HORMONES AND SPORT

Proof of the effect of testosterone on skeletal muscle

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Abstract

In spite of the widespread abuse of androgenic steroids by athletes and recreational body-builders, the effects of these agents on athletic performance and physical function remain poorly understood. Experimentally induced androgen deficiency is associated with a loss of fat-free mass; conversely, physiologic testosterone replacement of healthy, androgen-deficient men increases fat-free mass and muscle protein synthesis. Testosterone supplementation of HIV-infected men with low testosterone levels and of older men with normally low testosterone concentrations also increases muscle mass. However, we do not know whether physiologic testosterone replacement can improve physical function and health-related quality of life, and reduce the risk of falls and disability in older men or those with chronic illness. Testosterone increases maximal voluntary strength in a dose-dependent manner and thus might improve performance in power-lifting events. However, testosterone has not been shown to improve performance in endurance events. The mechanisms by which testosterone increases muscle mass are not known, but probably involve alterations in the expression of multiple muscle growth regulators.

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The abuse of androgenic steroids by athletes and the proposed anabolic applications of these agents in sarcopenia (loss of muscle mass and strength) associated with aging or chronic illness is based on the premise that these agents increase muscle mass and improve measures of skeletal muscle performance, and that androgen-induced changes in skeletal muscle performance translate into improvements in athletic performance and health-related outcomes (Fig. 1). The premise remains unsubstantiated. There is agreement that testosterone supplementation increases muscle mass and maximal voluntary strength in a variety of clinical and experimental paradigms (Tenover 1992, Urban *et al.* 1995, Bhasin *et al.* 1996, 1997, Brodsky *et al.* 1996, Katznelson *et al.* 1996, Wang *et al.* 1996, 2000, Synder *et al.* 2000), but we do not know whether testosterone improves athletic performance or health-related outcomes, and whether beneficial effects of androgens can be achieved without significant long-term adverse effects.

Opinion as to the effects of testosterone on the muscle in healthy eugonadal men has been enormously controversial for more than five decades (Wilson 1988, Bardin 1996, Casaburi *et al.* 1996*b*). The athletes who abuse androgenic steroids believe fervently that these drugs increase muscle mass and strength; however, the academic community decried their use, citing lack of verifiable evidence (Wilson 1988, Bardin 1996, Casaburi *et al.* 1996*b*). The historical aspects of the use of androgenic/anabolic steroids have been extensively reviewed (Wilson 1988, Bardin 1996). Although their use is most common among weight-lifters and heavy throwers, almost all types of athletes whose event requires explosive strength, including football players, swimmers and track and field athletes, have been known to use steroids. Their use has spread to high-school athletes and to amateur body-builders. Disqualification of highly celebrated athletes in recent years has focused substantial media attention on this issue.

Considerable debate has raged in the academic community for five decades on whether androgenic steroids had anabolic effects on the muscle, due in part to the shortcomings of previous studies; several reviews have discussed these study design issues (Wilson 1988, Bardin 1996). For instance, many of the studies that examined the effect of androgenic steroids were neither blinded nor randomized. Some studies included competitive athletes, whose desire to win at any cost prevent them from complying with a standardized regimen of diet and

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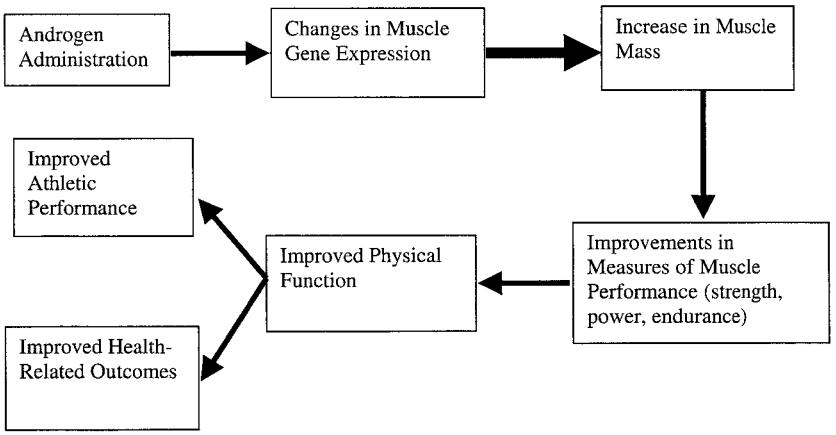

Figure 1 Rationale for the abuse of androgenic steroids by athletes and their potential application as anabolic therapy for sarcopenia associated with old age and chronic illness. This is based on the premise that these agents induce alterations in muscle gene expression that result in increased muscle mass and improved muscle performance. It is further assumed that increased muscle mass and performance will translate into improved physical function, athletic performance and health-related outcomes. Although androgenic steroids have been shown to increase muscle mass and maximal voluntary strength, their effects on physical function, health-related outcomes and athletic performance have not been rigorously studied. The heavy arrow indicates areas of certainty, and lighter arrows indicate areas of uncertainty.

exercise. Nutritional intake was not controlled in many of the studies; 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*. Therefore, the effects of androgen administration could not be separated from the effects of resistance exercise training. Most of the studies performed before the 1980s used relatively small doses of androgenic steroids, equivalent to or less than the replacement dose of testosterone used for the treatment of androgen-deficient men. In contrast, athletes use supraphysiological doses of androgenic steroids. Because of these problems of study design, the results of these previous studies were inconclusive. With the advent of magnetic resonance imaging and more refined methods for the assessment of body composition, it has become possible to detect small changes in muscle volume and fat-free mass with a greater degree of precision and accuracy than was feasible before. Consequently, studies published in the past 6 years by a number of groups have now established that testosterone supplementation does increase muscle mass and strength (Bhasin *et al.* 1996, Brodsky *et al.* 1996, Katznelson *et al.* 1996, Wang *et al.* 1996, 2000, Snyder *et al.* 2000).

A reduction in serum testosterone is associated with decreased fat-free mass

Healthy, hypogonadal men have lower fat-free mass and higher fat mass compared with those of age-matched eugonadal men (Katznelson *et al.* 1996, 1998). Mauras *et al.* (1998) have reported that experimental suppression of serum testosterone by administration of a gonadotropin-releasing hormone (GnRH) agonist analog 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. An age-associated decline in serum testosterone concentrations correlates with decreased appendicular muscle mass and reduced lower extremity strength in white and in African-American men (Morley *et al.* 1993, 1997).

Effects of physiologic testosterone replacement in healthy, young hypogonadal men

Testosterone replacement increases nitrogen retention in castrated males of several animal species (Kochakian *et al.* 1950), eunuchoidal men, boys before puberty, and women (Kenyon *et al.* 1940). Several recent studies have re-examined the effects of testosterone on body composition and muscle mass in hypogonadal men in more detail. We administered 100 mg testosterone enanthate intramuscularly weekly for 10 weeks to seven hypogonadal men after a 10–12 week period of androgen withdrawal (Bhasin *et al.* 1997). Testosterone replacement was associated with a $4{\cdot}5 \pm 0{\cdot}6$ kg ($P=0{\cdot}005$) increase in body weight because of a $5{\cdot}0 \pm 0{\cdot}8$ kg ($P=0{\cdot}004$) increase in fat-free mass, estimated from underwater weight, whereas body fat did not change. Similar increases in fat-free mass were observed using the deuterium water dilution method. Arm

Table 1 Effects of testosterone replacement on body composition in hypogonadal men

Study	Age (years)	Testosterone regimen	Change in fat-free mass	Change in fat mass	Change in muscle strength
Bhasin *et al.* (1997)	19–47	Testosterone enanthate 100 mg weekly for 10 weeks	5·0 ± 0·7 kg (9·9 ± 1·4%) increase by underwater weight and D_2O	No change in fat mass by underwater weight and D_2O	+22 ± 3%
Katznelson *et al.* (1996)	22–69	Testosterone enanthate or cypionate 100 mg weekly for 18 months	7 ± 2% increase by bioelectrical impedance	14 ± 4% decrease in percent body fat, 13 ± 4% decrease in subcutaneous fat	Not measured
Brodsky *et al.* (1996)	33–57	Testosterone cypionate 3 mg/kg every 2 weeks for 6 months	15% increase by DXA scan	11% decrease in fat mass	Not measured
Wang *et al.* (1996)	19–60	Sublingual testosterone 5 mg three times a day for 6 months	0·9 kg (2%) increase by DXA scan	No change in fat mass	No change in arm press, 8·7 kg increase in leg-press
Snyder *et al.* (2000)	22–78	Transdermal testosterone patch for 12–36 months	3·1 ± 3·3 kg increase by DXA scan	No change in fat mass	No change in isokinetic strength of knee extension
Wang *et al.* (2000)	19–68	Testosterone gel (50–100 mg/day) × 180 days	2·7 ± 0·3 kg increase by DXA scan	1 kg decrease in fat mass	Leg-press strength increased by 11–13 kg

D_2O, deuterium water.

and leg muscle cross-sectional areas, assessed by magnetic resonance imaging, increased significantly. Substantial increases in muscle strength were also noted after treatment.

Brodsky *et al.* (1996) reported a 15% increase in fat-free mass and an 11% decrease in fat mass in hypogonadal men treated with a replacement dose of testosterone enanthate. Their muscle mass increased by 20% and accounted for 65% of the increase in fat-free mass. The muscle accretion during testosterone treatment was associated with a 56% increase in fractional muscle protein synthesis. In another study, a cyclodextrin-complexed testosterone formulation produced a modest increase in fat-free mass (+0·9 kg) and muscle strength (+8·7 kg) in hypogonadal men (Wang *et al.* 1996); however, the testosterone dose used in that study was smaller than the doses used in previous studies. Taken together, these studies (Table 1) provide convincing evidence that physiologic androgen replacement in healthy, young hypogonadal men is associated with significant gains in fat-free mass, muscle size and maximal voluntary strength.

Effect of supraphysiologic doses of testosterone 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 (Wilson 1988, Bardin 1996, Casaburi *et al.* 1996*b*). We conducted a placebo-controlled, double-blind, randomized clinical trial to assess separately the effects of supraphysiologic doses of testosterone and resistance exercise on fat-free mass, muscle size and strength (Bhasin *et al.* 1996). Healthy eugonadal men, 19–40 years of age, who were within 15% of their ideal body weight, were randomly assigned to one of four groups: placebo but no exercise; testosterone but no exercise; placebo plus exercise; testosterone plus exercise. The men received 600 mg testosterone enanthate or placebo weekly for 10 weeks. Serum total and free testosterone concentrations, measured 7 days after each injection, increased fivefold; these were nadir values and serum testosterone concentrations at other times must have been greater. Serum concentrations of luteinizing hormone (LH) were markedly suppressed in the two testosterone-treated groups, but not the placebo-treated groups, providing additional evidence of compliance. Men in the exercise groups underwent weight-lifting exercises three times weekly; the training stimulus was standardized on the basis of the participants' initial one-repetition maximum (1RM) and the sessions were well supervised. Fat-free mass by underwater weighing, muscle size by magnetic resonance imaging, and muscle strength of the arms and legs in bench-press and squat exercises were measured before and after 10 weeks of treatment. The eugonadal men given testosterone alone had greater gains in muscle size in the arm (mean (± S.E.M.) change in

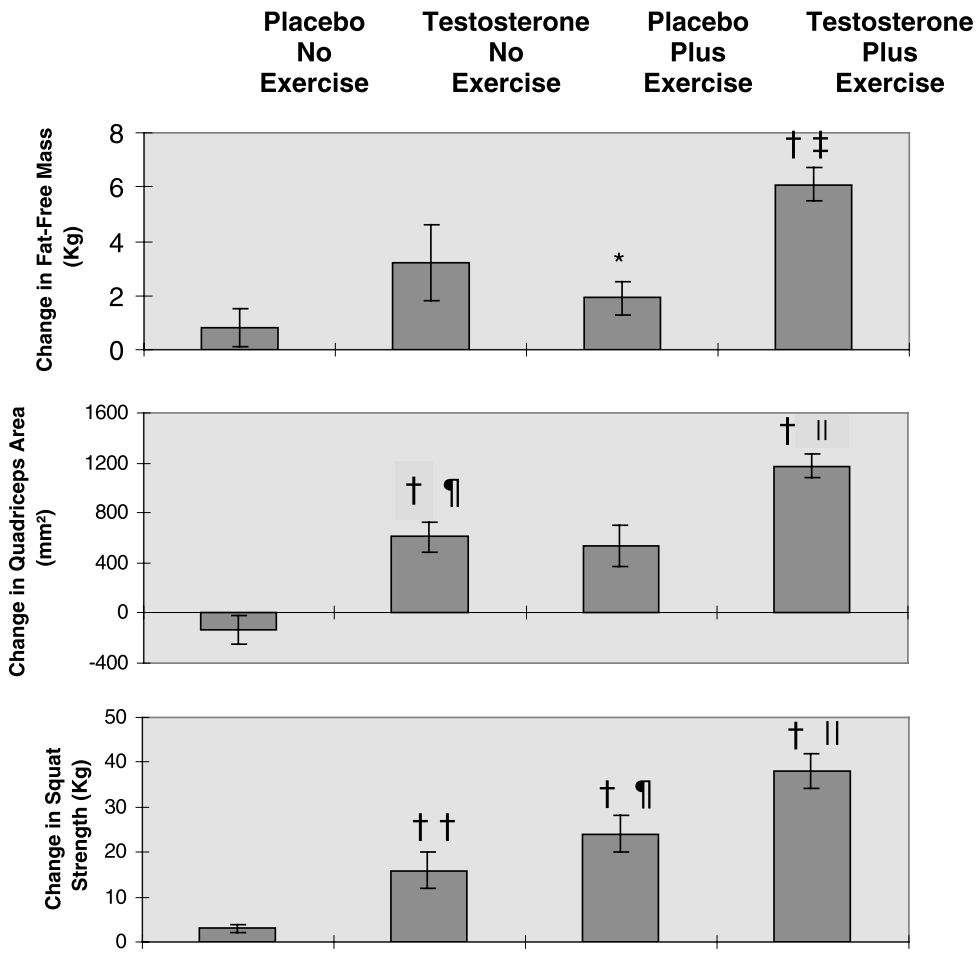

Figure 2 Effect of a supraphysiologic dose of testosterone on fat-free mass, muscle size, and strength in healthy, eugonadal men. Changes from baseline in (mean ± S.E.). Fat-free mass, quadriceps area, and muscle strength in the squat exercise over the 10 weeks of treatment. Changes significantly different from zero: **P*=0·017; †*P*<0·001; ††*P*=0·004. Other changes significantly greater than: ‡those in no-exercise groups (*P*<0·05); ¶that in placebo plus no-exercise group (*P*<0·05); ||those in all other groups (*P*<0·05). Adapted with permission from Bhasin *et al.* (1996).

triceps area 13·2 ± 3·3 compared with − 2·1 ± 2·9%, *P*<0·05; Fig. 2) and leg (change in quadriceps area 6·5 ± 1·3 compared with − 1·0 ± 1·1%, *P*<0·05) than those given placebo injections. Testosterone treatment was also associated with greater gains in strength in the bench-press (increase 10 ± 4 compared with − 1 ± 2%, *P*<0·05; Fig. 2) and squat exercise capacity (increase 19 ± 6 compared with 3 ± 1%, *P*<0·05) than were placebo-injections. Testosterone and exercise, given together, produced greater increase in fat-free mass (+9·5 ± 1·0%) and muscle size (+14·7 ± 3·1% in triceps area and +14·1 ± 1·3% in quadriceps area) than either placebo or exercise alone, and greater gains in muscle strength (+24 ± 3% in bench-press strength, and +39 ± 4% in squat exercise capacity) than were achieved in either non-exercising group. Serum concentrations of prostate-specific antigen (PSA) did not change during treatment and no abnormalities were detected in the prostate on digital rectal examination during the 10-week treatment period. These results demonstrate that supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass, muscle size and strength in healthy eugonadal men.

Griggs *et al.* (1989*a*) administered testosterone enanthate at a dose of 3 mg/kg per week to healthy, eugonadal men, 19–40 years of age. This was an open-label study that was not placebo-controlled. Muscle mass, estimated from creatinine excretion, increased by a mean of 20% and total body potassium mass estimated by 40 k counting increased 12% after 12 weeks of testosterone treatment. In a separate study, a similar dose of testosterone enanthate given for 12 months to men with muscular dystrophy was associated

Table 2 Effects of testosterone supplementation in older men

Study	Participants	Treatment regimen	Changes in body composition	Changes in muscle function	Comments
Tenover (1992)	60–75 years, serum testosterone <400 ng/dl	Testosterone enanthate 100 mg weekly for 3 months	1·8 kg increase in fat-free mass; no change in fat mass	No change in grip strength	Mild increases in PSA and hematocrit
Morley *et al.* (1993)	68–89 years, bioavailable testosterone <75 ng/dl	Testosterone enanthate 200 mg every 2 weeks for 3 months	No change in fat mass or body weight	Increase in grip strength	
Sih *et al.* (1997)	Healthy men, 51–79 years, serum bioavailable testosterone <60 ng/dl	Testosterone cypionate 200 mg every 2 weeks for 12 months	0·9 cm (3%) increase in mid-arm circumference; no change in fat mass	4–5 kg increase in grip strength	No change in PSA, increase in hematocrit
Urban *et al.* (1995)	Healthy elderly, 67 ± 2 years, testosterone <480 ng/dl	Testosterone enanthate weekly for 4 weeks to increase testosterone to 500–1000 ng/dl	Body composition not reported	Increase in hamstring and quadriceps work per repetition; no change in endurance	Approximately twofold increase in fractional muscle protein synthesis rate
Snyder *et al.* (1999)	Healthy older men, >65 years of age	Scrotal testosterone patch, 6 mg/day for 3 years	Lean body mass increased by 1·9 kg; fat mass decreased by 3 kg	No change in strength of knee extension and flexion	Improved perception of physical function
Tenover (2000)	Healthy, older men	Testosterone enanthate, ~150 mg/2 weeks for 3 years	Fat-free mass increased and fat mass decreased	Improvements in some measures of muscle strength	

with a 4·9 kg increase in lean body mass (approximately 10%) at 3 months; these gains were maintained for 12 months (Griggs *et al.* 1989*b*).

Young *et al.* (1993) examined fat-free mass by dual-energy X-ray absorptiometry (DXA) scan in 13 non-athletic, eugonadal men treated with 200 mg testosterone enanthate weekly for 6 months during the course of a male contraceptive study. This was an open-label study that included untreated men as controls. Testosterone treatment increased serum testosterone concentrations 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. Thus it is likely that strength training may augment the effects of androgen on the muscle.

Effects of testosterone replacement in older men with low testosterone concentrations

Several studies (Tenover 1992, 2000, Morley *et al.* 1993, Sih *et al.* 1997, Snyder *et al.* 1999) have now established that the use of testosterone supplementation to increase the testosterone in older men with low testosterone concentrations to values that are mid-normal for healthy young men is associated with a significant increase in lean body mass and a reduction in fat mass (Table 2). Although testosterone supplementation is associated with greater gains in grip strength than are achieved with placebo treatment, it remains unclear whether physiologic testosterone replacement can produce meaningful changes in muscle performance and physical function. In a recent study by Snyder *et al.* (1999), testosterone treatment of older men did not increase muscle strength or improve physical function, but these men were not uniformly hypogonadal and were unusually fit for their age. In addition, their muscle strength was measured by a method (Biodex dynamometer) that did not demonstrate a response even in frankly hypogonadal younger men treated with testosterone (Snyder *et al.* 2000). It is possible that testosterone might improve muscle strength and physical function in older men with clearly low testosterone concentrations. 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.

Effects of androgen replacement on body composition and muscle function in sarcopenia associated with chronic illnesses

Several different anabolic interventions have been examined in the treatment of human immunodeficiency virus (HIV)-related wasting, including appetite stimulants such as dronabinol and megesterol acetate, anabolic hormones such as human growth hormone (hGH) (Schambelan *et al.* 1996, Waters *et al.* 1996), insulin-like growth factor (IGF)-I (Waters *et al.* 1996) and androgens (Coodley & Coodley 1997, Grinspoon *et al.* 1998, Bhasin *et al.* 1998, 2000, Bhasin & Javanbakht 1999, Dobs *et al.* 1999, Sattler *et al.* 1999, Strawford *et al.* 1999*a*,*b*), and modulators of the immune response such as thalidomide. Dronabinol increases appetite, but has not been shown to increase lean body mass (Beal *et al.* 1995). Similarly, megesterol acetate treatment produces a modest weight gain but no significant change in lean body mass (Von Roenn *et al.* 1994). This progestational agent decreases serum testosterone concentrations and may produce symptoms of androgen deficiency.

In the two recently published clinical trials, treatment of HIV-infected men with hGH was associated with a 1·5 kg increase in lean body mass (Schambelan *et al.* 1996, Waters *et al.* 1996). Although greater gains in weight were recorded after 6 weeks of hGH treatment, these gains were not sustained with continued treatment for 12 weeks. It is conceivable that weight gain early in the course of treatment is due to water retention. Administration of hGH is associated with a high frequency of side effects, including edema, arthralgias, myalgias, and jaw pain. Not surprisingly, the treatment discontinuation rates were high (21–40%) in the two hGH studies. The annual cost of treating HIV-infected men with hGH is substantially greater than that of testosterone replacement therapy.

Several studies on the effects of androgen supplementation in HIV-infected men have been reported (Coodley & Coodley 1997, Bhasin *et al.* 1998, 2000, Bhasin & Javanbakht 1999, Grinspoon *et al.* 1998, Dobs *et al.* 1999, Sattler *et al.* 1999, Strawford *et al.* 1999*a*,*b*). However, many of these studies were not controlled clinical trials. Most of the studies were of short duration, ranging from 12–24 weeks. Of the five placebo-controlled studies of testosterone replacement in HIV-infected men with weight loss, three (Bhasin *et al.* 1998, 2000, Grinspoon *et al.* 1998) demonstrated an increase in fat-free mass and two (Coodley & Coodley 1997, Dobs *et al.* 1999) did not. In the three studies (Bhasin *et al.* 1998, 2000, Grinspoon *et al.* 1998) that showed gains in fat-free mass, patients with low testosterone concentrations had been specifically selected.

In a recent study (Bhasin *et al.* 2000), we determined the effects of testosterone replacement, with or without a program of resistance exercise, on muscle strength and body composition in androgen-deficient, HIV-infected men with weight loss and low testosterone concentrations. This was 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. Sixty-one eligible participants were randomly assigned to one of four groups: placebo, no exercise; testosterone, no exercise; placebo plus exercise; testosterone plus exercise (Bhasin *et al.* 2000). Placebo or 100 mg testosterone enanthate were given intramuscularly, weekly for 16 weeks. The exercise program was a three times weekly, progressive, supervised strength training program. Effort-dependent muscle strength in five different exercises was measured using the 1RM method. We paid particular attention to having the participants come back to the Exercise Laboratory on two or more occasions until they were familiar with the equipment and technique, and stability of measurement had been achieved. In the placebo only group, muscle strength did not change in any of the five exercises ($-0{\cdot}3$ to $-4{\cdot}0$%). This indicates that this strategy was effective in minimizing the influence of the learning effect. Men treated with testosterone alone, exercise alone, or combined testosterone and exercise experienced significant increases in maximum voluntary muscle strength in the leg-press (22–30%, Fig. 3), leg curls (18–36%), bench press (19–33%), and latissimus dorsi pulldowns (17–33%) exercises. The gains in strength in all the exercises were greater in men receiving testosterone or exercise alone than in those receiving placebo alone (Fig. 3). The change in leg-press strength was correlated with change in muscle volume ($r=0{\cdot}44$, $P=0{\cdot}003$) and change in fat-free mass ($r=0{\cdot}55$, $P<0{\cdot}001$).

We conclude that, when the confounding influence of the learning effect is minimized, as we achieved in this study, and appropriate androgen-responsive measures of muscle strength are selected, testosterone replacement is associated with a demonstrable increase in maximal voluntary strength, in HIV-infected men with low testosterone concentrations.

Strength training also promotes gains in lean body mass and muscle strength (Bhasin *et al.* 1996, 2000). Furthermore, supraphysiologic doses of androgens augment the anabolic effects of resistance exercise on lean body mass and maximal voluntary strength (Strawford *et al.* 1999*b*, Sattler *et al.* 1999).

These data suggest that testosterone can promote weight gain and increase in lean body mass, in addition to muscle strength, in HIV-infected men with low testosterone levels. We do not know, however, whether physiologic 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.

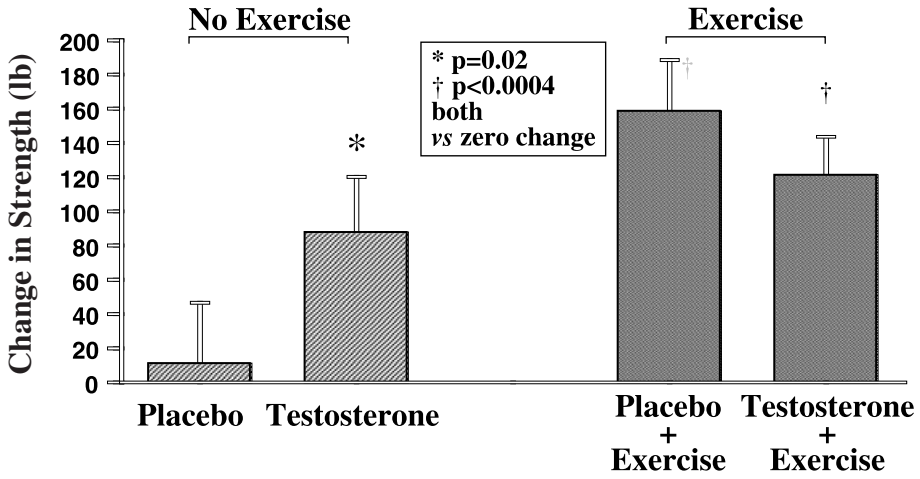

Figure 3 Effects of testosterone replacement with and without a program of resistance exercise in HIV-infected men with weight loss and low testosterone levels: muscle strength assessed by leg-press exercise. Treatment duration was 16 weeks, and the dose of testosterone enanthate was 100 mg weekly. Adapted from Bhasin *et al.* (2000).

Patterns of androgen abuse by athletes

Athletes abusing androgens not only use supraphysiologic doses, they often use several androgens simultaneously – a practice that is referred to as stacking (Catlin & Cowan 1992, Rogol & Yesalis 1995). For instance, typical replacement doses of testosterone used for hormone replacement of hypogonadal men are 100 mg testosterone enanthate intramuscularly weekly, or 5–10-mg testosterone administered daily by transdermal testosterone patch or gel. Some athletes might use as much as 1 g or more of testosterone enanthate weekly, and might then combine it with decadurabolin. Because each patch delivers only 5 mg testosterone daily, an individual will have to apply 20 patches daily to achieve testosterone delivery equivalent to 1 g testosterone enanthate given intramuscularly weekly. Because of the cost and the practical problems associated with applying such a large number of patches, the abuse of the transdermal testosterone patches is less likely to become a significant problem.

Testosterone is cleared rapidly from plasma; the duration of action is, therefore, largely determined by the pharmacokinetics of the formulation used. For instance, testosterone esters such as testosterone enanthate and cypionate, when injected in sesame oil, because of their hydrophobicity, are released slowly from the intramuscular oil depot into the blood stream. De-esterification of testosterone esters occurs rapidly in plasma; it is the slow release of testosterone from the muscle depot that accounts for their extended duration of action. Similarly, daily application of testosterone patches or gel is dictated largely by the rates of release of testosterone from these formulations into the skin and absorption across the skin into the general circulation. After discontinuation of androgen administration, the ability to detect prior androgen use would depend on the type of formulation, the dose, the sensitivity of the detection method, and the type of assay used. After injections of high doses of long-acting testosterone esters, circulating testosterone concentrations and testosterone to epitestosterone ratios in plasma might remain increased for several weeks, but suppression of endogenous LH persists for several weeks to months (Catlin & Cowan 1992). The biologic effects of testosterone on the muscle are testosterone dose- and concentration-dependent, and are mostly independent of the type of formulation used. Therefore, the gains in muscle mass and strength induced by pharmacologic administration of androgen would be expected to wear off after discontinuation of drug use; however, this issue has not been rigorously studied.

Testosterone effects on athletic performance

There is agreement that testosterone supplementation increases maximal voluntary strength, but that it does not improve specific tension. Therefore, testosterone would be expected to improve performance in weight-lifting events, because performance in these events is critically dependent upon maximal voluntary strength. It is not surprising that the abuse of androgenic steroids is most prevalent among power lifters. The effects of testosterone on other measures of muscle performance such as fatiguability and power (the rate of force generation) are unknown. Previous studies have failed to demonstrate any improvements in performance in endurance events (Casaburi *et al.* 1996*b*). The physiologic basis of the abuse of androgenic steroids by sprint runners or swimmers is not clear. It is possible that

testosterone might improve athletic performance in sprint events by decreasing reaction time, as testosterone has been shown to regulate neuromuscular transmission (Leslie *et al.* 1991, Blanco *et al.* 1997). Others have proposed that testosterone use might enhance recovery from exercise, thus allowing the athletes to train harder. It is also conceivable that testosterone might improve explosive power, an important determinant of performance in sprint and short distance swimming events. This speculation has not been tested. It is fair to state that unequivocal improvements in measures of athletic performance have not been demonstrated in any study.

Testosterone supplementation in other chronic illnesses

Patients with autoimmune disorders, particularly those receiving glucocorticoids, often experience a reduction in circulating testosterone concentrations, muscle wasting and bone loss (Reid *et al.* 1985, 1996, McAdams *et al.* 1986). In a placebo-controlled study, Reid *et al.* (1996) administered a replacement dose of testosterone to men receiving glucocorticoids. Testosterone replacement was associated with a greater increase in fat-free mass and bone density than were achieved with placebo.

There is a high frequency of low total and free testosterone concentrations, sexual dysfunction, infertility, delayed puberty, and growth failure in patients with end-stage renal disease (Handelsman 1993, 1998). Fat-free mass is decreased and physical function is markedly impaired in men with end-stage renal disease who are receiving maintenance hemodialysis (Johansen *et al.* 1999). Androgen administration does not consistently improve sexual dysfunction in these patients (Handelsman 1993, 1998). Similarly, the effects of androgen treatment on growth and pubertal development in children with end-stage renal disease remain unclear (Jones *et al.* 1980, Kassmann *et al.* 1992). Controlled clinical trials of nandrolone decanoate have reported increased hemoglobin concentrations with androgen treatment in men with end-stage renal disease who receive hemodialysis (Williams *et al.* 1974, Buchwald *et al.* 1977, Berns *et al.* 1992, Johansen *et al.* 1999). Before the advent of erythropoietin, testosterone was commonly used to treat anemia associated with end-stage renal disease. 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 end-stage renal disease who are receiving hemodialysis.

Chronic obstructive pulmonary disease (COPD) is a chronic 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 concentrations of anabolic hormones such as testosterone, growth hormone and IGF-I may contribute to muscle atrophy and dysfunction (Casaburi *et al.* 1996*a*). hGH increases nitrogen retention and lean body muscle in patients with COPD; however, the effects of hGH on ventilatory muscle strength and exercise tolerance remain to be established (Pape *et al.* 1991, Pichard *et al.* 1996, Burdet *et al.* 1997). Schols *et al.* (1995) examined the effects of a low dose of nandrolone or placebo in 217 men and women with COPD; these authors reported modest increases in lean body mass and ventilatory muscle strength.

Effects of testosterone on fat metabolism

Percent body fat is increased in hypogonadal men (Katznelson *et al.* 1998). Induction of androgen deficiency in healthy men by administration of a GnRH agonist leads to an increase in fat mass (Mauras *et al.* 1998). Some studies of young, hypogonadal men have reported a decrease in fat mass with testosterone replacement therapy (Brodsky *et al.* 1996, Katznelson *et al.* 1996), whereas others (Wang *et al.* 1996, Bhasin *et al.* 1997, Snyder *et al.* 2000) found no change. In contrast, long-term studies of testosterone supplementation in older men have consistently demonstrated a decrease in fat mass (Snyder *et al.* 1999). Epidemiologic studies (Barrett-Connor & Khaw 1988, Seidell *et al.* 1990) have shown that serum testosterone levels are lower in middle-aged men with visceral obesity. Serum testosterone concentrations correlate inversely with visceral fat area and directly with plasma high-density lipoprotein concentrations. Testosterone replacement in middle-aged men with visceral obesity improves insulin sensitivity and decreases blood glucose and blood pressure (Marin *et al.* 1992, 1995). Testosterone is an important determinant of regional fat distribution and metabolism in men (Marin *et al.* 1995), therefore it has been hypothesized that testosterone supplementation might be beneficial in HIV-infected men with the fat-redistribution syndromes.

Role of 5-α-reduction of testosterone in the muscle

Although the enzyme 5-α-reductase is expressed at low concentrations within muscle (Bartsch *et al.* 1980), we do not know whether conversion of testosterone to dihydrotestosterone (DHT) is required for mediating the effects of androgen 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 data

suggest that 5-α-reduction of testosterone is not obligatory for mediating its effects on the muscle.

Sattler *et al.* (1996) have reported that serum DHT concentrations are lower and the ratio of testosterone to DHT concentrations greater in HIV-infected men than in healthy men. These investigators have proposed that a defect in testosterone to DHT conversion may contribute to wasting in a subset of HIV-infected men. If this hypothesis were true, then it would be rational to treat such patients with DHT rather than testosterone. A DHT gel is currently under clinical investigation. However, unlike testosterone, DHT is not aromatized to estradiol. Therefore, there is concern that suppression of endogenous testosterone and estradiol production by exogenous DHT may produce osteoporosis.

Mechanisms of the anabolic effects of testosterone on muscle

Several studies are in agreement that testosterone produces muscle hypertrophy by increasing fractional muscle protein synthesis (Urban *et al.* 1995, Brodsky *et al.* 1996). However, the molecular basis of this anabolic effect is not known. Urban *et al.* (1995) have proposed that testosterone stimulates the expression of IGF-I and downregulates IGF binding protein-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 (Saartok *et al.* 1984) suggest that the androgen receptors in most tissues are either saturated or downregulated at testosterone concentrations that are at the lower end of the normal male range. Therefore, it is possible that the supraphysiologic doses of androgen produce muscle hypertrophy through androgen-receptor-independent mechanisms, such as through an antiglucocorticoid effect (Konagaya & Max 1986, Wu 1997). However, androgenic steroids have very low affinity for binding to glucocorticoid receptor; therefore, androgen modulation of glucocorticoid function through a post-receptor mechanism or through regulation of glucocorticoid-mediated gene expression has been postulated (Hickson *et al.* 1990, Tincello *et al.* 1997). We cannot exclude the possibility that some effects of androgen may be mediated through non-classical binding sites. The effects of testosterone on the muscle are modulated by a number of other factors such as the genetic background, growth hormone secretory status (Fryburg *et al.* 1997), nutrition, exercise, cytokines, thyroid hormones, and glucocorticoids. Testosterone may also affect muscle function by its effects on neuromuscular transmission (Leslie *et al.* 1991, Blanco *et al.* 1997). Finally, it is possible that athletes using supraphysiologic doses of testosterone might train harder because of the putative behavioral effects of testosterone; this could indirectly promote muscle hypertrophy.

The structure–activity relationships of androgenic steroids are not well understood. Until recently, it remained unclear whether the myotropic activity of androgens could be dissociated from their androgenic activity (Wilson 1988). Receptor binding studies in the rat seminal vesicle have suggested that the differences in the effects of nandrolone, an androgenic steroid that has been claimed to be more anabolic than androgenic in its actions, and testosterone, the prototypical androgen, might be related to the fact that 5-α-reduction increases the affinity of testosterone, but decreases the affinity of nandrolone for the androgen receptor (Bergink *et al.* 1985). Therefore, relative to testosterone, nandrolone might have a greater proportional effect in tissues with low 5-α-reductase activity such as the muscle, in comparison with tissues with high 5-α-reductase activity such as the prostate (Bergink *et al.* 1985, Toth & Zakar 1982). More recent data suggest that the tissue specificity of androgen action is determined by the combinatorial recruitment and activity of tissue-specific co-repressors and co-activators (Negro-Vilar 1999). By means of high-throughput molecular screening strategies, novel families of non-steroidal molecules with tissue and function selectivity have been identified (Negro-Vilar 1999); these observations have provided strong evidence that it may be possible to dissociate the myotropic and androgenic properties.

Effects of androgens on body composition in women

Supraphysiologic doses of testosterone increase nitrogen retention and promote weight gain in healthy, menstruating women (Kenyon *et al.* 1940). However, we do not know whether physiologic testosterone replacement can increase muscle mass and strength in older women or in women with clinical disorders associated with androgen deficiency. There are two assumptions that underlie the use of testosterone as an anabolic agent in sarcopenia in women: first, the testosterone dose–response curve is different in women and in men; second, clinically meaningful anabolic effects can be achieved in women, without the virilizing side effects. Both of these assumptions remain unsubstantiated. The data on the effects of androgen in women are very limited and difficult to interpret for several reasons. The existing testosterone formulations were designed to provide testosterone in men, and therefore most studies have used supraphyiologic doses of testosterone. Commercially available testosterone assays lack the sensitivity and precision to measure the low total and free testosterone concentrations in women. Because of the paucity of normal data, it is difficult to define androgen deficiency in women.

Women with polycystic ovary syndrome with high testosterone concentrations have greater fat-free mass than

age-matched controls. Davis *et al.* (2000) have shown that addition of testosterone to a regimen of estrogen replacement in post-menopausal women is associated with greater increments in fat-free mass than is achieved with estrogen alone.

Grinspoon *et al.* (1998), in a pilot study of HIV-infected women with weight loss, reported that a nominal dose of 150 μg testosterone delivered by the transdermal matrix patch was associated with positive trends in weight gain and some domains of health-related quality of life. However, the fat-free mass was not significantly changed. Therefore, it is not clear whether physiologic testosterone replacement can produce clinically meaningful changes in body composition and muscle function in women with androgen deficiency.

Summary

Replacement doses of testosterone when given to healthy hypogonadal men, and supraphysiologic doses when given to eugonadal men, increase fat-free mass, muscle size and strength. Testosterone supplementation in older men with low testosterone concentrations, and in HIV-infected men with weight loss and low testosterone concentrations is also associated with gains in fat-free mass and muscle strength. However, we do not know whether testosterone supplementation can improve physical function or other health-related outcomes in sarcopenia associated with aging or chronic illness. In spite of the widespread abuse of androgenic steroids by athletes and recreational body builders, the effects of testosterone on athletic performance are not well understood.

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