# Regulation of body composition by androgens

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**ABSTRACT. Human body can be viewed simplistically as being composed of fat-free and fat mass. With more sophisticated techniques, body composition can be broken down into fat mass, skeletal muscle mass, nonmuscle lean mass, visceral mass and bone mineral content.**
**Similarly, it is possible to obtain estimates of total body water and intracellular and extracellular water contents.**
**Regardless of the model of body composition assessment, it is evident that androgens are important determinants of body composition; there is no body compartment that is not directly or indirectly affected by androgens.**
**The effects of androgens on skeletal muscle mass have received the greatest attention in recent literature; however, growing body of evidence suggests that androgens also regulate fat mass, bone mineral content, nonmuscle soft tissues and body water.**
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## INTRODUCTION

Body composition refers to the chemical, elemental and molecular structure of tissues that comprise the human body. Depending on the complexity of the methods used to measure body composition, human body can be viewed simplistically as being composed of fat-free and fat mass. With more sophisticated techniques, body composition can be broken down into fat mass, skeletal muscle mass, non-muscle lean mass, visceral mass and bone mineral content (Ellis 2000). Similarly, it is possible to obtain estimates of total body water and intracellular and extracellular water contents. Regardless of the model of body composition assessment, it is evident that androgens are important determinants of body composition; there is no body compartment that is not directly or indirectly affected by androgens. The effects of androgens on skeletal muscle mass have received the greatest attention in recent literature (Woodhouse et al, 2001); however, growing body of evidence suggests that androgens also regulate fat mass, bone mineral content, non-muscle soft tissues and body water.

*Key-word:* Body composition, androgen.

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## TESTOSTERONE EFFECTS ON SKELETAL MUSCLE MASS

### *Correlational data*

Fat-free mass is lower and fat mass higher in healthy, hypogonadal men, in comparison to age-matched controls (Katznelson et al, 1997). Epidemiological studies of middle-aged and older men have also revealed a direct correlation between serum bioavailable testosterone concentrations and whole-body fat-free mass and appendicular skeletal muscle mass (Melton et al, 2000; Baumgartner et al, 1998; Perry et al, 2000). A cross-sectional study of inner city residents revealed that strength of knee extension and flexion is correlated with serum bioavailable testosterone concentrations (Perry et al, 2000).

### *Data from interventional studies*

Kochakian et al (1950) reported over 50 yr ago that testosterone supplementation in castrated males of many mammalian species increased nitrogen retention. Lowering of serum testosterone concentrations by administration of a long acting GnRH agonist in young men is associated with loss of fat-free mass and an increase in fat mass (Mauras et al, 1998). A number of studies (Bhasin et al, 1997; Katznelson et al 1996; Brodsky et al, 1996; Wang et al, 1996; Wang et al, 2000; Snyder et al, 2000) are in agreement that physiologic

testosterone replacement increases fat-free mass in young, hypogonadal men. Testosterone-induced increase in fat-free mass is predominantly due to an increase in skeletal muscle mass. Testosterone stimulates fractional muscle protein synthesis in androgen-deficient, young and older men (Brodsky et al, 1996; Urban et al, 1995; Ferrando et al, 2002).

The effects of supraphysiologic doses of androgen on the muscle have been a source of considerable controversy (Wilson 1988; Bardin 1996). Many of the earlier studies were inconclusive because of problems of study design. The doses of androgenic steroids used in these studies were relatively small compared to the much larger doses used by athletes and recreational body builders. Some of the studies were neither blinded nor randomized (Bardin 1996; Wilson 1988). The protein and energy intake were not standardized. 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 (Woodhouse et al, 2000). We conducted a randomized, controlled trial to determine the effects of a supraphysiological dose of testosterone with or without a standardized program of resistance exercise training (Bhasin et al, 1996). Healthy, young men with prior weight lifting experience, who had not engaged in a competitive event in the preceding year, were randomly assigned to one of four groups to receive placebo but no exercise, placebo plus exercise, testosterone enanthate but no exercise, or testosterone enanthate plus exercise. The dose of testosterone enanthate was 600-mg weekly and the treatment duration was 10 weeks. The exercise regimen was a progressive, periodized, thrice weekly, supervised, strength training program that was standardized based on the subject's initial one-repetition maximum strength. 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±2.9%, $p<0.05$] and leg (change in quadriceps area 6.5±1.3 vs –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 vs – 1±2%, $p<0.05$) and squat exercise capacity (increase 19±6 vs 3±1%, $p<0.05$) than 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 either non-exercising group. These data established that supraphysiologic doses of testosterone, especially when administered in conjunction with strength training, increase fat-free mass, muscle size and strength in healthy eugonadal men (Bhasin et al, 1996).

Griggs et al. (1989a) administered testosterone enanthate at a dose of 3 mg/kg/week to eugonadal men, 19-40 yr of age in an open-label study. Muscle mass, estimated from creatinine excretion, increased by 20% and $^{40}K$ mass increased 12% after 12 weeks of testosterone treatment. A similar dose of testosterone enanthate given for 12 months to men with muscular dystrophy, was associated with a 4.9 kg increase in lean body mass (Griggs et al., 1989b)

### *Relationship of testosterone dose and serum concentrations to anabolic effects on the muscle*

Testosterone increases muscle mass and strength, and regulates other physiologic processes, but we do not know whether testosterone effects are dose-dependent (Forbes 1985), and whether dose requirements for maintaining various androgen-dependent processes are similar. To determine the effects of graded doses of testosterone on body composition, 61 eugonadal men, 18-35 yr, were randomized to 1 of 5 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 testosterone enanthate for 20 weeks (Bhasin et al, 2001). 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). The changes in fat-free mass were highly dependent on testosterone dose ($p=0.0001$) and correlated with log testosterone concentrations ($r=0.73$, $p=0.0001$). Changes in leg press strength, leg power, thigh and quadriceps muscle volumes, hemoglobin, and IGF-I were positively correlated with testosterone concentrations, while changes in fat mass, and plasma HDL-cholesterol were negatively correlated. Sexual function, visual-spatial cog-

nition and mood, and prostate specific antigen (PSA) levels did not change significantly at any dose. Insulin sensitivity did not change at any dose (Singh et al, 2002). We conclude that changes in circulating testosterone concentrations are associated with testosterone dose- and concentration-dependent changes in fat-free mass, muscle size, strength and power, fat mass, hemoglobin, HDL-cholesterol, and IGF-I levels, in conformity with a single linear dose-response relationship (Bhasin et al, 2001). However, different androgen-dependent processes have different testosterone dose-response relationships.

We investigated whether testosterone dose and/or case variables including concentrations of hormones, growth factors, age, measures of body composition, muscle function, muscle morphometry or polymorphisms in androgen receptor could explain the variability in anabolic response to testosterone (Woodhouse et al, 2003). For the development of these prediction models, anabolic response was operationally defined as change in whole-body fat-free mass (by DEXA), appendicular fat-free mass (by DEXA) and thigh muscle volume (by MRI) during testosterone enanthate treatment. We used univariate and multi-variate analysis to identify the subset of baseline measures that best explained the variability in anabolic response to testosterone supplementation (Woodhouse et al, 2003). The 3 variable models of testosterone enantate dose, age and baseline PSA level explained 67% of the variance in change in whole-body fat-free mass. Change in appendicular fat-free mass was best explained (64% of the variance) by the linear combination of testosterone enanthate dose, baseline PSA and leg press strength, while testosterone enanthate dose, log of the ratio of LH to testosterone concentration (LH/T) and age explained 66% of the variation in change in thigh muscle volume (MRI). The models were further validated by using Ridge analysis and cross-validation in data subsets. Only the model using testosterone dose, age and PSA was a consistent predictor of change in fat-free mass in subset analyses. The length of CAG tract was only a weak predictor of change in thigh muscle volume and lean body mass in this small sample. These data demonstrate that anabolic response of young men to exogenous testosterone administration can largely be predicted by the testosterone dose. Further studies are needed to elucidate the genetic basis of natural variation in androgen responsiveness and to test the generalizability of the proposed prediction models (Woodhouse et al, 2003).

*Effects of testosterone replacement in older men with low testosterone levels and in men with chronic illness*

Increasing testosterone levels of older men with low testosterone levels to levels that are mid-normal for healthy, young men are associated with a significant increase in lean body mass and a reduction in fat mass (Tenover, 1992; Morley et al., 1993; Sih et al., 1997; Snyder et al., 1999; Kenny et al, 2001; Tenover, 1998). The gains in fat-free mass in these initial studies of testosterone supplementation were modest. Furthermore, although a few studies have reported improvements in grip strength during androgen supplementation of older men, none of the studies has examined the effects of testosterone supplementation on quadriceps strength, a major determinant of fall propensity. 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), which 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 levels.

Several studies on the effects of androgen supplementation in HIV-infected men have been reported (Coodley et al., 1997; Grinspoon et al., 1998; Bhasin et al., 1998; Bhasin et al., 1999; Dobs et al., 1999; Sattler et al., 1999; Strawford et al., 1999a; Strawford et al., 1999b; Bhasin et al., 2000). Of the 5 placebo-controlled studies of testosterone replacement in HIV-infected men with weight loss, 3 (Bhasin et al., 1998; Grinspoon et al., 1998; Bhasin et al., 2000) demonstrated an increase in fat-free mass and 2 (Dobs et al., 1999; Coodley et al., 1997) did not. The 3 studies (Bhasin et al., 2000; Bhasin et al., 1998; Grinspoon et al., 1998) that showed gains in fat-free mass, selected patients with low testosterone levels. 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 levels (Bhasin et al, 2000). 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 1 of 4 groups: placebo, no exercise; testosterone, no exercise; placebo plus exercise; or testosterone plus exercise (Bhasin et al., 2000). Placebo or 100 mg

testosterone enanthate 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 IRM method. 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 measurement had been achieved. In the placebo only group, muscle strength did not change in any of the five exercises (-0.3 to -4.0%). 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 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, or exercise alone compared to those receiving placebo alone. Testosterone treatment was associated with significant gains in fat-free mass ad muscle size that were greater than those associated with placebo administration alone. The change in leg press strength was correlated with change in muscle volume ($r=0.44$, $p=0.003$) and change in fat-free mass ($r=0.55$, $p<0.001$) (Bhasin et al, 2000). Thus, 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 increases in maximal voluntary strength, in HIV-infected men with low testosterone levels.

Strength training also promotes gains in lean body mass and muscle strength (Bhasin et al., 1996; Bhasin et al., 2000). Furthermore, supraphysiologic doses of androgens augment the anabolic effects of resistance exercise on lean body mass and maximal voluntary strength (Strawford et al., 1999b; Sattler et al., 1999). These data suggest that testosterone can promote weight gain and increase in 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 improve quality of life or physical function in HIV-infected men.

### *Mechanisms by which testosterone increases skeletal muscle mass*

The precise molecular mechanisms by which testosterone increases muscle mass are not well understood. The original observations of Kochakian (1950) that testosterone administration promotes nitrogen retention lead to speculation that testosterone stimulates fractional muscle protein synthesis. Indeed, a number of studies have demonstrated that testosterone replacement of young and older men with low testosterone concentrations increases fractional muscle protein synthesis rates (Brodsky et al 1996; Urban et al, 1995; Ferrando et al, 2002). Testosterone effects on muscle protein degradation have not been studied. However, this hypothesis does not explain several other observations. For instance, we have recently reported that testosterone-induced increase in muscle mass is associated with increased cross-sectional area of both type I and type II muscle fibers (Sinha-Hikim et al, 2002). In addition, testosterone administration is associated with a dose-dependent increase in the number of myonuclei and satellite cells. Muscle adaptation and remodeling in a number of models of muscle injury and anabolic response involves fusion of satellite cells with myofibers. Therefore, the observations that testosterone administration increases satellite cell number are significant. We do not know whether testosterone increases satellite cell number by stimulating satellite cell replication, inhibiting satellite cell apoptosis, or by stimulating differentiation of pluripotent muscle precursor cells into the myogenic lineage. Preliminary data from our laboratory suggest that testosterone promotes the commitment of muscle precursor cells into the myogenic lineage and inhibits differentiation of precursor cells into the adipogenic lineage (Taylor et al, 2002). This hypothesis provides an attractive unifying explanation for the reciprocal effects of testosterone on muscle and fat mass.

Testosterone serves not only as a hormone, but also as a prohormone. It is converted in the body to two active metabolites: 5-$\alpha$-dihydrotestosterone, and 17$\beta$-estradiol. We do not know whether 5-$\alpha$ reduction of testosterone to DHT is obligatory for mediating its effects on the muscle. The activity of 5-$\alpha$ reductase enzyme in the skeletal muscle is very low (Bartsch et al, 1980). Furthermore, the patients with congenital 5-$\alpha$ reductase deficiency undergo normal muscle development at puberty (Wilson 1996). Similarly, clinical experience indicates that patients with benign prostatic hyperplasia, who are treated with finasteride, an inhibitor of 5-$\alpha$ reductase, type 2, do not experience muscle atrophy. These data collectively suggest that testosterone conversion to DHT is not required for mediating its anabolic effects on the muscle. If this were indeed the case, then it would be desirable to develop selective androgen receptor modulators that are not 5-$\alpha$ reduced.

Patients with mutations of the CYP450aromatase gene (Carami et al, 1997) and mice with null mutations of the aromatase gene (Fisher et al, 1998)

have decreased muscle mass and higher fat mass. These data point to a complex role of aromatization of testosterone to estrogen in mediating its effects on the muscle.

## TESTOSTERONE EFFECTS ON WHOLE BODY FAT MASS AND REGIONAL FAT DISTRIBUTION

Hypogonadal men have higher fat mass than eugonadal controls. Similarly, aging-associated decline in serum testosterone is associated with increase in fat mass, although a cause and effect cannot be inferred from these epidemiological studies. Serum testosterone levels are lower in middle-aged men with visceral obesity (Seidell et al 1990; Barrett-Connor et al, 1988). Serum testosterone levels correlate inversely with visceral fat area and directly with plasma HDL levels (Seidell et al, 1990). Testosterone supplementation of middle-aged men with low-normal testosterone levels and mid-segment obesity has been reported to decrease visceral fat mass, improve insulin sensitivity, and reduce plasma glucose levels and blood pressure (Marin et al, 1992; Marin et al, 1995). Studies of testosterone supplementation in older men also uniformly demonstrate a decrease in whole body fat mass (Tenover 1998; Snyder et al, 1999). Our dose-response studies have shown that testosterone concentrations are inversely correlated with fat mass (Bhasin et al, 2001). Administration of high doses of testosterone decreases whole-body fat mass; the loss of body fat is evenly distributed in young men between trunk and appendices, and between superficial and deep compartments. However, in our dose-response study of young men, testosterone administration did not alter insulin sensitivity even at supraphysiological doses (Singh et al, 2002). We do not know whether testosterone supplementation would be beneficial in HIV-infected men with fat redistribution syndrome, especially those with visceral obesity.

## TESTOSTERONE EFFECTS ON BONE MASS

Testosterone deficiency is associated with progressive loss of bone mass. In one study performed in sexual offenders, surgical orchiectomy was associated with a progressive decrease in bone mineral density of a magnitude similar to that seen in women after menopause (Stepan et al, 1989). Similarly, reduction in serum testosterone levels by surgical orchiectomy (Daniell 1997; Eriksson et al, 1995) or the administration of a GnRH agonist (Goldray et al, 1993) for the treatment of prostate cancer and benign prostatic hypertrophy leads to loss of bone mass. Surgical orchiectomy in male rats or androgen blockade by administration of an androgen receptor antagonist leads to loss of bone mass (Goulding et al, 1993). Testosterone administration to healthy, testosterone-deficient men is associated with significant improvement in bone mineral density, although the bone density is not always normalized after 1-2 yr of testosterone replacement therapy (Katznelson et al, 1996; Behre et al, 1997; Leifke et al, 1998; Finkelstein et al, 1987). The reasons for the failure of testosterone replacement therapy to normalize bone mineral density in androgen-deficient men are not entirely clear. Some of the patients included in these studies had panhypopituitarism and therefore, also suffered from concomitant growth hormone deficiency. In addition, some participants had experienced testosterone deficiency before the onset and completion of pubertal development. If androgen deficiency occurs during this critical developmental period of bone accretion, the individual may end up with decreased peak bone mass, and subsequent testosterone administration may not be able to restore bone mass to levels seen in eugonadal age-matched controls (Finkelstein et al, 1987; Bonjour et al, 1991). Many of the studies of testosterone replacement were less than 3 yr in duration, and it is possible that a longer period of testosterone administration might be necessary to achieve maximal improvements in bone mineral density. Indeed, Behre et al. (1997) reported that bone mineral density in some hypogonadal men after many years of testosterone treatment using a scrotal transdermal patch did reach the levels expected for age-matched eugonadal controls. Finally, excessive glucocorticoid replacement might also contribute to suboptimal gains in bone mineral density.

The incidence of all fractures increases with advancing age; the rate of increase is particularly striking after 70 yr of age (Ray et al, 1997; Melton et al, 1998; Center et al, 1999; Nguyen et al, 1998; Boonen et al, 1997; Kenny et al, 1998; Stanley et al, 1991). Thirty percent of all hip fractures occur in elderly men (Center et al, 1999). The occurrence of any fracture in older men, particularly hip fracture, is associated with significantly increased risk for death, morbidity and disability (Ray et al 1997). Men with hip fractures have lower testosterone levels than age-matched controls (Boonen et al, 1997; Kenny et al, 2001; Stanley et al, 1991). Bone mineral density in older men is correlated with bioavailable testosterone and bioavailable estradiol concentrations (Greendale et al, 1998).

Two recent studies have examined the effects of long-term testosterone replacement in older men. In one study, Snyder et al (1999) treated 108, relatively healthy older men, with serum testosterone levels less than 475 ng/dl and bone mineral density of lumbar spine below the mean for healthy men ($<1.26$ g/cm$^2$), with scrotal patches designed to de-

liver either placebo or 6 mg testosterone nominally over the 24-h dosing interval. The treatment duration was 3 yr. Testosterone treatment was associated with significant increase in mean serum testosterone levels from 367 to 625 ng/dl. The bone mineral density increased significantly in both the placebo- and testosterone-treated men, but the change in bone mineral density was not significantly different between the two groups. Both groups of men in this study received calcium and vitamin D supplementation that might have been responsible for the increase in bone mineral density in placebo-treated men. The increase in bone mineral density was inversely correlated with initial testosterone levels; those with the lowest baseline testosterone levels experienced the greatest increase in bone mineral density during testosterone treatment.

In an unpublished clinical trial, Tenover (1998) administered either placebo or testosterone by biweekly injections of testosterone enanthate to older men with serum testosterone levels less than 350 ng/dl. Testosterone administration was associated with a greater increase in bone mineral density than that associated with placebo treatment. Fat-free mass increased and fat mass decreased in testosterone-treated men, but not in men receiving placebo-treatment. The results of these two studies suggest that in older men with unequivocally low testosterone levels, testosterone treatment increases bone mineral density, but that the beneficial effects of testosterone on bone mass might not be demonstrable in men with normal serum testosterone levels. This proposal is supported by data from a rat study (Vanderscheuren et al, 1992) in which surgically orchiectomized rats were treated with either a physiological or a supraphysiological dose of testosterone. The lower dose of testosterone that restored serum testosterone levels in castrated rats into the low normal range, increased bone mass to that seen in eugonadal controls; supraphysiological dose of testosterone did not further increase bone mass.

The effects of testosterone on fracture rates have not been studied. It is possible that testosterone might reduce fracture rates not just by its effects on bone mineral density, but also by reducing fall propensity. Testosterone administration, by augmenting quadriceps, might improve balance and reduce the risk of falls and thereby lead to further reduction in fracture risk.

### *Mechanisms of testosterone effect on the bone*

There is agreement that testosterone inhibits bone resorption in part through its conversion to estradiol by the action of the enzyme, aromatase. It is possible that testosterone might also directly stimulate osteoblastic bone formation through an androgen-receptor-mediated pathway. Androgen receptors were originally demonstrated in osteoblasts (Colvard et al, 1989), but more recent reports suggest that androgen receptors might also be expressed in bone marrow cells and osteoclasts (Bellido et al, 1995). Testosterone administration to androgen-deficient men decreases markers of bone resorption, and is associated with increases in markers of osteoblastic bone formation (Wang et al, 1996). Testosterone stimulates pituitary GH secretion and serum IGF-I levels, and these growth factors might have independent anabolic effects on the bone. Testosterone also regulates the expression of a number of other bone growth factors locally. Finally, testosterone increases muscle mass and strength; this may indirectly affect bone mass and fracture risk.

## TESTOSTERONE EFFECTS ON BODY WATER

The pioneers in the androgen field recognized that testosterone administration in androgen-deficient men and in healthy women was associated with significant retention of sodium, chloride, and potassium, sulfur and phosphate (Knowlton et al, 1942; Wilson 1996). Knowlton et al. (1942) reported that much of the early weight gain could be accounted for by water retention in association with retained electrolytes and protein. When administration of androgen is topped, sodium, potassium, and water are lost quickly (Knowlton et al, 1942; Wilson 1996). Significant water retention resulting in edema is unusual in healthy, hypogonadal men, who are receiving replacement doses of testosterone. However, supraphysiologic doses of testosterone can result in edema and exacerbate heart failure when given to men with pre-existing heart or kidney disease. In clinical trials of testosterone replacement in older men (Snyder et al, 1999; Sih et al, 1997, Tenover 1998; Kenny et al, 2001), the frequency of edema and congestive heart failure in testosterone-treated men has been very low.

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