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# Testosterone Replacement Increases Fat-Free Mass and Muscle Size in Hypogonadal Men*

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**ABSTRACT**

Testosterone-induced nitrogen retention in castrated male animals and sex-related differences in the size of the muscles in male and female animals have been cited as evidence that testosterone has anabolic effects. However, the effects of testosterone on body composition and muscle size have not been rigorously studied. The objective of this study was to determine the effects of replacement doses of testosterone on fat-free mass and muscle size in healthy hypogonadal men in the setting of controlled nutritional intake and exercise level.

Seven hypogonadal men, 19–47 yr of age, after at least a 12-week washout from previous androgen therapy, were treated for 10 weeks with testosterone enanthate (100 mg/week) by im injections. Body weight, fat-free mass measured by underwater weighing and deuterated water dilution, and muscle size measured by magnetic resonance imaging were assessed before and after treatment. Energy and protein intake were standardized at 35 Cal/kg·day and 1.5 g/kg·day, respectively.

Body weight increased significantly from 79.2 ± 5.6 to 83.7 ± 5.7 kg after 10 weeks of testosterone replacement therapy (weight gain, 4.5 ± 0.6 kg; $P = 0.0064$). Fat-free mass, measured by underwater weighing, increased from 56.0 ± 2.5 to 60.9 ± 2.2 kg (change, +5.0 ± 0.7 kg; $P = 0.0004$), but percent fat did not significantly change. Similar increases in fat-free mass were observed with the deuterated water method. The cross-sectional area of the triceps arm muscle increased from 2421 ± 317 to 2721 ± 239 $mm^2$ ($P = 0.045$), and that of the quadriceps leg muscle increased from 7173 ± 464 to 7720 ± 454 $mm^2$ ($P = 0.0427$), measured by magnetic resonance imaging. Muscle strength, assessed by one repetition maximum of weight-lifting exercises increased significantly after testosterone treatment. L-[1-$^{13}$C]Leucine turnover, leucine oxidation, and nonoxidative disappearance of leucine did not significantly change after 10 weeks of treatment. There was no significant change in hemoglobin, hematocrit, creatinine, and transaminase levels.

Replacement doses of testosterone increase fat-free mass and muscle size and strength in hypogonadal men. Whether androgen replacement in wasting states characterized by low testosterone levels will have similar anabolic effects remains to be studied. (*J Clin Endocrinol Metab* **82:** 407–413, 1997)

KOCHAKIAN demonstrated 50 yr ago that testosterone increases nitrogen retention in castrated male animals of many species (1–3). Similar effects on urinary nitrogen excretion were observed in eunuchoidal men, boys before puberty, and women (2–6). These data along with the gender-related differences in the size of many sexually dimorphic muscles, particularly masseter and levator ani in rodents, suggested that testosterone might have anabolic effects (2, 3, 5). Recognition of the anabolic properties of androgen prompted efforts by pharmaceutical companies to develop compounds that had anabolic properties but no androgenic activity; these compounds came to be known as the anabolic steroids (2–3, 5–9). Despite the lack of conclusive evidence, androgenic/anabolic steroids are widely abused because of the perception that these compounds increase muscle size and strength (2, 5–12). Although clinical experience indicates that hypogonadal men treated with testosterone replacement gain weight, the effects of testosterone on body composition and muscle size have not been rigorously studied in this patient population (1, 2, 5). Previous studies performed in the 1940s and 1950s used relatively insensitive methods for assessment of protein synthesis, did not control dietary intake or exercise level (1, 4), and did not assess body composition.

Recent years have witnessed a resurgence of interest in exploring the anabolic applications of androgens, particularly to reverse the sarcopenia associated with the human immunodeficiency virus, cancer, aging, and other chronic illnesses (13–18). We, therefore, examined the effects of testosterone replacement therapy on body composition and muscle size in otherwise healthy hypogonadal men. Energy and protein intake and exercise level were controlled throughout the 10-week treatment period. Body composition was assessed by underwater weighing and deuterium water

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methods. Those men who were previously receiving testosterone replacement therapy underwent a 12-week washout to maximize the chances of demonstrating androgen-induced changes in body composition.

## Materials and Methods

This study was approved by the institutional review boards of the Charles R. Drew University of Medicine and Science (Los Angeles, CA) and the Harbor-University of California-Los Angeles Research and Education Institute (Torrance, CA). All men gave informed written consent.

### *Subjects*

The study participants were hypogonadal men, 19–50 yr of age and otherwise in good health. Those with diabetes, systemic illness, or neoplastic disease were excluded. The men had previously been treated with testosterone esters or gonadotropins. Men who had ever used recreational drugs or had a history of psychiatric or behavioral disorders were excluded.

### *Study design*

Of the nine men who were recruited, two dropped out during the early treatment phase because of scheduling difficulties or compliance problems. The remaining seven men completed all aspects of the study. This was an open label, nonrandomized study. The study was divided into a washout period and a 10-week treatment period. At the end of the 10-week treatment period, the subjects resumed their usual treatment, but were asked to return 4 months later for evaluation.

### *Standardization of protein and energy intake*

Two weeks before the beginning of treatment (day 1), the subjects were instructed to consume a standardized daily 36 Cal/kg diet containing 1.5 g/kg protein and 100% of the RDA intake of vitamins, minerals, and trace elements. Dietary compliance was verified every 4 weeks by 3-day food records. Dietary intake was adjusted every 2 weeks based on changes in body weight.

### *Washout from previous testosterone treatment*

All subjects were required to stop testosterone treatment at least 12 weeks before the initiation of the study to reverse the effects of prior testosterone treatment. The subjects were asked not to undertake any weight lifting or heavy endurance exercise for 4 weeks before starting testosterone treatment.

### *Testosterone treatment*

The participants received 100 mg testosterone enanthate in sesame oil, im, weekly at the Clinical Research Center. This is the usual dose given for replacement therapy in men with hypogonadism and is believed to be physiological (19–21). Previous studies (19–21) had established that a dose of 100 mg given every week provides less fluctuations in serum testosterone levels than regimens employing 200 mg every 2 weeks or 300 mg every 3 weeks.

### *Exercise*

The men were asked not to undertake any weight lifting or moderate to heavy endurance exercise. These instructions were reinforced during their visits to the Clinical Research Center.

### *Evaluation procedures and outcome measures*

The primary outcome measure was fat-free mass determined by underwater weighing. In addition, body composition was assessed by the deuterium water dilution method. Muscle size was measured by magnetic resonance imaging, and muscle strength was determined by one repetition maximum of the bench press and squat exercises before and at the end of the 10-week treatment period. Body weight was recorded with minimal clothing on the same scale every 2 weeks. Serum total and free testosterone levels, LH, FSH, and sex hormone-binding globulin were measured during weeks −4, −2, and −1 before treatment and on days 2, 3, 7, 14, 28, 42, 56, and 70 of the treatment period. Blood counts and chemistries (including serum transaminase levels) were measured during weeks −4 and −1 before treatment; on days 28, 56, and 70 of the treatment period; and at the end of the 4-month recovery period. Periodic evaluations for adverse experiences were made during weeks −4 and −1 before treatment; on days 28, 56, and 70 of the treatment period; and 4 months after discontinuation of treatment.

### *Assessment of muscle size*

Muscle size was measured by magnetic resonance imaging of the arm and leg at the middiaphysial level, the junction of the upper third and middle third, and the junction of the middle third and lower third (22). The cross-sectional areas of the limb, the sc tissue, the muscle compartment, and the quadriceps or the triceps muscles were computed.

### *Body composition analysis*

Fat-free mass was estimated from body density measurements obtained by underwater weighing. During underwater weighing, the men were asked to exhale to residual lung volume, which was measured by helium dilution immediately before testing.

For the deuterium dilution method of analysis of body composition, the men ingested 20 g deuterium oxide by mouth and washed it down with an additional 100 mL tap water (23). Plasma samples were drawn at −15, 0, 120, 180, and 240 min. Preliminary studies had shown that a steady state of plasma deuterium concentrations is maintained between 120–240 min.

### *Muscle strength*

Effort-dependent muscle performance was assessed by the one repetition maximum method for the supine bench press and parallel squat exercises (24). Each man completed a sequence of increasingly more difficult lifts; the maximum amount of weight lifted, the one repetition maximum, was recorded as a measure of strength. The men were instructed in the proper technique and tested on two different occasions, several days apart, until stable measurements of strength were achieved.

### *Hormone measurements*

Serum LH and FSH were measured by immunofluorometric assays (25, 26), each with a sensitivity of 0.05 IU/L. The cross-reactivity of the free $\alpha$-subunit and other glycoproteins in the LH and FSH assays was less than 1%. Serum testosterone was measured by immunoassay, and free testosterone was measured by equilibrium dialysis (26), as previously described. Serum sex hormone-binding globulin was measured by immunoassays using reagents purchased from Delphia-Wallac (Turku, Finland) (22).

### *Study of protein dynamics*

After an overnight fast, the whole body leucine kinetics and oxidation were measured during a primed continuous iv infusion of L-[1-$^{13}$C]leucine (27). A bolus dose of 1 mg/kg L-[1-$^{13}$C]leucine and [$^{13}$C]sodium bicarbonate (0.08 mg/kg) was injected iv to prime the respective pools followed by a constant infusion of 1 mg/kg·h L-[1-$^{13}$C]leucine into a forearm vein (28). Samples of venous blood, drawn from a superficial hand vein (retrograde direction) in the opposite arm, and expired air were collected at 10 and 0 min before and 2, 6, 7, and 8 h after the start of the infusion. The exhaled air was collected in a latex bag, and a sample of the mixed exhalate was transferred to an air-tight glass vial for measurement of $^{12}CO_2$ and $^{13}CO_2$.

Plasma $\alpha$-keto-isocaproic acid, the intracellular conversion product and ketoacid of leucine, was chemically derivatized to trimethylsilyl quinoxalinol. Plasma $\alpha$-[$^{13}$C]keto isocaproic acid isotopic enrichment was determined using electron impact ionization gas chromatography-mass spectrometry (5980A-MSD, Hewlett-Packard, Palo Alto, CA). Separation of ketoacids was achieved using a DB-1 capillary column (12 m; id, 0.25 mm; 0.33-$\mu$m film) and selected ion monitoring of mass to charge (m/z) 233 and 232 was used to measure isotopic abundance (28). The

partial pressure of $CO_2$ in the expired air was measured using a mass spectrometer (model 1100 Medical Gas Analyzer, Perkin-Elmer), and the volume of gas was measured with a Colins gasometer (Instrumentation Associates, New York, NY). Expired air $^{13}CO_2$ and $^{12}CO_2$ were measured using an isotope ratio mass spectrometer (27).

The molar enrichment of the labeled species was calculated from mass spectra using the least square approach. Plasma leucine flux, leucine oxidation, and nonoxidative leucine disappearance were calculated using plasma [$^{13}$C]α-keto-isocaproic acid abundance at plateau as previously described. The whole body protein synthesis rate was calculated from the nonoxidative portion of leucine flux, assuming that the leucine content of protein in human tissue is 7.8%.

### *Statistical analysis*

The data were averaged across subjects to obtain group means and SEM. Baseline and week 10 values were compared using the paired *t* test. Significance was accepted as $P < 0.05$.

## Results

### *Subjects*

The subjects were healthy hypogonadal men, ranging in age from 21–47 yr (Table 1); three were Caucasian, two were African-American, one was Hispanic, and one was Asian-American. Four men had hypergonadotropic hypogonadism due to Klinefelter's syndrome. Two patients had hypogonadotropic hypogonadism; one of these two patients had idiopathic hypogonadotropic hypogonadism, and the other had panhypopituitarism due to resection of a craniopharyngioma. One man had hypogonadism in association with multiple autoimmune endocrine organ failures; however, this patient had LH and FSH levels in the normal range (Table 1).

There was no significant change in hemoglobin, hematocrit, or serum creatinine concentrations during the treatment period (Table 2). Serum aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, and alkaline phosphatase levels did not change significantly (Table 2).

### *Hormone levels*

Serum testosterone levels increased from a baseline of 2.5 ± 1.0 to 17.7 ± 3.2 nmol/L (mean ± SEM) on day 15 and were maintained in the normal male range throughout the treatment period (Table 3). These values represent nadir levels 7 days after each testosterone injection, and serum testosterone levels at other times were presumably higher. Free testosterone levels increased from a baseline of 66 ± 24 pmol/L to 257 ± 69 on day 29, 243 ± 42 on day 57, and 239 ± 28 during week 10 (Table 3). Serum LH levels decreased significantly from 13.9 ± 3.2 to 3.1 ± 1.5 U/L, and serum FSH levels decreased from 24.5 ± 4.5 to 6.0 ± 2.0 U/L during week 10 in the five hypergonadotropic men (Table 3).

### *Body weight*

All men experienced increases in body weight ranging from 2.8–7.0 kg, for an average gain of 4.5 ± 0.6 kg ($P = 0.0004$) or 5.8 ± 1.0% (Fig. 1). The subjects started to gain weight within 1 or 2 weeks after starting treatment, and there was progressive weight gain throughout the first 6 weeks of the treatment period (data not shown).

### *Fat-free mass*

Fat-free mass, measured by underwater weighing, increased significantly from 56.0 ± 2.5 to 60.9 ± 2.2 kg by an average of 5.0 ± 0.7 kg ($P = 0.0004$) or 8.9 ± 1.4% (Fig. 1). Thus, almost all the weight gain could be explained by the increase in fat-free mass. The percent fat did not significantly change during treatment (26.9 ± 3.0% at baseline *vs.* 25.7 ± 3.4% at 10 weeks; change, −1.3 ± 1.4 kg; $P$ = NS).

Similar increases in fat-free mass were observed with the deuterium water dilution method (Fig. 2; 56.1 ± 4.5 *vs.* 63.1 ± 5.3 kg, baseline *vs.* week 10; $P = 0.008$). Total body water increased from 40.9 ± 3.3 kg at baseline to 46.0 ± 3.9 kg at week 10; however, the percent water did not significantly change (52 ± 3% *vs.* 55 ± 3%; $P = 0.08$). Fat mass, derived by the deuterium water method, did not significantly change (22.8 ± 4.1 *vs.* 20.6 ± 3.4 kg; $P$ = NS).

### *Muscle size*

The cross-sectional area of the arm muscles increased significantly at all three levels (Table 4). The triceps muscle area increased by 12% (2421 ± 317 mm$^2$ at baseline *vs.* 2721 ± 239 mm$^2$ at week 10; $P = 0.046$). The cross-sectional area of the leg increased significantly; the quadriceps area increased by 8% from 7173 ± 464 at baseline to 7720 ± 454 mm$^2$ at week 10 ($P = 0.043$; Table 4). The sc fat area in the arm or thigh did not significantly change.

### *Muscle strength*

Strength in the bench press increased from 50.4 ± 4.1 to 61.4 ± 4.1 kg, for a gain of 22 ± 3% ($P < 0.002$). The squat strength increased from 70.0 ± 10.9 to 101.8 ± 12.7 kg ($P < 0.006$).

**TABLE 1.** Clinical characteristics of the hypogonadal men

| Subject no. | Age (yr) | Race | Wt (kg) | Ht (cm) | BMI (kg/m$^2$) | Diagnosis | LH (U/L) | FSH (U/L) | Testosterone (nmol/L) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 47 | B | 102.2 | 195.6 | 26.7 | Klinefelter's | 21.2 | 25.8 | 1.4 |
| 2 | 44 | C | 75.0 | 182.9 | 22.4 | Klinefelter's | 11.8 | 21.5 | 0.7 |
| 3 | 21 | C | 62.4 | 185.5 | 18.1 | IHH | 5.9 | 0.4 | 0.7 |
| 4 | 28 | B | 65.4 | 182.9 | 19.6 | Panhypopituitarism | 1.2 | 0.8 | 2.8 |
| 5 | 31 | A | 94.8 | 170.2 | 32.7 | Klinefelter's | 19.1 | 34.2 | 3.5 |
| 6 | 38 | C | 82.0 | 175.2 | 26.7 | Klinefelter's | 14.9 | 32.0 | 7.7 |
| 7 | 44 | H | 72.4 | 163.7 | 27.0 | Hypogonadism in association with autoimmune diseases of the adrenal and thyroid | 2.7 | 8.8 | 0.7 |

B, African-American; C, Caucasian; A, Asian; H, Hispanic; IHH, idiopathic hypogonadotropic hypogonadism; Klinefelter's, primary testicular failure due to Klinefelter's syndrome; Panhypopituitarism, multiple pituitary hormone deficiencies after resection of a craniopharyngioma.

**TABLE 2.** Hemoglobin, hematocrit, and serum creatinine, and transaminase concentrations before and during testosterone treatment

| | Baseline | Day 29 | Day 57 | 10 weeks | *P* |
|---|---|---|---|---|---|
| Hemoglobin (g/L) | 138.0 ± 7 | 139 ± 2 | 148 ± 4 | 143 ± 5 | NS |
| Hematocrit (L/L) | 0.402 ± 0.023 | 0.415 ± 0.008 | 0.443 ± 0.010 | 0.432 ± 0.013 | NS |
| Creatinine (mg/dL) | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.0 ± 0.1 | 1.0 ± 0.1 | NS |
| AST (U/L) | 26 ± 5 | 17 ± 2 | 19 ± 2 | 18 ± 2 | NS |
| ALT (U/L) | 30 ± 8 | 19 ± 4 | 23 ± 3 | 22 ± 4 | NS |
| GGT (U/L) | 52 ± 22 | 36 ± 16 | 38 ± 17 | 35 ± 14 | NS |
| Alkaline Phosphatase (U/L) | 88 ± 17 | 84 ± 17 | 84 ± 17 | 80 ± 16 | NS |

Data are the mean ± SEM. GGT, γ-Glutamyl transpeptidase.

**TABLE 3.** Serum total and free testosterone, LH, and FSH concentrations before and after 10 weeks of testosterone treatment

| | Baseline | Day 15 | Day 29 | Day 43 | Day 57 | Day 64 | Week 10 |
|---|---|---|---|---|---|---|---|
| Testosterone (nmol/L) | 2.5 ± 1.0 | 17.7 ± 3.2 | 15.6 ± 2.8 | 15.5 ± 3.9 | 19.5 ± 3.1 | 19.5 ± 4.0 | 26.6 ± 6.3 |
| Free testosterone (pmol/L) | 66 ± 24 | | 257 ± 69 | | 243 ± 42 | | 239 ± 28 |
| LH (IU/L) | 13.9 ± 3.2 | 9.8 ± 2.7 | 6.9 ± 2.4 | 6.2 ± 2.3 | 5.1 ± 2.6 | 4.6 ± 2.6 | 3.1 ± 1.5 |
| FSH (IU/L) | 24.5 ± 4.5 | 13.8 ± 3.4 | 11.6 ± 3.7 | 10.6 ± 3.6 | | | 6.0 ± 2.0 |

The hormone levels were measured on days 15, 29, 43, 57, and 64, 1 week after the previous testosterone injection; these levels, therefore, coincide with the nadir testosterone levels. Week 10 blood samples were obtained on day 68 ± 2, usually 4–6 days after the preceding testosterone injection on day 64. Data are the mean ± SEM. n = 7 for total and free testosterone levels. However, LH and FSH levels represent the mean ± SEM of four hypergonadotropic men and one man with low testosterone levels and normal LH and FSH levels in association with autoimmune multiple endocrinopathies. To convert total testosterone levels to nanograms per dL, divide by 0.0347; to convert values for free testosterone to picograms per mL, divide by 3.47.

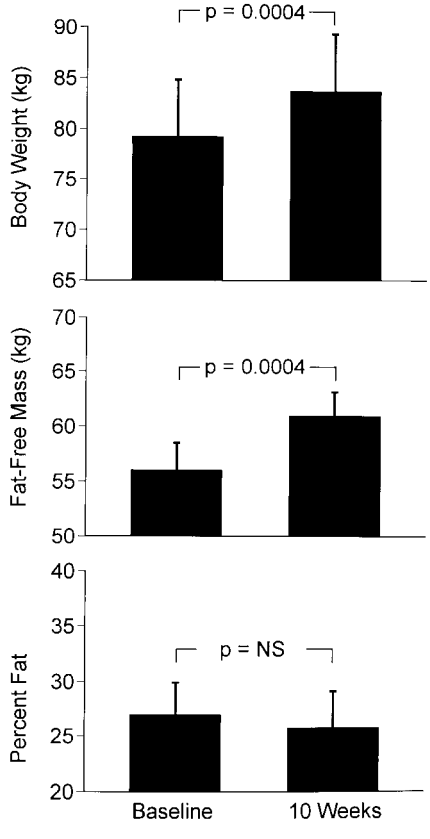


FIG. 1. Body weight, fat-free mass, and percent fat at baseline and after 10 weeks of testosterone replacement therapy. Fat-free mass and fat mass were derived from body density measurements by weighing the men in air and under water. *P* values are shown for comparisons of baseline and week 10 measurements. Data are the mean ± SEM.

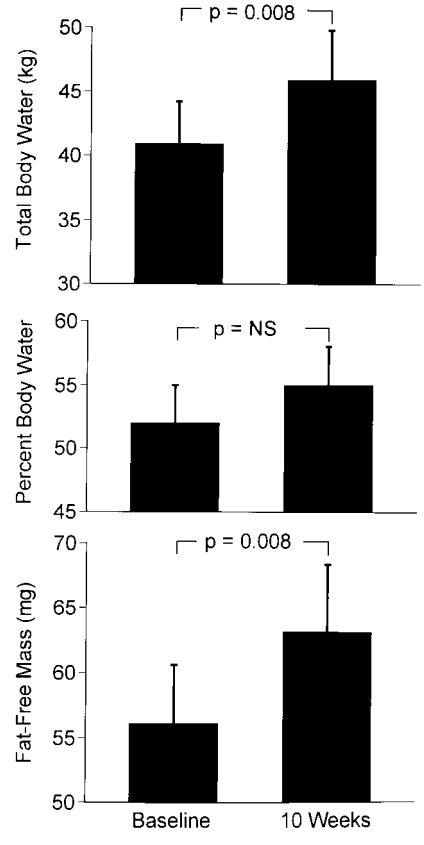


FIG. 2. Total body water, percent body water, and fat-free mass measured by the deuterated water method at baseline and after 10 weeks of testosterone replacement therapy. *P* values are shown for comparison of baseline and week 10 measurements. Data are the mean ± SEM.

**TABLE 4.** Cross-sectional area of the arm and thigh muscles before and after 10 weeks of testosterone treatment

| | Baseline | 10 weeks | *P* value |
|---|---|---|---|
| Arm | | | |
| Upper third | 3517 ± 310 | 4174 ± 382 | 0.0014 |
| Middiaphysial | 3888 ± 423 | 4470 ± 351 | 0.0069 |
| Lower third | 4002 ± 314 | 4392 ± 284 | 0.0027 |
| Triceps muscle area | 2421 ± 317 | 2721 ± 239 | 0.0455 |
| sc fat | 2733 ± 401 | 2663 ± 385 | NS |
| Thigh | | | |
| Upper third | 11301 ± 690 | 12489 ± 611 | 0.0008 |
| Middiaphysial | 14345 ± 808 | 15459 ± 899 | NS |
| Lower third | 14435 ± 1018 | 16102 ± 816 | 0.0018 |
| Quadriceps area | 7173 ± 464 | 7720 ± 454 | 0.0427 |
| sc fat | 7561 ± 1073 | 7062 ± 1116 | NS |

Data are the mean ± SEM. Cross-sectional areas of the muscle compartment in the arm and thigh, and the triceps and quadriceps muscles were computed from magnetic resonance images obtained at three levels: the junction of the upper and middle third of the limb, middiaphysial, and the junction of the middle and lower third of the limb.

**TABLE 5.** Whole body L-[1-$^{13}$C]leucine turnover before and after 10 weeks of testosterone treatment in hypogonadal men

| | Baseline | 10 weeks | *P* |
|---|---|---|---|
| Leucine flux ($\mu$mol/kg · min) | 2.00 ± 0.17 | 2.02 ± 0.11 | NS |
| Leucine oxidation ($\mu$mol/kg · min) | 0.45 ± 0.08 | 0.37 ± 0.04 | NS |
| Nonoxidative leucine disappearance ($\mu$mol/kg · min) | 1.56 ± 0.22 | 1.66 ± 0.11 | NS |

Whole body leucine turnover was determined during a primed, steady state, continuous infusion of L-[1-$^{13}$C]leucine. Leucine oxidation was calculated from the isotopic enrichment of $^{13}CO_2$ in the expired air collected during the steady state infusion of L-[1-$^{13}$C]leucine. Data are the mean ± SEM (n = 7 at each time point). The *P* value for the comparison of week 10 values against baseline is shown. NS, Week 10 value not statistically significant from the corresponding baseline.

*Protein metabolism*

Whole body leucine flux, oxidation, and nonoxidative leucine disappearance rates (Table 5) did not significantly change during testosterone treatment.

## Discussion

Our results demonstrate that testosterone replacement has substantial effects on body composition. Replacement doses of testosterone increase body weight, primarily by increasing fat-free mass. Although the percent fat did not change, it is possible that there may be significant changes in regional fat distribution during testosterone treatment that are not reflected in the whole body estimates of fat content. Muscle size increased in both the arm and leg, even though the subjects did not undertake resistance exercise other than their activities of daily life. Testosterone treatment was withdrawn for 12 weeks; we do not know whether a longer washout might have produced greater increases in fat-free mass.

It is surprising that the whole body leucine turnover, a surrogate for protein dynamics, did not significantly change during the 10-week treatment period despite substantial gains in fat-free mass. Several explanations are possible. First, testosterone may increase nitrogen balance and leucine turnover early in the course of treatment, and these early effects may have been missed because the measurements were performed only at the end of the 10-week treatment period. In support of this possibility, the weight gain started within the first week of treatment, and maximum weight gain had been achieved by 6 weeks of treatment. Second, small changes (3–5%) in nitrogen balance or leucine turnover may have occurred, but were not detected. Third, it is possible that testosterone may selectively increase muscle protein synthesis. Because muscle protein synthesis accounts for only 20% of whole body protein synthesis, and this tissue has a slow (1–2%) turnover, significant changes in the former may not be reflected in the whole body leucine turnover. We used leucine flux as a marker of whole body protein turnover, but no single amino acid can completely represent the entire amino acid pool.

Testosterone esters do not replicate either the diurnal or the pulsatile rhythm that characterizes endogenous testosterone secretion (6, 21). The significance of the pulsatile and diurnal hormone secretory rhythms in the regulation of protein and intermediary metabolism is not known.

It has been argued that testosterone-treated men might perform better on effort-dependent measures of muscle strength, such as the one repetition maximum because of the behavioral effects of testosterone on aggression (2–3). Several aspects of aggressive behavior in male animals, particularly territoriality and competition at the time of mate selection, are androgen dependent (29–32). However, the effects of testosterone on aggression in humans remain controversial (29–32). In a recent study (33), we were unable to discern any significant effect on angry behaviors in men receiving supraphysiological doses of testosterone. In this study, the gains in strength were associated with increases in muscle size, presumably reflecting muscle hypertrophy. Also, the exercise and activity levels were maintained constant throughout the treatment period. However, it is possible that some of the increase in strength might reflect androgen effects on motivation or aggression.

We did not measure the extracellular water; it is possible that some of the weight gain might have been due to water retention induced by testosterone. However, proportionate increases in estimates of fat-free mass by deuterium water and underwater weighing, and the lack of a significant change in the ratio of total body water (calculated by the deuterated water method) and fat-free mass (estimated from underwater weighing) suggest that the weight gain during treatment reflects significant changes in the body cell mass rather than extracellular water retention.

Similar data on the effects of testosterone replacement on weight gain and lean body mass were reported in a recent abstract (34). However, hypogonadal men reported in that abstract were studied over a 28-month period; exercise stimulus and dietary intake were not controlled. Body composition in that study was assessed by bioelectrical impedance, which is not as accurate a method as underwater weighing.

The greater gains in fat-free mass during pubertal development by boys than by girls are largely attributed to the higher testosterone levels in boys. Gregory *et al.* (35) reported similar anabolic effects of oral testosterone undecanoate in adolescent boys.

Previous data (22, 36–41) demonstrated that supraphysiological doses of testosterone increase muscle size and

strength in healthy men. Taken together with the observations reported in this manuscript, we conclude that both replacement and supraphysiological doses of testosterone augment fat-free mass and strength. Increasing serum testosterone concentrations from the hypogonadal to the midnormal range leads to an 8–10% increase in fat-free mass; when serum testosterone levels are increased from the midnormal to the supraphysiological range, further gains in fat-free mass and muscle size can be realized. It remains unclear whether the testosterone dose-response curve is linear with respect to its effects on fat-free mass, as proposed by Forbes (42), or whether there are two dose response-curves, one in the hypogonadal range with maximal response corresponding to the lower end of the normal male range, and a second dose-response curve in the supraphysiological range, representing a second mechanism of action, such as through an antiglucocorticoid effect (2, 3).

As the spectrum of hypogonadal states has expanded, there has been growing interest in exploring the anabolic applications of testosterone in clinical disorders characterized by loss of muscle mass and associated with a high prevalence of low testosterone levels. Examples of such wasting states include human immunodeficiency virus (HIV) infection (13–15), cancer cachexia, chronic obstructive lung disease (18), aging (16, 17, 43, 44), and chronic infections. Twenty to 70% of HIV-infected men have serum testosterone levels in the hypogonadal range depending on the stage of the disease (13–15). There is an inverse correlation between serum testosterone concentrations and weight loss in HIV-infected men, leading to speculation that low testosterone levels contribute to the loss of lean body mass, muscle wasting, and frailty. Our results indicate that testosterone replacement of hypogonadal men, who are not HIV infected, can increase fat-free mass and muscle size. The hypothesis that replacement doses of testosterone can augment lean body mass and promote weight gain in HIV-infected men or in sarcopenic states with low testosterone levels remains to be tested.

We studied only a few androgen-dependent outcomes; for example, bone mineral metabolism was not examined in this study. A single standardized replacement dose that restored serum testosterone levels into the midnormal range was used. Although this dose augments fat-free mass and muscle size, we do not know whether this represents an optimum replacement regimen. The dose dependency of testosterone effects on various metabolic and behavioral processes is not known. Experimental data in animals and clinical experience suggest that sexual function can be maintained in men by relatively low levels of testosterone. However, it is not known whether these low levels of testosterone can maintain protein or bone metabolism or whether the high androgen levels required to maintain bone density might adversely affect the lipid profile and insulin sensitivity. Detailed dose-response studies are needed to optimize testosterone replacement therapy.

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## Erratum

The article "Androgen or Estrogen Effects on Human Prostate," by B. Jin, L. Turner, W. A. W. Walters, and D. J. Handelsman (*Journal of Clinical Endocrinology and Metabolism*, 81:4290–4295, 1996) was inadvertently given the wrong title.

The correct title for this article is:

**The Effects of Chronic High Dose Androgen or Estrogen Treatment on the Human Prostate"**