Testosterone administration to older men improves muscle function: molecular and physiological mechanisms

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Ferrando, Arny A., Melinda Sheffield-Moore, Catherine W. Yeckel, Charles Gilkison, Jie Jiang, Alison Achacosa, Steven A. Lieberman, Kevin Tipton, Robert R. Wolfe, and Randall J. Urban. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab 282: E601–E607, 2002.—We investigated the effects of 6 mo of near-physiological testosterone administration to older men on skeletal muscle function and muscle protein metabolism. Twelve older men (≥60 yr) with serum total testosterone concentrations <17 nmol/l (480 ng/dl) were randomly assigned in double-blind manner to receive either placebo (n = 5) or testosterone enanthate (TE; n = 7) injections. Weekly intramuscular injections were given for the 1st mo to establish increased blood testosterone concentrations at 1 mo and then changed to biweekly injections until the 6-mo time point. TE doses were adjusted to maintain nadir serum testosterone concentrations between 17 and 28 nmol/l. Lean body mass (LBM), muscle volume, prostate size, and urinary flow were measured at baseline and at 6 mo. Protein expression of androgen receptor (AR) and insulin-like growth factor I, along with muscle strength and muscle protein metabolism, were measured at baseline and at 1 and 6 mo of treatment. Hematological parameters were followed monthly throughout the study. Older men receiving testosterone increased total and leg LBM, muscle volume, and leg and arm muscle strength after 6 mo. LBM accretion resulted from an increase in muscle protein net balance, due to a decrease in muscle protein breakdown. TE treatment increased expression of AR protein at 1 mo, but expression returned to pre-TE treatment levels by 6 mo. IGF-I protein expression increased at 1 mo and remained increased throughout TE administration. We conclude that physiological and near-physiological increases of testosterone in older men will increase muscle protein anabolism and muscle strength.

Most aging men show a reduction in circulating serum testosterone concentrations (16, 22). This reduction in serum testosterone concentration is a core physiological event in what is termed andropause. Andropause can be clinically characterized by decreased potency and libido, increased fatigability, and decreased muscle strength (13, 24). A significant decrease in serum total testosterone occurs as early as ages 50–59 (16). This decrease in testosterone production is associated with the loss of lean body mass (LBM) and muscle strength. When men are made hypogonadal with a gonadotropin-releasing hormone analog (14), LBM and muscle strength are lost. Once weakened, older individuals are prone to falls that prevent an independent living status and diminish the quality of life. As the population of older Americans grows, the need to develop therapies to counteract the aging-induced loss in skeletal muscle mass and function becomes critically important.

Previously we demonstrated that testosterone administration primes skeletal muscle for growth by increasing net protein synthesis in the fasted state (10, 18). The logical extrapolation of a continued increase in net protein synthesis is an increase in lean body mass and strength. Bhasin et al. (2) demonstrated that supraphysiological doses of testosterone can induce increases in muscle size and strength in younger men without concomitant exercise. This relationship holds true in relatively hypogonadal populations, where the increase of circulating testosterone increases muscle protein synthesis (23), LBM (3, 20), and muscle strength (3, 23). In an earlier study (23), we demonstrated that 1 mo of testosterone administration increased muscle anabolism and strength in six older men. We also demonstrated that the increase in muscle anabolism was associated with an increase in the expression of intramuscular mRNA for insulin-like growth factor I (IGF-I) (23). Because IGF-I has also been demonstrated to be a potent anabolic hormone (11), the relationship between testosterone administration and IGF-I levels was investigated in the present study.

Previous studies of testosterone administration in older men used a standard clinical dosing paradigm (3, 15, 21). Although this dosing is clinically feasible and...
METHODS

Subjects. Twelve healthy, older male subjects were randomly assigned in a double-blind fashion to receive either testosterone enanthate (TE) or placebo for 6 mo. Seven subjects [68 ± 3 (SE) yr; 91 ± 5 kg] were randomized to receive TE, whereas five subjects [67 ± 3 yr; 99 ± 7 kg] received a placebo consisting of sesame seed oil. The study was approved by the Institutional Review Board at The University of Texas Medical Branch (UTMB). Informed consent was obtained after the study was explained to each individual. Subjects were selected on the basis of the following inclusion criteria: 1) prostate-specific antigen (PSA) ≤4.0 μg/l (6), 2) serum total testosterone ≤17 nmol/l (480 ng/dl), 3) serum low-density lipoprotein (LDL) ≤200 mg/dl (7), 4) completion of a Bruce treadmill exercise test without significant findings of cardiovascular disease, and 5) no medical illnesses causing disability. The serum testosterone cutoff was chosen because it has been shown that 85% of healthy older men (age 60–98 yr) have serum testosterone concentrations <17 nmol/l but still in the low-normal range of >10 nmol/l (1). Exclusion criteria included a history of prostate cancer and severe coronary artery disease (due to the possible hypertrophic and atherogenic effects of testosterone), knee replacement (for reasons of strength determination), or use of a blood anticoagulant, e.g., Coumadin (for fear of excessive bleeding during biopsy and catheterization procedures). Because we wanted to determine the outcomes of testosterone without the confounding effects of exercise (2), we excluded subjects engaged in regular training (defined as 30 min of aerobic or resistance training activity ≥2 days/wk). These exclusion/inclusion criteria were similar to those of previously published studies by our group and others (21, 23).

Experimental protocol. The studies were performed at the General Clinical Research Center (GCRC) at UTMB. Subjects were studied at baseline, after 1 mo, and after 6 mo of treatment. Each GCRC admission consisted of ~3 days. On day 1, subjects were admitted in the afternoon and underwent Cybex II isokinetic dynamometer testing for muscular endurance. Subjects followed a standardized protocol that included 15 min of pretest stretching. Muscular endurance was defined as the total work performed for 20 repetitions at 240°/s. On the morning of day 2, subjects were weighed in hospital gowns, resting (recumbent) blood pressure was taken, and blood was drawn from the fastest subjects for hematological measures. Subjects were then taken for magnetic resonance imaging (MRI) of the lower body. Leg muscle volume was determined by analysis of images collected by MRI (GE Signa 1.5-Tesla whole body imager; General Electric, Milwaukee, WI) as previously described (9). Image data files generated at the MRI facility were analyzed for appendicular total and muscle volumes using NIH Image software (NIH Image public domain analysis package). Muscle volume (cm³) was computed as the addition of individual slice areas multiplied by the slice thickness (10 mm). After breakfast, subjects were taken to the UTMB Field House for one-repetition maximum (1RM) determinations for bicep curl, tricep extension, leg extension, and leg curl on specific equipment (Cybex) designed for each movement. Subjects were initially familiarized on the equipment after screening and selection. For 1RM testing, subjects first warmed up on a stationary bike set at 30 W for 10 min. The determination of 1RM was accomplished by increasing the load on each machine until successful completion of the movement was no longer possible. The heaviest load lifted was considered the 1RM. At approximately noon, subjects received dual-energy X-ray absorptiometry (DEXA) to determine LBM and fat masses. Body mass and bone components were determined with regional analysis software as previously described (8). Finally, subjects were referred to the Department of Urology at UTMB for prostate ultrasound and urine flow measurements. Prostate volume was measured by transrectal ultrasound, and urinary flow rate measures were made using a Life-Tech uroflowmeter (Life Tech, Houston, TX).

On day 3, subjects received a stable isotope infusion to determine skeletal muscle protein metabolism. Muscle protein net balance and fractional synthesis rate (FSR) of skeletal muscle were determined by infusion of the stable isotope [²H₅]ketoisocaproic acid, arteriovenous sampling, and muscle biopsies as previously described (10). Briefly, skeletal muscle FSR was calculated from the determination of the rate of tracer incorporation into the protein and the enrichment of the intracellular pool as the precursor

$$FSR = \frac{(E_{p2} - E_{p1})/E_M \cdot t}{60 \cdot 100}$$

where E₀ and Eₜ are the enrichments of the protein-bound [²H₅]leucine (from transamination of [²H₅]ketoisocaproic acid) from the biopsies at 2 and 5 h of isotope infusion; Eₚ represents the average intracellular [²H₅]leucine enrichment over the time of incorporation; and t is the time in minutes. The factors 60 and 100 are required to express FSR in percent per hour. Each biopsy was divided to be used for both Western blot and isotopic enrichment analyses.

After the isotope infusion study on day 3, subjects were given injections and discharged. Subjects returned every week for fasted blood draw and injections for the first 4 wk and then every 2 wk for the remainder of the study. Serum
total testosterone concentrations were measured on each occasion and adjusted to between 17 and 28 nmol/l (500 and 800 ng/dl; based on the concentration for the visit before each injection) to approximate concentrations found in young men. The aforementioned measurements were made at baseline and at 1 and 6 mo. However, at 1 mo, the MRI, DEXA, and urology measures were omitted. We designed the TE dosing paradigm for weekly injections for the 1st mo so that we could adjust TE doses and establish increased testosterone concentrations by the first measurements that were done at 1 mo. This paradigm was reproduced from our initial study (23). A biweekly injection paradigm would not have allowed TE dose adjustment before the assessments at 1 mo.

Clinical measures. Measurement of clinical parameters (see Table 2) such as testosterone (DPC, Los Angeles, CA), estradiol (DPC), blood lipids (Vitros 250 Chemistry System, Johnson & Johnson, Arlington, TX), PSA, liver function tests (Vitros 250), and hematocrit (Couter Onyx, Beckman Coulter, Brea, CA) were done on a monthly basis by a UTMB clinical laboratory. Subjects were also monitored monthly for breast tenderness and the presence of gynecomastia by history and physical examination. Serum testosterone concentrations were determined by the clinical laboratory, so that adjustments in TE doses could be made on the basis of the previous serum testosterone concentration.

Western blot analysis. Protein was isolated from muscle biopsy samples by slicing frozen muscle in very small pieces with a clean razor blade and thawing the tissue in lysis buffer (150 mM NaCl, 10 mM Tris, 1% Triton X-100, 1% Na deoxycholate, 0.1% SDS, 5 mM EDTA) containing protease inhibitors (1 mM phenylmethylsulfonyl fluoride, 1 mM benzamidine, 10 μg/ml aprotinin, 50 μg/ml leupeptin, 1 μg/ml pepstatin A) at a concentration of 3 ml of ice cold lysis buffer per gram of tissue. The tissue was homogenized with a Dounce homogenizer (4°C) and centrifuged at 15,000 g for 20 min, and the supernatant was removed and centrifuged again to result in total cell lysate. The androgen receptor (AR) antibody (Santa Cruz Biotechnology, Santa Cruz, CA) was incubated with 80 mg of cell lysate run on standard SDS-PAGE gel with a working solution concentration range of 1:15–20. The IGF-I antibody (Sigma) was used with a working solution concentration range of 1:100. This anti-actin antibody is a broad-based antibody that reacts with a working solution concentration range of 1:15–20. The IGF-I antibody (Santa Cruz Biotechnology) was incubated with 40 mg of cell lysate run on standard SDS-PAGE gel with a working solution concentration of 1:100. The actin “housekeeping” antibody (Sigma) was used with a working solution concentration range of 1:100–200. This anti-actin antibody is a broad-based antibody that recognizes an epitope located on the NH2-terminal region of actin and demonstrates a broad reactivity among multiple actin isoforms in various species. The housekeeping antibody was used to correct the results for protein loading of the gel. Western analysis allows the direct measurement of protein expression in the muscle biopsy samples.

Statistical analysis. Comparison of 1- and 6-mo measures to baseline values was accomplished by 2-way repeated-measures ANOVA with Dunnett’s multiple comparison test. Comparison of clinical outcome values over the 6-mo study period was accomplished by ANOVA with Dunnett’s multiple comparison test. Where 1-mo measures were omitted, a paired t-test was used to statistically compare 6-mo and baseline values. Statistical significance was P ≤ 0.05. Data are presented as means ± SE.

RESULTS

Clinical outcomes. Figure 1 shows the mean testosterone profiles of each group at 2-wk intervals over the 6-mo study period. Table 1 shows the individual testosterone concentrations for each of the seven subjects who received TE and the dose adjustment made for each individual. None were clinically hypogonadal at the beginning of this study. TE injections were adjusted by an independent clinician to maintain levels within the normal range (17–28 nmol/l). As can be seen in Table 1, the serum testosterone concentrations and the doses of TE administered were variable from individual to individual. Following such a paradigm, especially with the use of intramuscular injections, the older men were exposed to serum testosterone concentrations at various times during the 6-mo study that were above the physiological range. Therefore, this study assesses a mix between physiological and near-physiological administration. However, serum testosterone concentrations were greater in the treatment group at all time points after baseline (P < 0.05). Serum testosterone did not change in the placebo group. Table 2 delineates subject characteristics and laboratory values over the 6-mo study period. Treatment subjects remained normotensive, and liver function tests, blood lipid profiles, and PSA were unchanged. Estradiol increased upon treatment and, for the most part, remained elevated throughout the 6-mo period without causing breast tenderness or gynecomastia by report or examination. Hematocrit was elevated after 4 mo of TE and remained elevated until the end of the study.

Prostate volume was not significantly increased with TE administration. Prostate volume in the treatment group was 44 ± 15 ml at baseline, whereas the placebo group was 41 ± 8 ml. Six-month values were 47 ± 13 and 35 ± 7 ml, respectively, for the treatment and placebo groups. Urinary flow rate also did not change over time or as a result of treatment. Baseline flow rate was 8.3 ± 1.5 and 8.9 ± 1.3 ml/s, whereas 6-mo values were 7.5 ± 1.4 and 8.7 ± 1.6 ml/s for the treatment and placebo groups, respectively.

Western blot analysis. TE administration significantly increased skeletal muscle AR protein expression at 1 mo (P < 0.05), but AR returned to baseline levels at 6 mo. Figure 2 shows a representative autoradio-
gram of a Western blot for skeletal muscle AR from a subject receiving testosterone and a graph of the densitometry data from the treatment group. There was no correlation between the serum testosterone concentration at 1 mo and the change of AR expression from baseline to 1 mo for individuals. IGF-I protein expression in skeletal muscle increased at 1 mo and remained elevated at 6 mo (P < 0.05; Fig. 3). AR and IGF-I protein expression did not change in the placebo group (data not shown).

Physiological outcomes. The net balance of muscle protein was less negative in the fasted state in the treatment group than those in the placebo group. The more favorable treatment subjects were less catabolic when fasting than those in the placebo group. The more favorable net balance was due to a decrease in fasting protein breakdown, as fractional synthetic rate of muscle protein remained constant throughout (0.071 ± 0.02 to 0.084 ± 0.013 to 0.062 ± 0.016%/h at baseline and 1 and 6 mo, respectively).

The resultant improvement in net protein balance led to an increase in LBM. Table 3 outlines the changes in LBM and muscle strength over the 6-mo study period. The treatment group demonstrated increases in total and leg LBM, whereas the percentage of total body fat diminished. Leg muscle volume by MRI was also increased significantly after 6 mo of TE administration.

Table 2. Subject characteristics and laboratory values during 6 mo of testosterone or placebo treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
<th>4 mo</th>
<th>5 mo</th>
<th>6 mo</th>
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<tr>
<td>Weight, kg</td>
<td>91 ± 5</td>
<td>92 ± 5</td>
<td>92 ± 5</td>
<td>92 ± 5</td>
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<td>Systolic BP, mmHg</td>
<td>141 ± 7</td>
<td>144 ± 4</td>
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<td>150 ± 4</td>
<td>156 ± 5</td>
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<td>149 ± 3</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>78 ± 3</td>
<td>79 ± 3</td>
<td>82 ± 4</td>
<td>85 ± 4</td>
<td>87 ± 3</td>
<td>84 ± 3</td>
<td>83 ± 3</td>
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<tr>
<td>ALT U/l (9–51)</td>
<td>32 ± 3</td>
<td>30 ± 2</td>
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<td>29 ± 3</td>
<td>32 ± 3</td>
<td>28 ± 3</td>
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<td>AST U/l (13–40)</td>
<td>23 ± 2</td>
<td>23 ± 1</td>
<td>24 ± 3</td>
<td>22 ± 2</td>
<td>24 ± 2</td>
<td>25 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Chol. (mmol/l) (3.1–5.2)</td>
<td>4.81 ± 0.62</td>
<td>4.81 ± 0.28</td>
<td>4.71 ± 0.21</td>
<td>4.65 ± 0.28</td>
<td>4.73 ± 0.16</td>
<td>4.84 ± 0.16</td>
<td>4.50 ± 0.23</td>
</tr>
<tr>
<td>HDL (mmol/l) (0.78–1.8)</td>
<td>1.14 ± 0.13</td>
<td>1.01 ± 0.10</td>
<td>1.11 ± 0.13</td>
<td>1.06 ± 0.10</td>
<td>1.05 ± 0.13</td>
<td>1.09 ± 0.13</td>
<td>0.96 ± 0.13</td>
</tr>
<tr>
<td>LDL (mmol/l) (2.1–5.69)</td>
<td>2.97 ± 0.34</td>
<td>2.79 ± 0.28</td>
<td>2.79 ± 0.18</td>
<td>2.71 ± 0.26</td>
<td>2.77 ± 0.6</td>
<td>2.92 ± 0.18</td>
<td>2.69 ± 0.23</td>
</tr>
<tr>
<td>PSA, µg/l (&lt;4)</td>
<td>1.4 ± 0.4</td>
<td>1.9 ± 0.4</td>
<td>2.1 ± 0.7</td>
<td>2.0 ± 0.7</td>
<td>2.1 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.3 ± 0.9</td>
</tr>
<tr>
<td>E2, pmol/l (48–173)</td>
<td>103 ± 4</td>
<td>114 ± 4</td>
<td>114 ± 1</td>
<td>114 ± 1</td>
<td>114 ± 1</td>
<td>114 ± 1</td>
<td>114 ± 1</td>
</tr>
<tr>
<td>Hct. % (37–50)</td>
<td>40 ± 0.8</td>
<td>40 ± 0.7</td>
<td>43 ± 0.8</td>
<td>44 ± 0.9</td>
<td>45 ± 0.1</td>
<td>46 ± 0.8</td>
<td>44 ± 1</td>
</tr>
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</table>

Values are means ± SE. For each test parameter, the first line represents values for the testosterone group (n = 7), the second line represents values for the placebo group (n = 12). BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Chol., total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate-specific antigen; E2, estradiol; Hct, hematocrit. Normal ranges are given in parentheses by the test. *Statistical significance from the placebo group at each time point as determined by ANOVA with Dunnett’s multiple comparison test.

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Fig. 2. Androgen receptor (AR) protein expression in skeletal muscle during 6 mo of testosterone administration in older men. Top: representative Western blot from one of the 7 subjects assessed for protein expression of AR by use of standard Western analysis. Actin was used as an internal control for protein loading. Bottom: means ± SE from the 7 subjects that received testosterone. Five subjects who received placebo demonstrated no change throughout the study in AR expression (data not shown). Data are expressed as arbitrary units calculated as the ratio of the band densities of AR over the band densities of actin. *Statistical significance was determined by ANOVA, \( P < 0.05 \).

testosterone concentrations were consistently maintained above baseline values. The older men in this study demonstrated an increase in LBM that was comparable to that achieved with a standard replacement regimen that resulted in higher testosterone concentrations (5). We also found that, similar to younger men (2), testosterone will increase muscle anabolism and strength in older men. The strength increases of the older men in this study were greater than those demonstrated with standard replacement paradigms (15, 21) or with testosterone patch administration over

**DISCUSSION**

This study demonstrates that testosterone increases within or near the physiological range can produce increases in muscle anabolism, LBM, and muscle strength similar to supraphysiological administration. We monitored serum testosterone concentrations and adjusted the dose of TE to maintain testosterone concentrations in older men in ranges comparable to those of younger men. During the 6 mo of TE administration, some subjects experienced testosterone concentrations that exceeded the physiological; however,
36 mo (20). Our data suggest that a standard paradigm of testosterone administration that does not include individual dose adjustment may not always achieve desired outcomes if the subjects have not received adequate testosterone to stimulate metabolic changes in muscle. Because we studied only a small number of subjects, we cannot draw any conclusions regarding the risk-to-benefit ratio of testosterone administration in older men. However, we found no significant side effects in our small group other than an increase in hematocrit. Our data indicate that testosterone can improve muscle strength in older men when careful dosing ensures sustained blood testosterone increases. Our first study demonstrated that short-term administration with standard replacement dosages resulted in LBM and strength increases (23). The present study indicates that these LBM and strength increases can be maintained over 6 mo with careful dose adjustments that ensure primarily physiological testosterone levels. This study also demonstrates that the muscle’s response to testosterone changes over the 6-mo period of administration, indicating that alternative paradigms of testosterone administration (i.e., cyclic administration) can be of physiological benefit.

Testosterone administration resulted in some noteworthy effects on AR and IGF-I expression in skeletal muscle. AR protein expression was increased after 1 mo of TE but had returned to pretreatment levels by 6 mo. Physiologically, it is logical that androgen would enhance its own receptor expression as it stimulates muscle metabolism. We previously noted an upregulation of AR expression with oxandrolone administration (18) in young males, which also occurred concomitantly with an increase in muscle protein synthesis. The return of AR expression to pretreatment values after 6 mo of continuous androgen administration indicates a steady-state adaptation to the treatment paradigm. There is also the possibility that the AR response is nothing more than a response to the dosing paradigm. At 1 mo, older subjects were receiving TE weekly rather than every 2 wk, and their mean serum testosterone concentrations were more in the supraphysiological range than they were at 6 mo. However, this relationship is weakened by the fact that individual testosterone concentrations at 1 mo did not correlate with the change in AR expression from baseline to 1 mo. This pattern of AR expression raises the possibility that cycling of testosterone administration could produce effects on skeletal muscle analogous to continuous administration. Such a paradigm would be beneficial by administering significantly less testosterone for similar anabolic outcomes, thus minimizing the possibility of side effects.

IGF-I accompanies increases in muscle mass and strength (17). In frail elderly, progressive resistance training that increases muscle mass and strength also increases intramuscular IGF-I concentrations (19). Clinically, we previously demonstrated that older men given testosterone for 1 mo increased IGF-I transcripts in muscle while decreasing the inhibitory IGF-binding protein (23). The present study agrees with our previous work in that IGF-I protein expression increased at 1 mo and further demonstrates that this increase was maintained throughout the 6 mo of testosterone administration. This confirms that the increase in IGF-I mRNA noted in our earlier study (23) translates into an actual increase of IGF-I protein. A corollary to these studies found that young men who were made hypogonadal for 10 wk by Lupron showed a decrease in muscle strength and a decrease in intramuscular IGF-I mRNA concentration (14). Taken together, these data indicate a mechanistic importance of IGF-I on muscle anabolism.

Although the intracellular mechanism stimulating muscle protein anabolism requires further clarification, it is clear that testosterone improves net protein balance of skeletal muscle. This effect is pronounced in the fasted state as net protein balance becomes less negative. We have previously demonstrated (10, 18) that one of the primary effects of testosterone (during fasting) is the efficient reutilization of intracellular amino acids (derived from protein breakdown) for protein synthesis. However, the present study demonstrates that, even if breakdown is decreased, ample amino acid precursors are present to support the initial rate of protein synthesis. Thus testosterone administration may ameliorate the loss of skeletal muscle nitrogen during fasting in this older population by preventing the loss of intracellular amino acids. Not only is the appearance of amino acids from protein breakdown reduced, but those that are derived from protein breakdown are efficiently utilized to maintain protein synthesis, as we have previously demonstrated (10, 18). This retention of nitrogen during fasting, when combined with the anabolic stimulus of a meal alone (4, 25), may lead to muscle (LBM) accretion over time and explain the anabolic effects of chronic testosterone administration.

In summary, the present study demonstrates that careful and near-physiological testosterone administration in older men will increase LBM and muscle strength similarly to younger men. However, further consideration should be given to the specific androgen and length and type of administration regimen to be used in older men and to large-scale studies initiated to determine the risk-to-benefit ratio of testosterone administration in older men.

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