

## Testosterone and Growth Hormone Improve Body Composition and Muscle Performance in Older Men

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**Context:** Impairments in the pituitary-gonadal axis with aging are associated with loss of muscle mass and function and accumulation of upper body fat.

**Objectives:** We tested the hypothesis that physiological supplementation with testosterone and GH together improves body composition and muscle performance in older men.

**Design, Setting, and Participants:** One hundred twenty-two community-dwelling men  $70.8 \pm 4.2$  yr of age with body mass index of  $27.4 \pm 3.4$  kg/m<sup>2</sup>, testosterone of 550 ng/dl or less, and IGF-I in lower adult tertile ( $\leq 167$  ng/dl) were randomized to receive transdermal testosterone (5 or 10 g/d) during a Leydig cell clamp plus GH (0, 3, or 5 µg/kg · d) for 16 wk.

**Main Outcome Measures:** Body composition by dual-energy x-ray absorptiometry, muscle performance, and safety tests were conducted.

**Results:** Total lean body mass increased ( $1.0 \pm 1.7$  to  $3.0 \pm 2.2$  kg) as did appendicular lean tissue ( $0.4 \pm 1.4$  to  $1.5 \pm 1.3$  kg), whereas total fat mass decreased by  $0.4 \pm 0.9$  to  $2.3 \pm 1.7$  kg as did trunk fat ( $0.5 \pm 0.9$  to  $1.5 \pm 1.0$  kg) across the six treatment groups and by dose levels for each parameter ( $P \leq 0.0004$  for linear trend). Composite maximum voluntary strength of upper and lower body muscles increased by  $14 \pm 34$  to  $35 \pm 31\%$  ( $P < 0.003$  in the three highest dose groups) that correlated with changes in appendicular lean mass. Aerobic endurance increased in all six groups (average  $96 \pm 137$  sec longer). Systolic and diastolic blood pressure increased similarly in each group with mean increases of  $12 \pm 14$  and  $8 \pm 8$  mm Hg, respectively. Other predictable adverse events were modest and reversible.

**Conclusions:** Supplemental testosterone produced significant gains in total and appendicular lean mass, muscle strength, and aerobic endurance with significant reductions in whole-body and trunk fat. Outcomes appeared to be further enhanced with GH supplementation. (*J Clin Endocrinol Metab* 94: 1991–2001, 2009)

**A**lterations in body composition, physical function, and substrate metabolism occur with advancing age. Loss of skeletal muscle mass (sarcopenia) (1, 2) contributes to declines in muscle strength and function along with diminished quality of

life (3). In the Baltimore Longitudinal Aging Study, quadriceps strength decreased about 30% between 50–70 yr of age (4). In the Copenhagen Heart Study, leg strength in 80-yr-olds was 20–30% lower than in 70-yr-olds (5, 6). Substantial losses in

strength may result in difficulty rising from a chair, climbing stairs, generating gait speed, and maintaining balance (7), eventually resulting in frailty. These changes contribute to loss of independence, social isolation, depression, and inactivity, thereby increasing the risk for disability, osteoporosis, and bone fractures. Advancing age is also associated with upper body obesity and insulin resistance, both risk factors for accelerated atherogenesis (8).

Coincident with these age-related deteriorations in clinical status, endogenous production of anabolic hormones declines (9). Approximately 25–30% of men over 60 yr of age have hypogonadal testosterone levels (10) that may be associated with sarcopenia, muscle weakness, and upper body obesity (9, 11, 12). Restoring testosterone to youthful levels has increased synthesis of myofibrillar proteins (13), total body cell mass (14), muscle strength (13, 15), and reduced trunk and visceral fat; blood pressure; lipids; and improved insulin sensitivity (16, 17). It is unclear whether these benefits translate to enhanced functional performance (18). Declines in GH and IGF-I may also contribute to these age-related comorbidities in persons with normal testosterone levels (9, 19). After puberty, 24-h GH production decreases progressively by about 14% per decade and up to 70% by the eighth decade of life (20–22). Similarly, circulating levels of IGF-I, a mediator of several but not all anabolic effects of GH, decline through the eighth to ninth decades with levels below the 2.5 percentile in 85–90% of older men (9) along with losses of lean tissue and increases in adiposity (23, 24). In obese adults, GH supplementation may reduce abdominal fat (25–28).

Better understanding of the relative contributions of the testosterone and GH/IGF-I axes to sarcopenia, impaired muscle performance, and obesity could have therapeutic implications (29). Only two single-site studies investigated the effects of administering these hormones in combination but both used supraphysiological doses of recombinant human (rh) GH and failed to demonstrate substantive improvements in muscle performance (30, 31). Our hypothesis was that endogenous testosterone and GH are important independent but complementary regulators of skeletal muscle mass and function, central obesity, and substrate metabolism throughout life into advanced age. To test this hypothesis, we conducted a multicenter study in older, community-dwelling men with levels of testosterone and IGF-I typical of their age to determine the effects of augmenting testosterone with a transdermal gel on muscle mass, physical performance, and adiposity and whether these effects could be augmented by increasing GH-IGF-I status with physiological doses of recombinant human GH.

## Subjects and Methods

### Study design

The Hormonal Regulators of Muscle and Metabolism in Aging study was a randomized, controlled, double-masked investigation of physiologic supplementation with testosterone and rhGH in older community-dwelling men who had levels of testosterone and IGF-I typical of older men. Randomization was two tiered (Fig. 1). Eligible participants were randomized first to either low or high eugonadal levels of testosterone

using a Leydig cell clamp to fully suppress endogenous testosterone, thereby minimizing potential confounding. Treatment with exogenous testosterone alone often leads to variable inhibition of LH and endogenous testosterone production, resulting in substantial heterogeneity of serum testosterone levels during therapy. Participants were further randomized (second tier) to placebo or one of two doses of rhGH. Treatment duration was 16 wk; postintervention outcomes were determined during wk 16 and 17.

### Study participants

Subjects providing local institutional review board-approved informed consent were screened at the University of Southern California (USC), Tufts University, and Washington University to enroll participants from different geographic areas to assure generalizability of outcomes. Eligibility required that men 65–90 yr of age have serum IGF-I in the lower tertile for adults (<167 ng/ml; 21.9 nmol/liter) and morning total serum testosterone in the lower half (150–550 ng/dl; 5.21–19.1 nmol/liter) of the adult male range. Other eligibility criteria included prostate-specific antigen (PSA) 4.0 ng/ml or less, hematocrit 50% or less, and fasting blood glucose less than 126 mg/dl (6.99 mmol/liter).

### Study interventions

All subjects were treated monthly from baseline to wk 12 using a Leydig cell clamp with a long acting GnRH agonist (leuprolide acetate depot, 7.5 mg im; TAP Pharmaceutical Products Inc., Deerfield, IL) and either 5 g (groups A–C) or 10 g (groups D–F) of 1% testosterone transdermal gel (Solvay Pharmaceuticals Inc., Marietta, GA) was applied each morning for 16 wk. Participants also self-administered 0, 3, or 5 µg/kg rhGH (Genentech Inc., South San Francisco, CA; groups A/D, B/E, and C/F, respectively) as sc injections 2–3 h after dinner each evening (Fig. 1).

The 5- and 10-g doses of testosterone were chosen to produce a spectrum of serum levels via the Leydig cell clamp that were in the low normal range typical of older men or mid- to high-normal levels typical of younger men, respectively (32). The 3 µg/kg dose of rhGH was chosen because 3.3 but not 2.0 µg/kg · d increased whole-body protein synthesis in GH-deficient adults (33). The 5 µg/kg · d dose was chosen to produce a greater anabolic stimulus but was expected to be low enough to minimize adverse effects that have occurred with higher doses (34, 35).

### Safety

Study participants were evaluated for adverse events at wk 4, 8, 12, and 16. At each visit, blood pressure was measured thrice in each arm with 5-min intervals between readings; the lowest value was used for analysis. An independent Data Safety Monitoring Board held prescribed interim safety analyses after the first 30 and 70 participants had completed study therapies and recommended that the study continue. Adverse events were monitored until resolution and sex hormones were measured 12 wk after completion of study therapy in all participants.

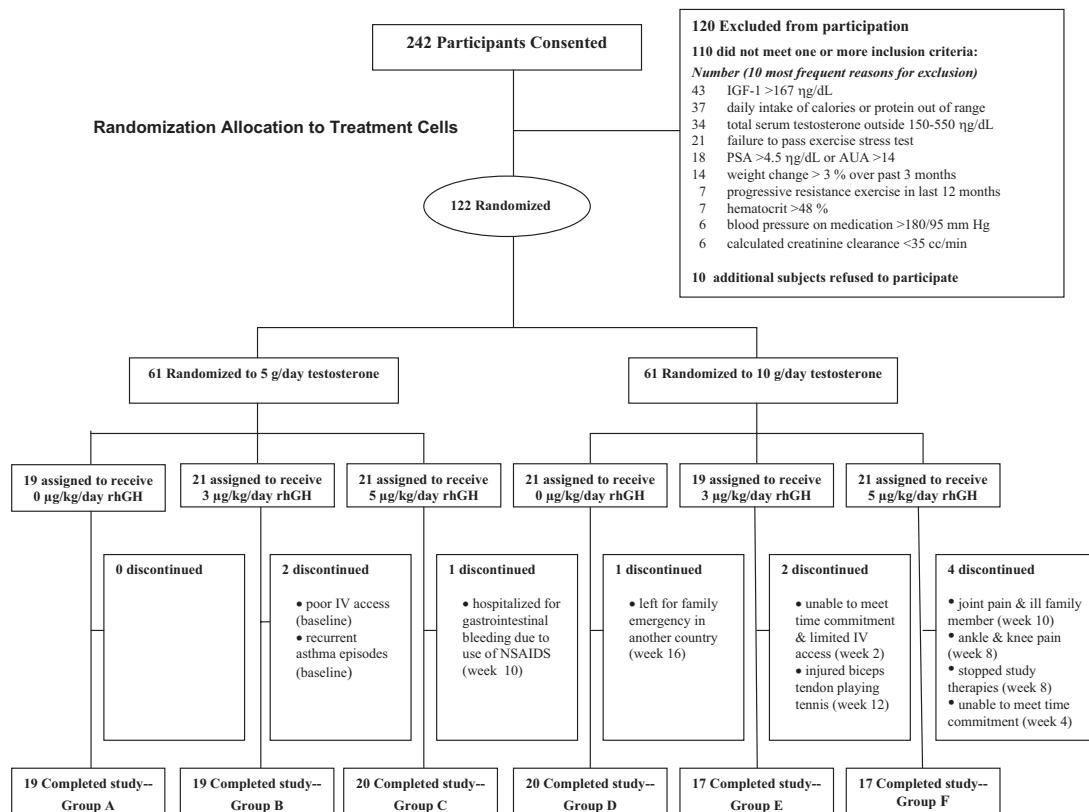
### Outcome measures

#### Body composition

Whole-body and regional lean and fat mass were quantified by dual-energy x-ray absorptiometry (DEXA), calibrated using a soft tissue phantom. Scans were analyzed at the USC Reading Center by an experienced DEXA-certified bionutritionist blinded to study assignment.

#### Muscle performance

Maximal voluntary muscle strength was assessed using the one-repetition maximum (1-RM) method (36) twice before randomization to minimize learning effects and after completion of study therapies (wk 17) for the bilateral leg press, leg extension, leg flexion, latissimus pull-down, and chest press (37). To normalize and consolidate whole-body strength assessments, results are presented as percentage change from baseline for the composite sum of 1-RM values for the five strength exercises.



**FIG. 1.** Schema depicts the subjects screened for study, most common reasons for exclusion, numbers of eligible subjects enrolled and how they were randomized to study therapies, reasons for study discontinuation during the 16 wk of treatment interventions, and final numbers of evaluable subjects in the six allocation groups. NSAID, nonsteroidal antiinflammatory drug.

## Aerobic capacity

At baseline and wk 16, peak O<sub>2</sub> consumption (VO<sub>2</sub>) was assessed by cycle ergometry having subjects pedal at 60 rpm with 15 or 20 W/min ramp protocols. Peak VO<sub>2</sub> was the highest O<sub>2</sub> consumption when subjects could not maintain a pedaling rate of 55 rpm or greater. After a 45-min rest period, aerobic endurance was determined as the length of time participants could cycle at 60 rpm at a constant workload of 80% of peak work (watts) achieved during the baseline peak VO<sub>2</sub> test.

## Hormone assays

For screening, total testosterone was measured using immunoassays in the local clinical university laboratories and IGF-I at Quest Diagnostics (San Juan Capistrano, CA). Testosterone, IGF-I, and insulin levels were determined after completion of the study by batch testing serum samples obtained at baseline and wk 16. Testosterone levels were quantified using a validated liquid chromatography-tandem mass spectrometry assay (38) at Boston Medical Center [interassay coefficients of variation (CVs) at 250 and 500 ng/dl (8.68 and 17.4 nmol/liter) were 5 and 3%, and intraassay CV was 3 and 2%, respectively]. IGF-I and insulin levels were determined in the USC GCRC Endocrine Core Laboratory. For IGF-I, samples were analyzed using an automated immunoassay analyzer [Immulite 1000; Siemens Healthcare Diagnostics, Deerfield, IL; sensitivity 20 ng/ml (2.6 nmol/liter), interassay CV 3.6% and intraassay CV 6.6%]. Insulin levels were analyzed using an automated enzyme immunoassay (Tosoh AIA 600 II analyzer; Tosoh Bioscience, Inc., South San Francisco, CA; sensitivity 0.31 µIU/ml, interassay CV 6.1%, intraassay CV 4.8%). homeostasis model assessment insulin resistance index (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were used to assess insulin resistance and sensitivity, respectively (39, 40).

## Statistical considerations

### Sample size considerations

Sample size calculations were determined for changes in body composition based on effect sizes demonstrated in several of our prior studies of anabolic androgens in similar older populations (41–43). With 18 subjects per group (total n = 108), this provided greater than 95% power to detect: 1) a mean increase in total lean body mass (LBM) of 1.5 kg or decrease in total fat of 1.5 kg within each of the six treatment interventions,(paired *t* test with Bonferroni adjusted significance level of 0.05/6 = 0.0083), and 2) a between-group mean difference in total LBM or fat mass of 1.0 kg, (using a two group *t* test with an adjustment to account for all 15 pairwise comparisons). For the secondary outcomes including appendicular LBM, trunk fat, measures of muscle performance, and safety parameters, these analyses were exploratory without *a priori* power calculations. To account for an anticipated 10% dropout rate, 122 subjects were enrolled. Using one-way ANOVA with pairwise comparisons (adjusting for multiple comparisons), a sample size of 18 per group provided 80% power to detect at the 0.05 level small effect sizes of 0.19 or greater for the other outcomes.

### Statistical analysis

Analyses were conducted for evaluable subjects (n = 112) who completed 16 wk of hormone treatments. Baseline characteristics were compared across the six intervention groups using one-way ANOVA for continuous variables and chi-square or Fisher's exact test for discrete variables. The primary analyses were directed at comparisons of DEXA and muscle performance outcomes across and within the six groups. One-way ANOVA was used to compare baseline and wk 17 values across the six treatment groups, and one-way analysis of covariance (ANCOVA) was used to compare the primary

**TABLE 1.** Baseline characteristics for treatment groups

Daily dose by study group	Testosterone, 5 g			Testosterone, 10 g			P value <sup>a</sup>
	GH 0 (n = 19) Group A	GH 3 µg (n = 19) Group B	GH 5 µg (n = 20) Group C	GH 0 (n = 20) Group D	GH 3 µg (n = 17) Group E	GH 5 µg (n = 17) Group F	
	72.7 ± 5.1 <sup>b</sup>	71.3 ± 3.9	70.0 ± 4.1	70.2 ± 4.6	69.9 ± 3.2	70.5 ± 3.9	
Age, yr							0.32
Ethnicity/race							
Caucasian	14 (74%)	18 (95%)	18 (90%)	15 (75%)	15 (88%)	16 (94%)	0.24
Minority	5 (26%)	1 (5%)	2 (10%)	5 (25%)	2 (12%)	1 (6%)	
Medical history							
Hypertension	9 (47%)	4 (21%)	7 (35%)	3 (15%)	3 (18%)	4 (24%)	0.20
History of cardiovascular disease	2 (11%)	1 (5%)	5 (25%)	2 (10%)	0 (0%)	3 (18%)	0.21
Elevated cholesterol <sup>c</sup>	5 (26%)	7 (37%)	6 (35%)	8 (45%)	5 (29%)	6 (35%)	0.95
History of smoking	7 (37%)	7 (37%)	8 (40%)	6 (30%)	9 (53%)	4 (24%)	0.61
Blood pressure							
Systolic blood pressure, mm Hg	121 ± 15	117 ± 13	113 ± 13	118 ± 15	119 ± 13	116 ± 12	0.57
Diastolic blood pressure, mm Hg	70 ± 8	68 ± 7	66 ± 7	68 ± 5	68 ± 6	69 ± 9	0.57
Laboratory values							
Hematocrit, %	43.3 ± 3.5	43.3 ± 1.6	44.1 ± 2.5	42.1 ± 2.9	43.2 ± 2.7	43.2 ± 2.2	0.34
Creatinine clearance, ml/min <sup>d</sup>	79.8 ± 9.3	76.3 ± 21.5	88.3 ± 22.1	81.0 ± 15.5	87.4 ± 16.9	82.6 ± 22.2	0.33
Albumin, g/dl	4.0 ± 0.3	4.2 ± 0.4	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.3	0.43
Alanine aminotransferase, U/liter	29.1 ± 8.4	30.4 ± 6.9	31.1 ± 10.7	30.0 ± 10.0	31.6 ± 12.3	32.0 ± 10.3	0.95
Prostate							
AUA score	4.1 ± 3.7 <sup>c</sup>	4.1 ± 2.8	5.2 ± 4.0	4.8 ± 4.0	4.6 ± 5.2	5.1 ± 4.0	0.91
PSA ng/ml	1.8 ± 1.0	1.3 ± 0.7	1.5 ± 1.0	1.4 ± 0.8	1.7 ± 0.8	1.4 ± 0.9	0.45
Hormones							
TSH, mIU/liter	2.1 ± 1.0	2.2 ± 1.3	2.1 ± 1.3	1.9 ± 1.1	2.3 ± 1.3	2.6 ± 1.7	0.71
Total testosterone, ng/dl	385 ± 106	377 ± 103	373 ± 89	350 ± 98	359 ± 89	311 ± 94	0.24
IGF-I, ng/ml	101 ± 23	109 ± 24	115 ± 31	105 ± 32	127 ± 30	114 ± 32	0.11
Metabolic measurements							
Fasting glucose, mg/dl	92 ± 9	93 ± 8	93 ± 10	89 ± 9	92 ± 18	94 ± 9	0.78
HOMA-IR <sup>e</sup>	1.52 ± 0.83	1.53 ± 1.48	1.81 ± 1.05	1.33 ± 0.61	1.54 ± 1.15	1.73 ± 0.93	0.76
QUICKI <sup>e</sup>	0.16 ± 0.01	0.16 ± 0.02	0.17 ± 0.01	0.16 ± 0.01	0.16 ± 0.02	0.16 ± 0.02	0.55
Total cholesterol, mg/dl	172 ± 24	174 ± 29	171 ± 33	180 ± 28	179 ± 27	174 ± 33	0.91
HDL cholesterol, mg/dl	43 ± 8	46 ± 17	40 ± 11	45 ± 9	44 ± 14	42 ± 12	0.65
LDL cholesterol, mg/dl	104 ± 30	105 ± 28	101 ± 26	110 ± 25	112 ± 24	105 ± 27	0.86
Fasting triglycerides, mg/dl	127 ± 65	113 ± 41	142 ± 69	126 ± 63	115 ± 50	131 ± 73	0.72
Body composition							
Weight, kg	79.1 ± 10.4	80.0 ± 13.2	86.0 ± 11.2	85.9 ± 14.0	86.1 ± 13.9	83.7 ± 11.4	0.31
Body mass index, kg/m <sup>2</sup>	26.8 ± 3.5	25.9 ± 3.0	28.2 ± 3.2	28.5 ± 3.8	27.6 ± 3.2	27.3 ± 3.2	0.19
Muscle performance							
Peak VO <sub>2</sub> , ml/kg · min	23.9 ± 6.2	26.2 ± 4.0	24.1 ± 3.5	24.1 ± 6.8	23.8 ± 3.7	25.4 ± 4.1	0.68

SI conversions: alanine aminotransferase (µkat per liter = units per liter × 0.0167); glucose (millimoles per liter = milligrams per deciliter × 0.0555); testosterone (nanomoles per liter = nanograms per deciliter × 0.0347); IGF-I (nanomoles per liter = nanograms per milliliter × 0.131); cholesterol (total, LDL, HDL; millimoles per liter = milligrams per deciliter × 0.0259); triglycerides (millimoles per liter = milligrams per deciliter × 0.0113). AUA, American Urological Association.

<sup>a</sup> ANOVA for continuous variables;  $\chi^2$  or Fisher's exact test for discrete variables.

<sup>b</sup> Mean ± 1 SD for continuous variables and frequency (percent) for discrete variables.

<sup>c</sup> Elevated cholesterol is use of cholesterol-lowering medication.

<sup>d</sup> Creatinine clearance = [(140 – age) × wt]/72 × serum creatinine.

<sup>e</sup> HOMA-IR = [(I<sub>f</sub>) × (G<sub>f</sub>)]/22.5; QUICKI = 1/[log(I<sub>f</sub>) + log(G<sub>f</sub>)], where (I<sub>f</sub>) is the fasting insulin level (microunits per milliliter) and (G<sub>f</sub>) is the fasting glucose level (millimoles per liter) for HOMA-IR.

outcome change score (wk 17 minus baseline) values adjusted for the baseline value as a covariate across the six treatment groups. Tukey pairwise comparisons ( $n = 15$ ) were used to assess differences in the baseline adjusted change scores between the six treatment interventions.

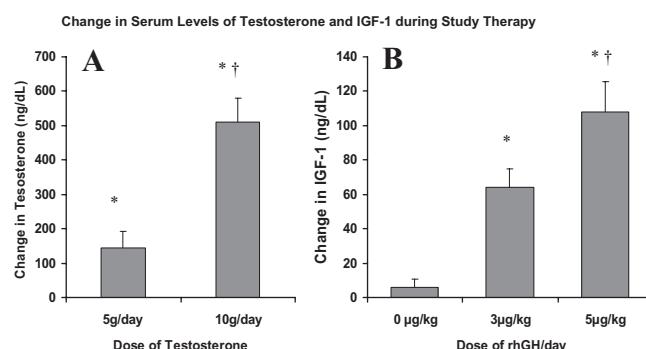
Linear trend was assessed using the Wald test to examine dose responses across the six groups, and a two-way ANCOVA was used to determine whether there were interactions between testosterone (two levels) and GH (three levels) interventions. In addition, we performed paired t tests for each variable within each of the six treatment group to test whether the change scores were significant at the  $0.05/6 = 0.0083$  alpha level using a Bonferroni adjustment for multiple analyses. Finally,

adverse events were contrasted across groups using Fisher's exact test. Changes in safety parameters were tested using the paired *t* test or signed rank test. Statistical analyses were carried out using the Statistical Analysis System 9.1 (SAS Institute Inc., Cary, NC).

## Results

### Study population

The first study participant was enrolled in June 2003 and the final participant completed evaluation in May 2007. Two hun-



**FIG. 2.** Changes (mean  $\pm$  1 se) in serum testosterone (A) and IGF-I (B) from baseline to wk 16 according to dose. \*, Within group significant changes ( $P < 0.05$ ); †, significant difference in change ( $P < 0.001$ ) between 5 and 10 g/d testosterone dose groups and significant differences in change ( $P < 0.05$ ) for IGF-I between the 3 or 5  $\mu\text{g}/\text{kg} \cdot \text{d}$  and the 0  $\mu\text{g}/\text{kg} \cdot \text{d}$  rhGH dose groups.

dred forty-two subjects were consented and screened for eligibility (Fig. 1). Of these, 122 eligible subjects were randomized to study interventions; 10 dropped out of study after randomization (three from the 5 g/d testosterone arm and seven from the 10 g/d testosterone arm); one of the dropouts was randomized to rhGH placebo, four to 3  $\mu\text{g}/\text{kg} \cdot \text{d}$  rhGH and five to 5  $\mu\text{g}/\text{kg} \cdot \text{d}$  rhGH. Thus, 112 participants completed all assessments at wk 17 and serve as the primary data set for analysis. Baseline characteristics before study interventions, including average body mass index of  $27.4 \pm 3.4 \text{ kg/m}^2$ , testosterone of  $360 \pm 98 \text{ ng/dL}$  ( $12.5 \pm 3.4 \text{ nmol/liter}$ ), and IGF-I (an indirect measure of GH status) of  $111 \pm 29 \text{ ng/dL}$  ( $14.5 \pm 3.8 \text{ nmol/liter}$ ) were similar among the six groups (Table 1). Participants were ambulatory, free-living men with peak  $\text{VO}_2$  typical of older persons without functional limitations (44).

### Changes in testosterone and IGF-I levels

As expected, testosterone and rhGH administration produced dose-related increments in serum testosterone and IGF-I concentrations (Fig. 2). Testosterone levels increased in 58 subjects receiving 5 g/d by  $143 \pm 379 \text{ ng/dL}$  ( $4.96 \pm 13.2 \text{ nmol/liter}$ ;  $P < 0.001$ ), which was lower ( $P < 0.001$ ) than the increase of  $510 \pm 503 \text{ ng/dL}$  ( $17.7 \pm 17.5 \text{ nmol/liter}$ ;  $P < 0.001$ ) in 54 subjects receiving 10 g/d. Changes in serum testosterone concentrations did not differ significantly among the three groups (A–C) receiving testosterone gel at 5 g/d or the three groups (D–F) receiving 10 g/d. Treatment with rhGH at 0, 3, and 5  $\mu\text{g}/\text{kg} \cdot \text{d}$  increased serum IGF-I levels by  $6 \pm 28 \text{ ng/dL}$  ( $0.79 \pm 3.7 \text{ nmol/liter}$ ;  $n = 39$ ;  $P = 0.15$ ),  $64 \pm 44 \text{ ng/dL}$  ( $8.4 \pm 5.8 \text{ nmol/liter}$ ;  $n = 36$ ,  $P < 0.001$ ), and  $108 \pm 51 \text{ ng/dL}$  ( $14.1 \pm 6.7 \text{ nmol/liter}$ ;  $n = 37$ ,  $P < 0.001$ ), respectively, with a significant trend across the rhGH dose groups ( $P < 0.001$ ). The higher testosterone dose alone was associated with a small but significant increase in IGF-I in group D that did not receive rhGH ( $14 \pm 28 \text{ ng/dL}$ ,  $1.8 \pm 3.7 \text{ nmol/liter}$ ;  $P = 0.03$ ), consistent with the reported enhanced hepatic synthesis of IGF-I in response to the higher dose of testosterone (45).

### Changes in body composition

The mean increases in total LBM at wk 17 ranged from  $1.0 \pm 1.7 \text{ kg}$  in group A to  $3.0 \pm 2.2 \text{ kg}$  in group F ( $P = 0.0002$ , linear trend) with maximum gains in groups E and F of 6.9 and 7.5 kg,

respectively. Using the Bonferroni adjustment ( $P < 0.008$ ), significant changes occurred in groups C–F. The mean decrease in total fat at wk 17 ranged from  $-0.8 \pm 1.3 \text{ kg}$  in group A to  $-2.3 \pm 1.7 \text{ kg}$  in group F ( $P = 0.0002$ , linear trend; Table 2 and Fig. 3) with maximal losses of  $-6.4 \text{ kg}$  and  $-7.1 \text{ kg}$  in groups E and F, respectively. Bonferroni-adjusted significant changes occurred in groups C, E, and F. Changes in regional mass (appendicular lean and trunk fat) at wk 17 followed similar patterns and levels of significance (Table 2 and Fig. 3). At wk 17, total LBM increased more for the 54 subjects receiving 10 g/d than for the 58 subjects receiving 5 g/d ( $2.3 \pm 2.0 \text{ vs. } 1.3 \pm 1.7 \text{ kg}$ ,  $P = 0.003$ ). Total fat decreased more for subjects receiving 10 g/d than for those receiving 5 g/d ( $-1.8 \pm 2.1 \text{ vs. } -0.9 \pm 1.2 \text{ kg}$ ,  $P = 0.003$ ). There was also a linear trend across the placebo, 3  $\mu\text{g}/\text{kg} \cdot \text{d}$ , and 5  $\mu\text{g}/\text{kg} \cdot \text{d}$  rhGH doses for increases in total LBM ( $1.3 \pm 1.6$ ,  $1.8 \pm 2.1$ , and  $2.3 \pm 2.0 \text{ kg}$ , respectively,  $P = 0.02$ ) and decreases in total fat ( $-1.0 \pm 1.9$ ,  $-1.3 \pm 1.8$ , and  $-1.7 \pm 1.5 \text{ kg}$ , respectively,  $P = 0.05$ ). Two-way ANCOVA showed no interactions of the two hormones on body composition changes (Table 2).

In pairwise analyses at wk 17, increase in total LBM in group F ( $3.0 \pm 2.2 \text{ kg}$ ) was greater than in groups A and B ( $1.0 \pm 1.7$  and  $1.1 \pm 1.8 \text{ kg}$ ,  $P = 0.02$  and  $P = 0.03$ , respectively). Fat losses in groups E and F ( $-2.3 \pm 2.0$  and  $-2.3 \pm 1.7 \text{ kg}$ ) were greater than losses in group B ( $-0.4 \pm 0.9 \text{ kg}$ ,  $P = 0.01$  for both).

### Changes in muscle performance

#### Maximal voluntary muscle strength

By wk 17, three interventions (groups D–F) produced significant ( $P < 0.008$ ) improvements ranging from  $23 \pm 27\%$  up to  $35 \pm 31\%$  ( $P = 0.08$  for linear trend) for composite maximal voluntary strength with the greatest increases in groups receiving combined treatment with 10 g testosterone gel plus rhGH (groups E and F, Table 3). Pairwise comparisons showed no differences between the groups ( $P \geq 0.50$ ). For 95 subjects with paired data, improvements in composite strength for the 58 subjects receiving 5 g/d testosterone ( $18 \pm 38\%$ ) and 54 subjects receiving 10 g/d ( $30 \pm 27\%$ ) were similar ( $P = 0.09$ ) as were changes for those receiving placebo *vs.* any dose of rhGH ( $22 \pm 39\% \text{ vs. } 25 \pm 30\%$ ,  $P = 0.76$ ).

For the 95 subjects with paired DEXA and composite strength tests at baseline and wk 17, increases in strength were correlated with increases in total LBM ( $r = 0.32$ ,  $P = 0.001$ ). Increases in strength and appendicular lean mass were also correlated ( $r = 0.30$ ,  $P = 0.003$ ). There were no significant treatment interactions for testosterone and rhGH group assignments by two-way ANCOVA for composite strength at wk 17 compared with baseline.

#### Aerobic endurance

For 86 subjects undergoing paired testing, endurance times increased in each of the six groups (averaging  $96 \pm 137 \text{ sec}$  longer) by study wk 16 and reaching Bonferroni-adjusted significance ( $P < 0.008$ ) in groups A and E (Table 3). Improvements in aerobic endurance at wk 16 were unrelated to the dose of testosterone or rhGH. In pairwise analyses, improve-

**TABLE 2.** Change in body composition by treatment group

Body composition	Testosterone, 5 g/d			Testosterone, 10 g/d			P values
	rhGH 0 (n = 19) Group A	rhGH 3 µg (n = 19) Group B	rhGH 5 µg (n = 20) Group C	rhGH 0 (n = 20) Group D	rhGH 3 µg (n = 17) Group E	rhGH 5 µg (n = 17) Group F	
Total LBM, kg							
Baseline	55.6 ± 5.0 <sup>a,*</sup>	57.7 ± 8.3	59.2 ± 8.1	59.0 ± 6.0	58.9 ± 7.4	59.1 ± 5.8	0.56 <sup>b</sup>
Week 17	56.6 ± 4.7	58.8 ± 8.7	60.9 ± 8.3	60.6 ± 6.3	61.5 ± 7.8	62.1 ± 6.1	0.20 <sup>b</sup>
Change (wk 17–baseline)	1.0 ± 1.7*	1.1 ± 1.8*	1.7 ± 1.5	1.6 ± 1.4	2.6 ± 2.1	3.0 ± 2.2**	0.01 <sup>c</sup>
P value <sup>f</sup>	0.7 (−2.0, 4.5) <sup>d,*</sup>	0.7 (−1.4, 4.8)	1.5 (−2.4, 4.4)	1.5 (−0.8, 4.7)	1.9 (0.2, 7.5)	2.6 (−0.7, 6.9)	0.0002 <sup>e</sup>
	0.02	0.02	<0.0001	0.0001	<0.0001	<0.0001	0.52 <sup>g</sup>
Appendicular LBM, kg							
Baseline	24.2 ± 2.4	25.2 ± 3.8	26.0 ± 3.7	25.8 ± 2.7	25.8 ± 3.7	26.1 ± 3.1	0.49
Week 17	24.6 ± 2.4	25.6 ± 3.9	26.7 ± 3.8	26.7 ± 2.5	27.0 ± 3.8	27.6 ± 3.2	0.10
Change (wk 17–baseline)	0.5 ± 1.0*	0.4 ± 1.4*	0.7 ± 0.7	0.9 ± 1.1	1.2 ± 1.1	1.5 ± 1.3**	0.01
P value	0.6 (−1.2, 2.9)	0.0 (−2.0, 3.5)	0.9 (−0.8, 1.8)	0.8 (−0.6, 2.8)	1.1 (−0.8, 3.5)	1.6 (−0.5, 4.4)	0.0002
	0.06	0.25	0.0002	0.002	0.0003	<0.0002	0.77
Total fat mass, kg							
Baseline	20.9 ± 6.5	19.5 ± 5.8	23.8 ± 4.6	24.2 ± 9.2	24.3 ± 7.7	21.7 ± 8.1	0.21
Week 17	20.1 ± 6.5	19.1 ± 6.0	22.5 ± 4.3	23.1 ± 8.4	22.0 ± 7.3	19.4 ± 7.8	0.31
Change (wk 17–baseline)	−0.8 ± 1.3	−0.4 ± 0.9*	−1.3 ± 1.1	−1.1 ± 2.3	−2.3 ± 2.0**	−2.3 ± 1.7**	0.002
P value	−0.5 (−4.1, 1.0)	−0.2 (−2.0, 1.0)	−1.3 (−4.3, 1.3)	−0.7 (−7.0, 2.6)	−1.7 (−6.4, 0.9)	−2.1 (−7.1, 0.1)	0.0004
	0.02	0.06	<0.0001	0.048	0.0003	<0.0001	0.11
Trunk fat, kg							
Baseline	12.2 ± 4.1	10.8 ± 3.5	13.9 ± 2.5	13.7 ± 5.1	13.9 ± 4.8	11.9 ± 4.8	0.12
Week 17	11.7 ± 4.0	10.5 ± 3.6	12.9 ± 2.4	13.1 ± 4.7	12.3 ± 4.5	10.4 ± 4.7	0.16
Change (wk 17–baseline)	−0.5 ± 0.9	−0.3 ± 1.0*	−1.0 ± 1.0*	−0.6 ± 1.5	−1.5 ± 1.3**	−1.5 ± 1.0**	0.004
P value	−0.5 (−2.4, 0.8)	−0.4 (−1.8, 2.8)	−1.1 (−3.2, 0.5)	−0.5 (−4.6, 1.7)	−1.2 (−4.6, 0.2)	−1.6 (−4.5, 0.1)	0.0003
	0.02	0.08	0.0003*	0.08	<0.0001	<0.0001	0.15

<sup>a</sup> Data are means ± 1 SD.<sup>b</sup> One-way ANOVA across treatment groups at baseline and wk 17.<sup>c</sup> One way ANCOVA for change (wk 17–baseline) across treatment groups, adjusting for baseline.<sup>d</sup> Median (range).<sup>e</sup> Wald test for trend across treatment group.<sup>f</sup> Paired t test for mean change from baseline to wk 17.<sup>g</sup> Two-way ANCOVA test for interaction.\*, \*\* Pairs of groups with different characters (\* vs. \*\*) are significantly different using the Tukey pairwise comparison procedure ( $P < 0.05$ ).

ment in aerobic endurance was greater for group F than D ( $P = 0.03$ ). There was no linear trend across the six treatment cells.

### Safety measures and adverse events

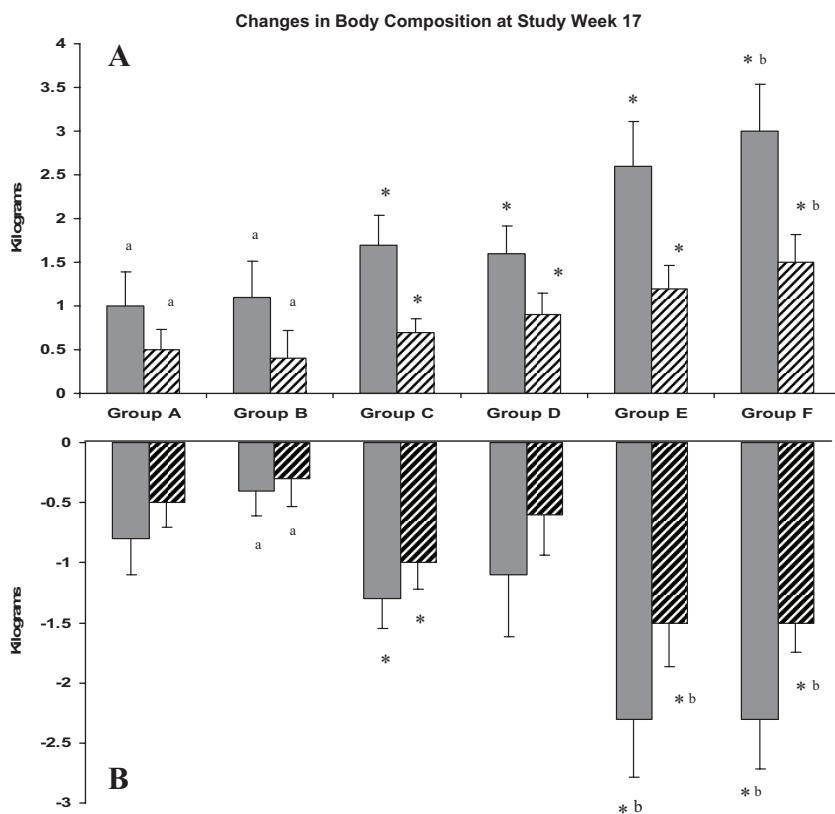
Gonadal function as measured by testosterone and LH returned to baseline levels in all participants within 12 wk of discontinuing study therapy (data not shown). New adverse symptoms or physical findings occurring in greater than 5% of subjects were generally similar for the interventions ( $P > 0.05$ , Table 4). Aching or muscle pains occurred in 24 of 73 subjects receiving rhGH and 13 of 39 subjects receiving no rhGH ( $P = 0.28$ ) and could not be related to dose levels. However, breast engorgement or nipple pain occurred transiently during study therapy but more often in the 54 subjects receiving 10 g of testosterone compared with the 58 receiving 5 g of testosterone daily ( $P = 0.006$ ). Changes in American Urological Association scores were similar among five of the groups after 16 wk of therapy but increased minimally by 2 ± 4 in group D ( $P = 0.04$ ).

Table 5 shows the changes in blood pressure, laboratory tests, and metabolic measures for the 112 subjects (for complete details of changes in individual treatment groups see supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online Web site at <http://jcem.endojournals.org>). Similar but significant increases in systolic and diastolic blood pressure oc-

curred with each of the six interventions (average change 12 ± 14 and 8 ± 8 mm Hg, respectively). At follow-up over the ensuing 12 wk after discontinuation of study therapies, the average increases in systolic and blood pressure were lower but still elevated by 9 ± 14 and 6 ± 10 mm Hg, respectively ( $P < 0.001$  for both compared with baseline). Hematocrit increased significantly in four of the six groups; eight subjects had increases to 50–52%, one to 53% and none to 54% or greater. After discontinuation of study interventions, hematocrit returned to less than 50% in all subjects. Although PSA increased in subjects by 0.2 ± 0.8 ng/ml, it increased significantly only in group F (from 1.1 ± 0.9 to 1.8 ± 1.1 ng/ml,  $P = 0.003$ ); no subject had a PSA increment greater than 1.4 ng/ml and values returned to baseline on repeated testing.

### Metabolic effects

Fasting blood sugar increased by 3 ± 10 mg/dl (0.17 ± 0.56 mmol/liter;  $P = 0.002$ ) across the entire study population but did not reach Bonferroni-adjusted significance ( $P < 0.008$ ) in any of the six groups (supplemental Table 1). HOMA-IR and QUICKI, indices of insulin resistance, changed minimally but were likewise unchanged in each of the six groups. Total and low-density lipoprotein (LDL) cholesterol were unchanged in the entire cohort or any of the six groups. High-density lipoprotein (HDL) cholesterol increased by 3.5 ± 6.7 mg/dl (0.09 ± 0.17 mmol/liter;  $P < 0.0001$ ) for the 112 participants but only increased signif-



**FIG. 3.** DEXA-derived changes (mean  $\pm$  1 se) in LBM and fat mass for each treatment group from baseline to wk 17. A, Increases in total LBM (solid bars) and appendicular lean mass (hatched bars). Changes across groups are significant for linear trend for total lean mass ( $P = 0.0002$ ) and appendicular lean ( $P = 0.0002$ ). B, Decreases in total body fat mass (solid bars) and trunk fat (hatched bars). Changes across groups are significant for linear trend for total fat mass ( $P = 0.0004$ ) and trunk fat ( $P = 0.0003$ ). \*, Bonferroni adjusted within group changes ( $P < 0.008$ ). Pairs of treatment groups with different letters (e.g. a vs. b) are significantly different by one-way ANCOVA with pairwise comparison (Tukey adjusted;  $P < 0.05$ ).

ificantly in group E by  $4 \pm 6$  mg/dl ( $0.10 \pm 0.16$  mmol/dl;  $P = 0.004$ ). Fasting triglycerides decreased by  $-18 \pm 57$  mg/dl ( $0.20 \pm 0.64$  mmol/liter;  $P = 0.0002$ ) but only significantly in group F by  $-40 \pm 77$  ( $0.45 \pm 0.87$  mmol/liter;  $P = 0.003$ ).

## Discussion

This is the first study to investigate the combined effects of 16 wk of physiological transdermal testosterone during a Leydig cell clamp and GH administration in older community-dwelling men. There were demonstrable benefits with the six different interventions with greater gains in whole-body and appendicular skeletal muscle mass, reductions in whole-body and trunk fat, and improvements in global measures of muscle performance with the higher dose levels. In particular, combined supplementation with testosterone and GH produced mean increases in total lean mass of up to about 3 kg (maximum increase of 7.5 kg) and mean decreases in fat of up to about 2.3 kg (maximum decrease of 7.1 kg) by wk 17 that were in the upper range of changes reported with physiological testosterone (14, 18, 30, 46–52) or GH (30, 31, 53–59) administered to older men for 3–12 months. These changes occurred in the context of a relatively low frequency of largely expected adverse outcomes (60, 61).

By wk 17, maximal voluntary strength of the major muscle groups of the upper and lower body increased significantly by  $23 \pm 27\%$  up to  $35 \pm 31\%$  in the three highest dose groups (D–F). However, paired muscle strength data were obtained for only 95 subjects. Intermittent musculoskeletal symptoms (e.g. flare of unilateral knee osteoarthritis) prevented some participants from performing all five strength tests, and other subjects showed different levels of motivation during testing sessions, despite coaching efforts to achieve maximal performance. These factors or insufficient sample size per treatment cell may have limited our ability to demonstrate statistical interactions or dose effects of the two hormones on muscle strength. Nevertheless, increases in muscle strength validated that the increases in lean tissue demonstrated by DEXA were due to accretion of myofibrillar protein and not just hydration effects. Furthermore, the increases in voluntary strength were of a similar magnitude to the losses reported in longitudinal studies of aging through the eighth to ninth decades of life (4–6), suggesting that the treatment effects were physiologically relevant.

There were also sizable improvements in aerobic endurance for all six groups that ranged from  $51 \pm 77$  to  $160 \pm 200$  sec at wk 17. Collectively, the global improvements in skeletal muscle strength and aerobic endurance were more substantial than previously reported in studies of testosterone, rhGH, or combination of the two hormones during treatment in older men, which showed minimal if any benefits (13, 18, 30, 31, 46–59). These improvements in muscle performance for our subjects with relatively intact functional status will be important if such effects can be translated to allow more functionally impaired individuals with sarcopenia or frailty to perform physical tasks and activities of daily living with less effort.

Analysis of the  $2 \times 3$  factorial design showed no statistical interactions among the treatment interventions with the changes in body composition or skeletal muscle strength, consistent with our *a priori* hypothesis that these hormones would have important independent but complementary effects likely reflecting different mechanisms of action. However, there were apparent dose-related effects for some parameters and possibly additive effects when these hormones were coadministered. Indeed, accrual of total and appendicular LBM was highly significant by linear trend analysis as was the loss of total and trunk fat mass with benefits increasing in magnitude from lower to higher dose combinations (i.e. groups A–F). Furthermore, total LBM increased significantly more for subjects randomized to 10 g than 5 g of testosterone per day, and the improvements were greater for subjects who received any dose of rhGH vs. placebo. Similarly, loss in total and trunk fat was greater with the higher dose of testosterone.

**TABLE 3.** Change in composite maximum voluntary strength and aerobic endurance

	Testosterone, 5 g/d			Testosterone, 10 g/d			P value
	rhGH 0 (n = 19) Group A	rhGH 3 µg (n = 19) Group B	rhGH 5 µg (n = 20) Group C	rhGH 0 (n = 20) Group D	rhGH 3 µg (n = 17) Group E	rhGH 5 µg (n = 17) Group F	
Composite strength (1-RM)							
Number of paired subjects	16	16	17	17	14	15	
Change at wk 17, %	22 ± 50 <sup>a</sup> 15 (−104, 117) <sup>c</sup>	14 ± 34 10 (−35, 90)	19 ± 28 18 (−24, 79)	23 ± 27 22 (−17, 83)	32 ± 22 34 (−3, 73)	35 ± 31 29 (−22, 91)	0.50 <sup>b</sup> 0.08 <sup>d</sup>
P value <sup>e</sup>	0.10	0.12	0.01	0.003	0.001	0.001	0.55 <sup>f</sup>
Aerobic endurance, sec							
Number of paired subjects	14	15	16	14	13	14	
Baseline	318 ± 90	411 ± 157*	332 ± 122	336 ± 119	260 ± 69**	320 ± 81	0.02 <sup>g</sup>
Week 16	457 ± 204	498 ± 235	399 ± 169	390 ± 144	355 ± 88	510 ± 219	0.16 <sup>g</sup>
Change at wk 16	143 ± 166 102 (−38, 600)	69 ± 122 78 (−112, 349)	67 ± 114 45 (−76, 422)	51 ± 77 51 (−91, 246)	95 ± 90 75 (−53, 287)	160 ± 200 140 (−56, 730)	0.17 <sup>b</sup> 0.03 <sup>d</sup>
P value	0.007	0.045	0.03	0.03	0.003	0.01	0.57 <sup>f</sup>

<sup>a</sup> Data are means ± 1 SD.<sup>b</sup> One-way ANCOVA for change (wk 17–baseline) across treatment groups, adjusting for baseline.<sup>c</sup> Median (range).<sup>d</sup> Wald test for trend across treatment group.<sup>e</sup> Paired t test for mean change from baseline to wk 17.<sup>f</sup> Two-way ANCOVA test for interaction.<sup>g</sup> One-way ANOVA across treatment groups at baseline and wk 17.<sup>\*</sup>, \*\* Pairs of groups with different characters (\* vs. \*\*) are significantly different using the Tukey pairwise comparison procedure ( $P < 0.05$ ).

Two recent studies of testosterone monotherapy (5 mg/d by patch for 2 yr or testosterone undecanoate 80 mg/d orally for 6 months) in older men failed to demonstrate improvements in LBM or muscle performance (51, 52). In both studies, increments in testosterone levels during treatment, unlike the current study, were minimal or did not increase into the normal range, possibly explaining the absence of benefits in those studies. Only two other studies investigated combined therapy with these two hormones in older men (30, 31). The first study involved 10 men who received serial treatment for 1 month with testosterone (5 mg/d by patch)

alone, rhGH (6.25 µg/kg · d) alone and the combination of each with 3-month intervening washout periods (30). There were no changes in lean mass or strength with the three interventions. In the second study, 74 men were randomized to receive testosterone (100 mg im biweekly), rhGH (20–30 µg/kg three times per week), the combination, or placebos for 26 wk (31). Lean mass increased by 3.1 kg with testosterone alone and 4.3 kg with the combination. There was a marginal increase ( $P = 0.05$ ) in composite 1-RM strength of six upper and lower body muscle strength tests and a modest 2.3 ml/kg · min increase in maximal O<sub>2</sub> uptake only with

**TABLE 4.** Emergent adverse events during study therapies

New symptom or finding	Testosterone, 5 g/d			Testosterone, 10 g/d			P value*
	GH 0 (n = 19) Group A	GH 3 µg (n = 19) Group B	GH 5 µg (n = 20) Group C	GH 0 (n = 20) Group D	GH 3 µg (n = 17) Group E	GH 5 µg (n = 17) Group F	
Large joint pain or knee swelling	40 (36%) <sup>a</sup>	4	6	8	12	6	0.16
Pretibial or ankle edema	39 (35%)	6	7	10	6	4	0.68
General aching or muscle pains	33 (29%)	6	7	2	3	7	0.07
New skin rash (local/general) or bruises	26 (19%)	4	3	3	4	6	0.54
Transient new cough/nasal congestion	17 (15%)	0	5	3	3	2	0.21
Back pain	14 (13%)	0	3	1	3	5	0.11
Transient hot flashes after treatment	13 (12%)	1	2	4	3	1	0.77
Breast engorgement or nipple pain	16 (14%)	2	1	0	5	3	0.051 <sup>b</sup>
Hand or wrist stiffness or pain	8 (7%)	1	4	1	1	0	0.32
Mean ± SD							
Change in AUA score	n/a	0.3 ± 3.4	1.0 ± 5.0	0.2 ± 2.2	2.2 ± 4.4	−0.2 ± 3.6	1.2 ± 5.0
							0.50

AUA, American Urological Association.

<sup>a</sup> Total number with symptom.<sup>b</sup> P = 0.006 by Fisher's exact test comparing 58 subjects receiving 5 g vs. 54 subjects receiving 10 g testosterone daily.

**TABLE 5.** Change in safety measures during study therapy

Safety parameter	n	Baseline		Wk 16		Wk 16 from baseline Mean ± SD	P value <sup>a</sup>	Groups with changes at P < 0.008
		Mean ± SD	n	Mean ± SD	n			
Systolic blood pressure, mm Hg	112	117 ± 14	112	130 ± 18	112	12 ± 14	<0.0001	A, D, F
Diastolic blood pressure, mm Hg	112	68 ± 7	112	76 ± 9	112	8 ± 8	<0.0001	A, B, C, D, E, F
Hematocrit, %	112	43.2 ± 2.7	112	45.2 ± 3.6	112	2.0 ± 3.2	<0.0001	D, E, F
PSA, ng/ml	112	1.5 ± 0.9	112	1.7 ± 1.2	112	0.2 ± 0.8	0.0002	F
Alanine aminotransferase, U/liter	112	31 ± 10	112	31 ± 11	111	0.3 ± 10.2	0.43	None
Fasting blood glucose, mg/dl	111	92 ± 11	112	95 ± 13	111	3.1 ± 10.2	0.002	None
HOMA-IR <sup>b</sup>	111	1.57 ± 1.03	112	2.15 ± 2.18	111	0.6 ± 2.1	0.01	None
QUICKI <sup>b</sup>	111	0.16 ± 0.02	112	0.16 ± 0.02	111	-0.004 ± 0.02	0.003	None
Total cholesterol, mg/dl	112	175 ± 29	112	177 ± 30	112	2.2 ± 27.3	0.20	None
HDL cholesterol, mg/dl	112	43 ± 12	112	47 ± 12	112	3.5 ± 6.7	<0.0001	E
LDL cholesterol, mg/dl	112	106 ± 27	112	110 ± 29	112	3.8 ± 23.2	0.08	None
Fasting triglycerides, mg/dl	112	126 ± 61	112	108 ± 46	112	-18.2 ± 57.0	0.0002	F

<sup>a</sup> P values from paired t test or Wilcoxon signed rank test.

<sup>b</sup> HOMA-IR = [(I<sub>f</sub>) X (G<sub>f</sub>)]/22.5; QUICKI = 1/[log (I<sub>f</sub>) + log (G<sub>f</sub>)], where (I<sub>f</sub>) is the fasting insulin level (microunits per milliliter) and (G<sub>f</sub>) is the fasting glucose level (millimoles per liter) for HOMA-IR.

the combination. The design in those trials differed substantially from the current investigation, including use of different formulations and routes of administration of testosterone, higher nonphysiological dosing with rhGH, and different durations of treatment (1 month to 2 yr). Thus, it is difficult to compare those studies with our investigation that used much smaller doses of rhGH approximating physiological replacement; neither of the previous studies showed the global increases in lean tissue and muscle performance demonstrated in the current trial.

Adverse events occurring during therapy were generally modest and included the small but reversible increases in hematocrit (2.0 ± 3.2%) and PSA (0.2 ± 0.8 ng/dl) at wk 16, both typical of testosterone therapy (60). However, the increases in systolic and diastolic blood pressure of 12 ± 14 and 8 ± 8 mm Hg, respectively, across the six groups that persisted, albeit at lower levels for up to 3 months after study therapies had been discontinued, were not anticipated. Previous testosterone and GH treatment studies generally showed no effect or decreases in blood pressure (17, 26), although GH has been reported to increase blood pressure (62). It is possible that increases in blood pressure, which also occurred without rhGH, were related to expansion of intravascular volume (62) as reflected by the 35% occurrence of new lower extremity edema or due to an unexpected high frequency of certain polymorphisms of the androgen receptor CAG repeat (63). Regardless, this important outcome must be investigated further in future studies of these anabolic hormone therapies.

There were no worrisome metabolic changes and some improvements. Fasting blood glucose increased by about 3 mg/dl (~0.17 mmol/liter), but mean levels remained well below the threshold for impaired fasting glucose (<110 mg/dl, <6.11 mmol/liter) in all groups. Similarly, insulin resistance as assessed by the HOMA-IR and QUICKI indices, worsened minimally across the study population but did not reach significance in any of the six groups. Total and LDL cholesterol were unchanged but HDL cholesterol improved by 3.5 ± 6.7 mg/dl (0.09 ± 0.17 nmol/liter) and fasting triglycerides decreased by -18 ± 57 mg/dl (-0.20 ± 0.64 mmol/liter) for the entire study cohort. We do not know whether more prolonged therapy would further

reduce upper body fat or enhance physical activity and thereby improve metabolic parameters associated with cardiovascular disease risks or adversely affect these metabolic parameters.

In conclusion, combined administration of physiological doses of testosterone and rhGH resulted in substantial gains in lean mass, voluntary muscle strength, and aerobic endurance along with reductions in total and trunk fat that were of greater magnitude than treatment with testosterone alone. An Institute of Medicine Expert Panel has recommended conducting focused short-term efficacy trials of testosterone in older persons with symptomatic impairments before embarking on larger, long-term safety trials (64). In this context, our preliminary findings provide the basis to carefully evaluate the health benefits and safety of strategies that augment both androgen and GH/IGF-I status in future controlled studies before using these agents together in clinical practice to treat complications of aging. Future efficacy trials to evaluate such strategies should be conducted in older persons with functional limitations, especially those with sarcopenia or frailty.

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