Effects of Testosterone and Progressive Resistance Exercise in Healthy, Highly Functioning Older Men With Low-Normal Testosterone Levels

Article in The Journal of Clinical Endocrinology and Metabolism · March 2013
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Effects of Testosterone and Progressive Resistance Exercise in Healthy, Highly Functioning Older Men With Low-Normal Testosterone Levels


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Context: Aging in men is associated with reduced testosterone (T) levels and physiological changes leading to frailty, but the benefits of T supplementation are inconclusive.

Objective: We studied the effects of T supplementation with and without progressive resistance training (PRT) on functional performance, strength, and body composition.

Design, Setting, and Participants: We recruited 167 generally healthy community-dwelling older men (66 ± 5 years) with low-normal baseline total T levels (200–350 ng/dL).

Intervention: Subjects were randomized to placebo or transdermal T gel [2 doses targeting either a lower (400–550 ng/dL) or higher (600–1000 ng/dL) T range] and to either PRT or no exercise for 12 months.

Main Outcome Measure: The primary outcome was functional performance, whereas secondary outcomes were strength and body composition.

Results: A total of 143 men completed the study. At 12 months, total T was 528 ± 287 ng/dL in subjects receiving any T and 287 ± 65 ng/dL in the placebo group. In the PRT group, function and strength were not different between T- and placebo-treated subjects, despite greater improvements in fat mass (P = .04) and fat-free mass (P = .01) with T. In the non-PRT group, T did not improve function but improved fat mass (P = .005), fat-free mass (P = .03), and upper body strength (P = .03) compared with placebo. There were fewer cardiovascular events in the T-treated groups compared with placebo.

Conclusions: T supplementation was well tolerated and improved body composition but had no effect on functional performance. T supplementation improved upper body strength only in non-exercisers compared with placebo. (*J Clin Endocrinol Metab* 98: 1891–1900, 2013)

Abbreviations: AUA, American Urological Association; CS-PFP, continuous-scale physical functional performance test; FFM, fat-free mass; FM, fat mass; HCT, hematocrit; PRT, progressive resistance exercise training; PSA, prostate-specific antigen; 1-RM, 1-repetition maximum; T, testosterone.
Aging in men is associated with unfavorable changes in body composition, strength, and physical function (1–3), which may increase the risk of frailty and disability, loss of independence, reduced quality of life, and increased mortality (4). Similar alterations in young hypogonadal men are largely reversed with testosterone (T) replacement (5), suggesting that low T levels may be responsible, in part, for the physiological alterations that occur with advancing age. Decreased T production with aging is partially offset by reduced clearance, frequently resulting in low-normal T levels. Although the physiological importance and clinical approach to treatment of T levels in this low-normal range is unclear, there is considerable interest in T replacement or supplementation in aging men to preserve or improve function and prevent frailty.

A consistent finding of T treatment in older men is an increase in lean mass and a decline in fat mass (FM) (6–14). To date, most studies have shown little to no effect of T supplementation on measures of strength or physical function (6, 8–14). An important limitation of previous studies is the lack of a concurrent exercise intervention. Exercise improves body composition, strength, and physical function, and this response is maintained even into very old age (15, 16). T levels may be an important determinant of the anabolic response of muscle to exercise, creating a favorable hormonal environment that may augment exercise-induced responses in strength, power, and physical function. Although a positive association has been observed between exercise-induced increases in strength and serum T in older men (17), little is known about the potential interaction between T supplementation and strength training.

We sought to determine the independent and combined effects of 12 months of T supplementation and progressive resistance exercise training (PRT) on physical function, strength, and body composition in older men with low-normal baseline T levels (200–350 ng/dL). We also sought to determine differences in the frequency of adverse effects between lower-range (400–550 ng/dL) and higher-range (600–1000 ng/dL) T supplementation.

Subjects and Methods

Subjects

Subjects were untrained community dwelling men ≥60 years of age with an average of 2 separate baseline fasting morning total T samples between 200 and 350 ng/dL; stable medication regimen for ≥3 months; body mass index <35 kg/m²; stable weight for the past 6 months; and a Mini Mental State Examination (18) score ≥24. All volunteers were screened using a graded maximal exercise test to eliminate subjects with evidence of active coronary artery disease. Additional exclusion criteria included exercise-limiting conditions, an abnormal digital rectal examination or transrectal ultrasound, a prostate-specific antigen (PSA) above the age-adjusted normal level, an American Urological Association (AUA) symptom score (19) >20, a history of prostate or breast cancer, uncontrolled hypertension, diabetes, untreated dyslipidemia, hematocrit (HCT) >52%, use of androgenic steroids or other drugs that could affect T levels, and other clinically important illnesses or conditions that could affect the outcome measures.

Study design

The study was approved by the Colorado Multiple Institutional Review Board, and all subjects provided written informed consent. The study was designed and conducted by the study team, with industry support limited to provision of 1% T (Androgel; Abbott Laboratories, Chicago, Illinois) and matching placebo gel. The study was a 12-month, randomized, placebo-controlled trial of T supplementation crossed with PRT (3 times/wk vs none). Randomization was performed using a documented permuted block randomization with random block sizes. Subjects and investigators (except the study pharmacist and statistician) were blinded to drug treatment. Outcome measures were assessed at baseline and 26 and 52 weeks by research personnel blinded to treatment group.

The T gel and matching placebo were provided in 2.5- or 5.0-g packets. All subjects were initiated on two 2.5-g packets daily (2 placebo packets in the placebo group, 1 T gel and 1 placebo packet in the lower-range T group, and 2 T gel packets in the higher-range T group). Serum T levels were monitored by the pharmacist approximately every 2 weeks for the first 12 weeks with dose titrations made in 2.5-g increments to achieve a level of 400 to 550 ng/dL in the lower-range group and 600 to 1000 ng/dL in the higher-range group; sham adjustments were made in the placebo group. The maximum dose of T gel used was 10 g/d.

Safety monitoring included assessment of PSA, AUA score, HCT, alanine amino transferase and aspartate amino transferase at baseline and 4, 12, 26, and 52 weeks. Subjects with a confirmed increase in PSA ≥0.75 ng/mL over baseline or an AUA score ≥20 stopped the study drug until medically cleared by the study urologist and their primary healthcare provider if appropriate. Subjects with a HCT ≥54% underwent phlebotomy to lower HCT to ≤52%. If the HCT persisted at ≥54%, or was >55% at any time, the study drug dose was reduced. The Epworth Sleepiness Score (20) and arterial oxygenation by pulse oximetry were measured at baseline and 12, 26, 36, and 52 weeks to monitor for hypoxemia.

The PRT intervention included 4 upper-body (bench press, incline press, overhead pull-down, and seated row), and 3 lower-body (knee extension, knee flexion, and seated leg press) exercises. The maximal weight a participant could lift once [1-repetition maximum (1-RM)] for each exercise was assessed at baseline and 2 weeks and then monthly in the PRT groups to define the appropriate training progression. Resistance was progressively increased from 50% to 80% of the last 1-RM whenever 3 full sets could be completed. Subjects were asked to attend supervised exercise sessions 3 d/wk. Overall physical activity level was measured in all participants using the Yale Physical Activity Survey for Older Adults (21).

Outcome measures

The primary outcome was the change from baseline in the total score on the continuous-scale physical functional perfor-
Endurance, respectively. CS-PFP were evaluated as individual measures of power and from 0 to 100. The stair climbing and 6-minute walk tasks of the change (22, 23). Total and individual domain scores are scaled floor or ceiling effects and is valid, reliable, and sensitive to measure performance in higher-functioning adults with minimal coordination, and endurance (22). The CS-PFP was developed to requiring upper and lower body strength and flexibility, balance, Isokinetic strength at the knee and elbow (flexion and extension at 120°) was measure by dyna-sorptiometry (Hologic Discovery, Bedford, Massachusetts). Joints were tested in a fixed order. Movement test (CS-PFP) between the placebo plus PRT group compared with any-T (lower- and higher-range groups combined) plus PRT groups. The CS-PFP comprises 15 everyday tasks requiring upper and lower body strength and flexibility, balance, coordination, and endurance (22). The CS-PFP was developed to measure performance in higher-functioning adults with minimal floor or ceiling effects and is valid, reliable, and sensitive to change (22, 23). Total and individual domain scores are scaled from 0 to 100. The stair climbing and 6-minute walk tasks of the CS-PFP were evaluated as individual measures of power and endurance, respectively.

Muscle strength was assessed by 1-RM measurements for each of the 7 exercises. Average (bilateral) grip strength was assessed with a hand dynamometer. Leg extensor power was evaluated using a Nottingham leg extensor power rig (watts). Isokinetic strength at the knee and elbow (flexion and extension at 120°), ankle (dorsiflexion and extension at 60°), and shoulder (internal and external rotation at 120°) was measured by dynamometry (newton-meters). Joints were tested in a fixed order. Body composition was measured using dual-energy x-ray absorptiometry (Hologic Discovery, Bedford, Massachusetts).

Total serum T and SHBG were measured by ELISA using a Nottingham leg extensor power rig (watts). Muscle strength was assessed by 1-RM measurements for each of the 7 exercises. Average (bilateral) grip strength was assessed with a hand dynamometer. Leg extensor power was evaluated using a Nottingham leg extensor power rig (watts). Isokinetic strength at the knee and elbow (flexion and extension at 120°), ankle (dorsiflexion and extension at 60°), and shoulder (internal and external rotation at 120°) was measured by dynamometry (newton-meters). Joints were tested in a fixed order. Body composition was measured using dual-energy x-ray absorptiometry (Hologic Discovery, Bedford, Massachusetts).

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Results

Subjects

A total of 167 volunteers were randomized. Twenty-three subjects dropped out of the study and refused follow-up, 1 subject died, and 143 (86%) completed the study and were included in the analysis (Figure 1). There were no differences in baseline characteristics between subjects in the any-T and placebo groups (Table 1) or between the PRT and non-PRT groups (data not shown).

Treatment adherence

Adherence to the drug intervention was similar among groups. The mean possession ratio (days of gel dispensed/days in the study) was 88% ± 9% for placebo, 85% ± 15% for the lower-range T group, and 88% ± 12% for the higher-range T group. The average final T dose was 5.0 ±

Figure 1. The flow of subjects through the study. A total of 167 men were randomized, and 143 men completed follow-up testing and were included in the analysis.
Table 1. Baseline Characteristics of Participants by Drug Assignmenta

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 47)</th>
<th>T (any) (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.5 ± 5.2</td>
<td>66.5 ± 5.8</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>54 (96.4%)</td>
<td>103 (92.8%)</td>
</tr>
<tr>
<td>African-American</td>
<td>1 (1.8%)</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0.0%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.8%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>54 (96.4%)</td>
<td>110 (99.1%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (3.6%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Education, y</td>
<td>3 (5.4%)</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>8 –12</td>
<td>53 (94.6%)</td>
<td>106 (95.5%)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>128.2 ± 16.5</td>
<td>126.1 ± 14.8</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75.8 ± 8.5</td>
<td>75.8 ± 7.8</td>
</tr>
<tr>
<td>VO2 max, ml/kg/min</td>
<td>25.1 ± 4.9</td>
<td>25.3 ± 5.7</td>
</tr>
<tr>
<td>Yale Physical Activity Survey, kcal/wk</td>
<td>5607 ± 3031</td>
<td>5969 ± 3553</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUA, American Urologic Association; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate specific antigen; VO2, maximal oxygen uptake.

a Data are presented as mean ± SD or number (percent).

Physical function

Among non-PRT subjects, those randomized to placebo had greater improvement in lower body strength compared with any-T (Table 2 and Figure 2). There was no significant improvement in physical function with any-T in either PRT or non-PRT subjects and no improvement in physical function with PRT in either any-T–treated or placebo-treated subjects.

Muscle strength and power

Among subjects randomized to PRT, those receiving any-T averaged a 1.2-kg greater decrement in FM, a 1.7-kg greater increment in fat-free mass (FFM), and a 0.3-kg greater increment in arm FFM compared with placebo subjects (Table 3 and Figure 2). Among non-PRT subjects, those receiving any-T averaged a 1.7-kg greater decrease in FM, a 0.9-kg greater decrease in appendicular FFM, and a 0.3-kg greater increase in arm FFM compared with those receiving placebo.

Body composition

Among subjects randomized to PRT, those receiving any-T had greater improvement in lower body strength compared with placebo (non-PRT group: 9.4 ± 2.1 and 6.4 ± 3.2 sessions per month; P < .001; 78% and 53% of sessions) compared with placebo (any-T group: 8.9 ± 2.9 and 7.0 ± 2.7 sessions per month; P < .001; 74% and 58% of sessions). Maximal oxygen uptake and Yale Physical Activity Survey scores did not change in any group.

Adverse events

There were no differences in the frequency of prespecified adverse events between placebo- and any-T–treated groups except for HCT (Table 4). Compared with the lower-range group, subjects in the higher-range group were more likely to have an elevated HCT.

We observed no significant increases in PSA in any group. At 12 months, the mean PSA was 1.49 (range 0.21–4.70) ng/mL in the placebo groups, 1.56 (0.21–4.50) ng/mL in the lower-range T group, and 1.78 (0.50–4.60) ng/mL in the higher-range T group. Thirty subjects were referred for urological evaluation; 2 of these had a prostate biopsy. There were no cases of prostate cancer.
Table 2. Change From Baseline to 12 Months in Physical Function, Strength, and Power by Exercise Groupa

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 22 PRT and 25 No PRT)</th>
<th>Any-T (n = 49 PRT and 47 No PRT)</th>
<th>Δ Change (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRT</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Physical function (Range 0–100)</strong></td>
<td></td>
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<tr>
<td>CS-PFP total</td>
<td>69.1 ± 9.9</td>
<td>70.5 ± 14.6</td>
<td>-0.4 (−4.2, 3.8)</td>
<td>.93</td>
</tr>
<tr>
<td>Upper body strength</td>
<td>75.8 ± 10.8</td>
<td>78.6 ± 14.8</td>
<td>0.7 (−6.1, 4.6)</td>
<td>.79</td>
</tr>
<tr>
<td>Upper body flexibility</td>
<td>78.2 ± 12.2</td>
<td>75.4 ± 12.7</td>
<td>2.3 (−2.6, 7.1)</td>
<td>.36</td>
</tr>
<tr>
<td>Lower body strength</td>
<td>64.1 ± 11.8</td>
<td>67.3 ± 15.9</td>
<td>−0.5 (−5.5, 4.4)</td>
<td>.84</td>
</tr>
<tr>
<td>Balance</td>
<td>68.9 ± 10.8</td>
<td>69.7 ± 15.3</td>
<td>0.8 (−4.1, 4.5)</td>
<td>.93</td>
</tr>
<tr>
<td>Endurance</td>
<td>69.0 ± 10.5</td>
<td>70.0 ± 15.1</td>
<td>0.1 (−4.0, 4.3)</td>
<td>.95</td>
</tr>
<tr>
<td>Stair climb speed, s</td>
<td>4.8 ± 1.1</td>
<td>4.7 ± 1.7</td>
<td>0.2 (−0.8, 0.7)</td>
<td>.16</td>
</tr>
<tr>
<td>6-min walk, m</td>
<td>536.4 ± 65.0</td>
<td>560.1 ± 132.6</td>
<td>2.2 (−39.5, 46.0)</td>
<td>.88</td>
</tr>
<tr>
<td><strong>Strength (1-RM, kg)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Upper body</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bench press</td>
<td>58.4 ± 17.7</td>
<td>58.7 ± 15.9</td>
<td>−1.5 (−8.7, 5.6)</td>
<td>.67</td>
</tr>
<tr>
<td>Incline press</td>
<td>50.7 ± 15.4</td>
<td>50.6 ± 14.6</td>
<td>−1.9 (−8.5, 4.8)</td>
<td>.58</td>
</tr>
<tr>
<td>Overhead pulldown</td>
<td>80.5 ± 20.2</td>
<td>79.0 ± 16.6</td>
<td>−3.4 (−11.3, 4.6)</td>
<td>.41</td>
</tr>
<tr>
<td>Seated row</td>
<td>53.8 ± 14.3</td>
<td>53.6 ± 12.3</td>
<td>−1.4 (−7.6, 4.7)</td>
<td>.65</td>
</tr>
<tr>
<td>Avg upper body</td>
<td>61.0 ± 15.6</td>
<td>60.5 ± 14.0</td>
<td>−1.5 (−7.5, 4.5)</td>
<td>.63</td>
</tr>
<tr>
<td>Grip strength</td>
<td>41.7 ± 10.9</td>
<td>40.5 ± 11.0</td>
<td>−1.9 (−6.3, 2.5)</td>
<td>.40</td>
</tr>
<tr>
<td>Lower body</td>
<td></td>
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<tr>
<td>Knee extension</td>
<td>65.6 ± 23.8</td>
<td>63.1 ± 20.2</td>
<td>0.5 (−8.0, 9.0)</td>
<td>.90</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>47.6 ± 14.6</td>
<td>49.4 ± 12.2</td>
<td>−2.6 (−8.3, 3.2)</td>
<td>.38</td>
</tr>
<tr>
<td>Seated leg press</td>
<td>135.7 ± 43.9</td>
<td>129.3 ± 35.4</td>
<td>−0.1 (−14.0, 13.7)</td>
<td>.99</td>
</tr>
<tr>
<td>Avg lower body</td>
<td>83.9 ± 27.1</td>
<td>80.3 ± 20.3</td>
<td>−1.6 (−10.9, 7.7)</td>
<td>.74</td>
</tr>
<tr>
<td><strong>Power (Power Rig, watts)</strong></td>
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<tr>
<td>Leg extensor</td>
<td>229.3 ± 50.8</td>
<td>245.3 ± 68.8</td>
<td>−18.1 (−46.7, 10.5)</td>
<td>.21</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a Data are mean ± SD. Δ Change = change from baseline (any-T) minus change from baseline (placebo). P values are for placebo vs any-T, conditioned on baseline values.

Discussion

In otherwise healthy older men with low-normal baseline T levels, any-T supplementation and PRT independently decreased FM and increased FFM and upper body strength by 3% and 9%, respectively.

More subjects in the any-T-treated groups reported serious adverse events. However, there were fewer cardiovascular events among any-T–treated than among placebo-treated subjects (P value = .001).
strength, but neither had an effect on physical function. Although the combination of any-T plus PRT produced greater changes in body composition than PRT alone, there were no additive effects of any-T plus PRT on strength or physical function.

**Physical function**

Physical function assessed by CS-PFP total score did not improve with any-T supplementation, either alone or combined with PRT. This is consistent with previous studies of T supplementation alone reporting no improvements in physical function (measured via stair climb, timed up-and-go, or walking speed) in healthy (7, 8, 25) and frail older men (12) and with studies of T combined with resistance exercise in younger HIV-positive men with serum T < 349 ng/dL (26) and in frail elderly men with serum T < 480 ng/dL (27). In contrast, improvement in physical function has been demonstrated with 6 months of T gel (10 g/d) in men ≥ 65 years with mobility limitations and serum T 100 to 350 ng/dL (28), with 6 months of T gel (0.05 g/d) in frail men ≥ 75 years with serum T < 346 ng/dL (11) and with 13 months of im T alone or combined with...
Muscle strength and power

Treatment.

cient sensitivity to detect small changes associated with T treatment. This test may also lack suffi-

timal adherence to the PRT intervention. Participants in

flect the lack of an endurance component and/or subop-

speed and chair rise and CS-PFP scores in older adults with

effects on physical function, as measured by improved gait

CS-PFP scores. PRT alone and combined with endur-

unclear. In the present study, PRT alone did not improve

body, which supports other controlled trials of T supple-

lation alone. The improvements in strength with any-T

strength with T plus PRT compared with either interven-

alone compared with placebo were limited to the upper

body, which supports other controlled trials of T supple-

mentation in healthy older men (9, 12, 25, 31). This may

reflect the higher level of regular exercise of the lower body

in healthy older adults, However, Bhasin et al (32) found

improvements in leg press strength in healthy older men that
were correlated with both T dose and level. In the present study, exploratory analyses revealed a similar effect

of serum T level achieved on the improvement in leg press strength but no apparent effect of T dose or serum T level on any other strength measures (Supplemental Table 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).

Although the effects of PRT on muscle strength in older adults are well established (29, 33), to our knowledge, this is the first trial to examine the effects of T plus PRT in generally healthy older men with low-normal serum T. An association between exercise-induced increases in strength and serum T in older men (17) suggests that T administration may augment muscle hypertrophy with PRT in older men, producing greater gains in strength. In young men, supraphysiological T supplementation plus weight training produced greater improvements in upper and lower body. These findings support the concept that T may promote muscle hypertrophy in older men, similar to reports in younger men (12, 26).

Finasteride in healthy men ≥65 years with serum T < 350 ng/dL (9). The reasons for the lack of improvements in the present study and the inconsistencies in the literature are unclear. In the present study, PRT alone did not improve CS-PFP scores. PRT alone and combined with endurance training has previously been shown to have modest effects on physical function, as measured by improved gait speed and chair rise and CS-PFP scores in older adults with and without functional limitations (22, 29). This may reflect the lack of an endurance component and/or suboptimal adherence to the PRT intervention. Participants in our study also had a high baseline level of physical function, with CS-PFP total scores close to those reported in healthy adults 35 to 44 years of age (30). By comparison, scores of 54.2 ± 11.0 and 23.6 ± 8.7 have been reported for community-dwelling older adults and long-term care residents with minimal dependency, respectively (22). The CS-PFP has not previously been used in studies of T treatment and may not measure aspects of physical function responsive to T treatment. This test may also lack sufficient sensitivity to detect small changes associated with T treatment.

**Muscle strength and power**

We observed improvements in strength with both any-T and PRT but found no additional improvements in strength with T plus PRT compared with either intervention alone. The improvements in strength with any-T alone compared with placebo were limited to the upper body, which supports other controlled trials of T supplementation in healthy older men (9, 12, 25, 31). This may reflect the higher level of regular exercise of the lower body in healthy older adults, However, Bhasin et al (32) found improvements in leg press strength in healthy older men that were correlated with both T dose and level. In the present study, exploratory analyses revealed a similar effect of serum T level achieved on the improvement in leg press strength but no apparent effect of T dose or serum T level on any other strength measures (Supplemental Table 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).
lower body strength than either T or exercise alone (34). However, in a population of young HIV-infected men with weight loss and serum T < 349 ng/dL, both im T and resistance exercise increased muscle mass and strength, but the combination resulted in no additional gains (26). Sullivan et al. (27) also found a trend toward greater improvements in FM and FFM than placebo plus PRT. The effects of T with or without PRT were more pronounced in upper body FFM, which supports our finding with respect to strength. Previous studies of the combined effects of T plus PRT have been limited to young healthy men, chronically ill HIV-positive men, and older men in combination with megesterol acetate, with inconclusive results (26, 34, 39). To our knowledge, this is the first study to show that T treatment may augment PRT-induced changes in body composition in generally healthy older men.

It is unclear why the favorable changes in body composition consistently demonstrated with T supplementation in older men have not reliably translated into gains in overall strength or physical function. A threshold level of T may be needed to achieve increases in FFM sufficient to enhance strength and physical function (14). Because only 32% of men in the lower-range and 20% of men in the higher-range T group achieved target T levels at 52 weeks, we may not have reached the threshold for sufficient increases in FFM. Furthermore, the measured T levels were highly variable, indicating significant variability in ab-

### Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Category/Event</th>
<th>Placebo (n = 47)</th>
<th>Any-T (n = 96)</th>
<th>T (Lower Range) (n = 47)</th>
<th>T (Higher Range) (n = 49)</th>
<th>( P_a )</th>
<th>( P_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prespecified adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCTa</td>
<td>3 (3)</td>
<td>13 (17)</td>
<td>2 (4)</td>
<td>11 (13)</td>
<td>.27</td>
<td>.008</td>
</tr>
<tr>
<td>PSAb</td>
<td>9 (14)</td>
<td>12 (12)</td>
<td>5 (9)</td>
<td>7 (13)</td>
<td>.46</td>
<td>.57</td>
</tr>
<tr>
<td>AUA symptom scorec</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>.55</td>
<td>1.00</td>
</tr>
<tr>
<td>Liver function testsd</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence/hyoxiae</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>.30</td>
<td>.50</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Syncope/presyncope</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>.60</td>
<td>.50</td>
</tr>
<tr>
<td>Total cardiovascular</td>
<td>10 (11)</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Other (noncardiovascular)</td>
<td>20 (53)</td>
<td>68 (119)</td>
<td>31 (55)</td>
<td>37 (64)</td>
<td>.003</td>
<td>.24</td>
</tr>
<tr>
<td>All other nonserious adverse events</td>
<td>9 (12)</td>
<td>13 (13)</td>
<td>6 (6)</td>
<td>7 (7)</td>
<td>.47</td>
<td>.78</td>
</tr>
</tbody>
</table>

\( P_a \) = exact likelihood ratio \( \chi^2 \) test for equal proportions placebo vs any-T, number of subjects. \( P_b \) = exact likelihood ratio \( \chi^2 \) test for equal proportions lower-range T vs higher-range T, number of subjects.

a HCT \( \geq 54\% \).

b Increase of \( \geq 0.75 \text{ ng/mL} \) over baseline at any time point (confirmed by a second measurement in 2 weeks).

c AUA symptom score \( \geq 20 \).

d Alanine aminotransferase or aspartate aminotransferase \( > 2 \) times the upper limit of normal.

e Somnolence = Epworth Sleepiness Score (20) > 16; hypoxia is defined as arterial oxygen saturation by pulse oximetry < 88%.

In the present study, older men randomized to any-T alone achieved an average 1.0-kg decrease in FM and 1.0-kg increase in FFM, compared with an average 2.0-kg decrease and 2.7-kg increase, respectively, reported in a systematic review of T therapy in older men (37). Participants randomized to placebo plus PRT had a 0.6-kg decrease in FM and a 0.4-kg increase in FFM, somewhat less than found in a recent meta-analysis of PRT in older adults (38). The combination of T plus PRT produced greater improvements in FM and FFM than placebo plus PRT. The effects of T with or without PRT were more pronounced in upper body FFM, which supports our finding with respect to strength. Previous studies of the combined effects of T plus PRT have been limited to young healthy men, chronically ill HIV-positive men, and older men in combination with megesterol acetate, with inconclusive results (26, 34, 39). To our knowledge, this is the first study to show that T treatment may augment PRT-induced changes in body composition in generally healthy older men.

**Body composition**

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sorption and/or adherence. The lack of ongoing regular dosage titration makes actual T exposure difficult to assess. Although the study was not powered to examine lower- and higher-range T groups separately, exploratory analyses by T group and with T level as a continuous variable did not affect the primary conclusions (Supplemental Tables 1 and 2).

**Adverse events**

Other than dose-dependent elevations in HCT, there were no differences in adverse events with lower-range compared with higher-range T. There were more serious adverse events reported in the any-T–treated groups compared with placebo. These were defined as any complaint for which the subject sought any medical attention; thus, the clinical significance is uncertain. In contrast to the Testosterone in Older Men with Mobility Limitations (TOM) trial (40), we observed fewer cardiovascular events in the any-T–treated groups compared with placebo, which may reflect the healthier population in the present study. T supplementation may be of most interest in older, frail men likely to have cardiovascular risk factors, and the safety of long-term use in this population remains unclear.

**Conclusions**

In this study of generally healthy older men with low-normal T levels, 52 weeks of T supplementation, PRT, and T plus PRT improved body composition and upper body strength but not physical function. Although T plus PRT produced greater improvements in body composition than either intervention alone, this did not translate into enhanced strength or physical function. T supplementation was well tolerated and associated with a lower rate of cardiovascular endpoints in this population. Whether T supplementation with or without PRT improves physical function in specific populations of older men requires further study.

**Acknowledgments**

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This work was supported by the National Institute on Aging (NIA) R01 AG019339.

Disclosure Summary: The authors have nothing to disclose.

**References**


21. Dipietro L, Caspersen CJ, Ostfeld AM, Nadel ER. A survey for...


