone administration, are associated with testosterone dose- and concentration-dependent changes in fat-free mass; muscle size, strength, and power; and fat mass. Changes in hemoglobin, HDL cholesterol, and IGF-I levels also conformed to a single linear dose–response relationship; however, different androgen-dependent processes have different testosterone dose–response relationships.

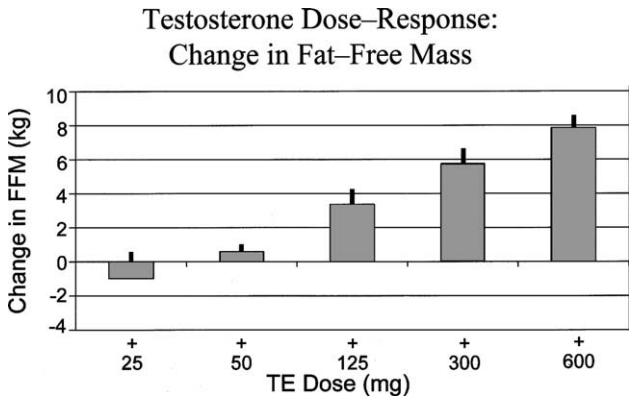

Fig. 1. Dose-dependent effects of testosterone on fat-free mass in healthy, young men. In this study, healthy men, 18–34 years of age, were treated with a long-acting GnRH agonist and graded intramuscular doses of testosterone enanthate ranging from 25 mg weekly to 600 mg weekly, as shown, for 20 weeks. Fat-free mass was measured by DXA scan at baseline and after 20 weeks of treatment. Change in fat-free mass was calculated as the difference between post-treatment and baseline value. Data are mean ± SEM. (Reprinted, with permission, from Bhasin et al., Am. J. Physiol. Endocrinol. Metab. 281 (2001) E1172–E1181).

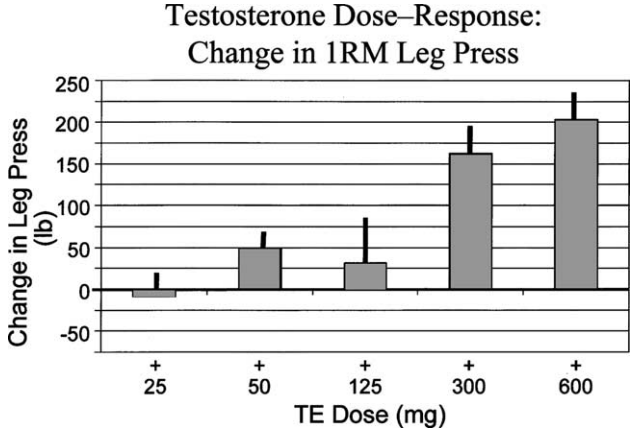

Fig. 2. Dose-dependent effects of testosterone on maximal voluntary leg press strength in healthy, young men. In this study, healthy men, 18–34 years of age, were treated with a long-acting GnRH agonist and graded intramuscular doses of testosterone enanthate ranging from 25 mg weekly to 600 mg weekly, as shown, for 20 weeks. Change in leg press strength was calculated as the difference between post-treatment and baseline value. Data are mean ± SEM. (Reprinted, with permission, from Bhasin et al., Am. J. Physiol. Endocrinol. Metab. 281 (2001) E1172–E1181.

5. Mechanisms of anabolic effects

A number of studies have given support to the prevalent view that testosterone produces muscle hypertrophy by increasing fractional muscle protein synthesis [5,59]. Recent observations, however, suggest that increased muscle protein synthesis probably occurs as a secondary event and may not be the sole or primary mechanism by which testosterone induces muscle hypertrophy [60].

In order to determine whether testosterone-induced increase in muscle size is due to muscle fiber hypertrophy or hyperplasia, muscle biopsies were obtained from vastus lateralis in 39 men before and after 20 weeks of combined treatment with GnRH agonist and weekly injections of 25, 50, 125, 300 or 600 mg TE [60].

Changes in cross-sectional areas of both types I and II muscle fibers were dependent on increasing testosterone doses, and significantly correlated with total (Pearson correlation coefficient $r = 0.35$ for type I; $r = 0.44$ for type II fibers, $P < 0.0001$) and free (Pearson correlation coefficient $r = 0.34$ for type I and 0.35 for type II fibers, $P < 0.005$) testosterone concentrations during treatment. The men receiving 300 and 600 mg of TE weekly experienced significant increases from baseline in areas of type I muscle fibers (baseline vs 20 weeks, 3176 ± 163 vs $4201 \pm 163\,\mu m^2$, $P < 0.05$ at 300 mg dose; and 3347 ± 253 vs $4984 \pm 374\,\mu m^2$, $P = 0.006$ at 600 mg dose). The men in the 600-mg group also had significant increments in cross-sectional area of type II fibers (4060 ± 401 vs $5526 \pm 544\,\mu m^2$, $P = 0.03$). The relative proportions of types I and II fibers did not change significantly after treatment in any group. The myonuclear number per fiber increased significantly in men receiving the 300- and 600-mg doses of TE, and was significantly correlated with testosterone concentration and muscle fiber cross-sectional area [60].

These findings demonstrate that increases in muscle volume in healthy eugonadal men treated with graded doses of testosterone are associated with concentration-dependent increases in muscle fiber cross-sectional area and myonuclear number, but not muscle fiber number. We conclude that the testosterone-induced increase in muscle volume is due to muscle fiber hypertrophy. In our study, the myonuclear number increased in direct relation to the increase in muscle fiber diameter. Therefore, it is possible that muscle fiber hypertrophy and increase in myonuclear number were preceded by testosterone-induced increase in satellite cell number and their fusion with muscle fibers. The mechanisms by which testosterone might increase satellite cell number are not known, but may include, an increase in satellite cell replication, inhibition of satellite cell apoptosis and/or increased differentiation of stem cells into the myogenic lineage. We do not know which of these processes is the site of regulation by testosterone. The hypothesis that testosterone promotes muscle fiber hypertrophy by increasing the number of satellite cells should be further tested. Because of the constraints inherent in obtaining multiple biopsy specimens in humans, the effects of testosterone on satellite cell replication and stem cell recruitment would be more easily studied in an animal model.

The molecular mechanisms that mediate androgen-induced muscle hypertrophy are not well understood; however, Urban et al. [59] have proposed that testosterone stimulates the expression of IGF-I and down-regulates insulin-like growth factor binding protein-4 (IGFBP-4) in the muscle. Reciprocal changes in IGF-I and its binding protein thus provide a potential mechanism for amplifying the anabolic signal.

It is not clear whether the anabolic effects of supraphysiologic doses of testosterone are mediated through an androgen receptor-mediated mechanism. In vitro binding studies suggest that the maximum effects of testosterone should be manifest at about 300 ng/dl, i.e., serum testosterone levels at the lower end of the normal male range [61]. Therefore, it is possible that supraphysiologic doses of androgen produce muscle hypertrophy through androgen receptor-independent mechanisms, such as through an anti-glucocorticoid effect [62]. We cannot exclude the possibility that some androgen effects may be mediated through nonclassical binding sites. Testosterone effects on the muscle are modulated by a number of other factors, such as genetic background, growth hormone secretory status [63], nutrition, exercise, cytokines, thyroid hormones and glucocorticoids. Testosterone may also affect muscle function by its effects on neuromuscular transmission [64,65].

5.1. 5-α reduction and aromatization of testosterone in muscle

Although the enzyme 5-α-reductase is expressed at low concentrations within muscle [66], we do not know whether conversion of testosterone to dihydrotestosterone (DHT) is required for mediating androgen effects on muscle. Men with benign prostatic hypertrophy who are treated with the 5-α-reductase inhibitor do not experience muscle loss. Similarly, individuals with congenital 5-α-reductase deficiency have normal muscle development at puberty. These findings suggest that 5-α reduction of testosterone is not obligatory for mediating its effects on muscle.

Several investigators have reported that serum DHT levels are lower and testosterone to DHT levels are higher in HIV-infected men than in healthy men [67]. They proposed that a defect in testosterone to DHT conversion may contribute to wasting in a subset of HIV-infected men. If this hypothesis was true, it would be rational to treat these patients with DHT rather than

testosterone. A DHT gel is currently under clinical investigation for that indication. Unlike testosterone, DHT is not aromatized to estradiol; therefore, suppression of endogenous testosterone and estradiol production by exogenous DHT may produce osteoporosis.

Studies in aromatase knock-out mice have revealed higher fat mass and lower muscle mass in mice that are null for the P450-linked CYP-aromatase gene. Results from these gene-targeting experiments suggest that aromatization of testosterone might also be important in mediating androgen effects on muscle.

6. Testosterone and fat metabolism

Percent body fat is higher in hypogonadal men compared with eugonadal controls [10]. Induction of androgen deficiency in healthy men by administration of a GnRH agonist leads to an increase in fat mass [11]. Some studies of young, hypogonadal men have reported a decreased fat mass with testosterone replacement therapy [5,8], while others found no change [3,7,9]. In contrast, long-term studies of testosterone supplementation in older men have consistently demonstrated a decrease in fat mass [16,22,24,25]. Epidemiologic studies have shown that serum testosterone levels are lower in middle-aged men with visceral obesity [68,69]. Serum testosterone levels correlate inversely with visceral fat area and directly with plasma HDL levels. Testosterone replacement of middle-aged men with visceral obesity improves insulin sensitivity and decreases blood glucose and blood pressure [70,71]. In our dose–response studies, administration of graded doses of testosterone to men was associated with a dose-dependent decrease in fat mass [57]. Loss of fat mass at higher doses was evenly distributed in the trunk and appendices as well as in superficial and deep compartments. Thus, decreased intra-abdominal and intermuscular fat was associated with high doses of testosterone. Testosterone is an important determinant of regional fat distribution and metabolism in men [71].

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