Single and Combined Effects of Growth Hormone and Testosterone Administration on Measures of Body Composition, Physical Performance, Mood, Sexual Function, Bone Turnover, and Muscle Gene Expression in Healthy Older Men

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We examined the effects of GH and/or testosterone (T) administration on body composition, performance, mood, sexual function, bone turnover, and muscle-gene expression in healthy older men. Ten men [mean (SEM) age, 68 (2.5) yr; height, 171.5 (2.4) cm; and weight, 80 (3.0) kg] completed each of the following 1-month, double-blind interventions after a baseline (B) study in randomized order with an intervening 3-month washout: transdermal T patch (5.0 mg/day); recombinant human GH (6.25 μg/kg sc daily); and combined hormones (GHT). ANOVA with repeated measures was used to evaluate interventional effects. Integrated serum GH concentrations [mean (SEM)] were elevated comparably by GH and GHT: [B = 383 (55), GH = 1107 (120), T = 459 (151), and GHT = 1189 (46) μg/liter-min; P < 0.0001]. Serum IGF-I concentrations also increased commensurately after GH and GHT: [B = 168 (14), GH = 285 (16), T = 192 (25), and GHT = 294 (25) μg/liter; P < 0.0001]. GHT administration increased total estradiol: [B = 110 (20), GH = 11 (1.5), T = 22 (2.8), and GHT = 24 (2.5) pg/ml; P < 0.0001]. No significant changes occurred in strength, flexibility, percentage body fat, or sexual function and mood. However, fat-free mass increased under combined GHT exposure: [B = 55 (1.3), GH = 56 (1.1), T = 55 (1.5), GHT = 57 (1.7) kg; P < 0.03]. Balance improved in response to GH intervention (P < 0.05), as did 30-m walk time during T and GHT interventions [B = 6.6 (0.3), GH = 6.2 (0.7), T = 5.9 (0.3), GHT = 5.5 (0.3) sec; P = 0.04] and stair climb time for all three interventions [B = 32.2 (1.4), GH = 29.8 (1.2), T = 30.5 (1.4), and GHT = 29.9 (1.2) sec (P = 0.0034), wherein the effects of GH, T, and GHT were different from that of B]. Muscle IGF-I gene expression increased by 1.9-fold during GH administration and by 2.3-fold during GHT administration (P < 0.05, compared with B). Myostatin and androgen receptor gene expression were not affected. Serum osteocalcin increased in response to the GH and GHT interventions: [B = 4.8 (0.52), GH = 5.7 (0.54), T = 4.7 (0.33), and GHT = 5.5 (0.39); P < 0.009]. There were no significant adverse events during 30 patient-months of intervention. We conclude that 1 month of GH and/or T administration improves certain measures of balance and physical performance in older men and increases muscle IGF-I gene expression. (J Clin Endocrinol Metab 87: 5649–5657, 2002)

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EALTHY AGING IN men is marked by a progressive reduction in the daily production of GH (1–3) and testosterone (T) (4–12). Daily mean serum GH concentrations decline exponentially, with a half-time of approximately 7 yr beginning in the young adult (age 18–25 yr; Refs. 1–3). The hyposomatotropism of aging is associated with increased fatigue, decreased physical performance, reduced lean body mass, and an accumulation of abdominal visceral fat mass (1–3). T bioavailability falls in parallel, such that T production is reduced by nearly one third by age 70 and one half by age 80. Hypogonadal-like features may emerge concurrently in the aging male, e.g. loss of bone and muscle mass, diminished libido and potency, impaired psychological well-being, and variable reduction in red cell mass (5, 6, 10, 11).

Albeit unproven, an emergent hypothesis is that impoverished anabolic drive by GH and T in the aging male may contribute to loss of well-being, energy, strength, libido, and skeletal and muscle mass and to the accumulation of visceral fat (1–12). The resultant relative physical frailty, potential loss of independent activity status, evident decline in exercise capacity, and higher risk of falls and fractures can seriously impair quality of life (13, 14). Recent limited interventional studies of either GH or T supplementation indicate that important anabolic effects can be elicited in GH-deficient, hypogonadal, and healthy older men, such as enhanced lean body mass, greater strength and muscle protein synthesis, increased bone mineral content, and an improved sense of well-being (13–32). However, higher doses of androgen may cause polycythemia, diminish plasma high-
density lipoprotein (HDL) concentrations, worsen sleep apnea, and stimulate prostate growth (23, 33–36). Likewise, GH supplementation may induce peripheral edema, arthropalgias, carpal tunnel syndrome, gynecomastia, and mild glucose intolerance (17–19, 37–39). One approach to addressing the foregoing concerns would be to limit the amounts of T or GH administered. A second consideration is to combine GH and T repletion at nearly physiological doses. In the latter regard, few interventional studies in older individuals have implemented combined GH and T supplementation.

On the basis of the physiological anabolic synergy expected between GH and androgen in normal puberty, the present clinical investigation explores the impact of 2-fold T and GH supplementation in healthy older men. This population is relatively hypoandrogenemic and hyposomatotropic by young adult standards. We hypothesized that combined near-physiological supplementation with GH and T would enhance selected endpoints of trophic hormone action, such as muscle strength, functional performance, skeletal mass, mood, sexual function, and body composition and elicit few side effects. We tested this postulate via a prospectively randomized, double-blind, within-subject crossover intervention design comprising the single and combined administration of recombinant human (rh)GH sc (6.25 μg/kg) and T transdermally (5.0 mg/d) for 1 month each.

We monitored biochemical indices of GH, muscle IGF-I, myostatin and androgen receptor (AR) gene expression, strength, balance, physical performance, percentage body fat, mood and sexual function, and any adverse impact on serum HDL concentrations, hematocrit, fasting plasma insulin/glucose ratios and glycosylated hemoglobin.

Subjects and Methods

Human subjects

The protocol was approved by the Human Investigation Committees of the University of Virginia Health Sciences Center and the McGuire Hunter Holmes Veterans Affairs Medical Center. Inpatient studies were carried out in the General Clinical Research Center (GCRC) at the University of Virginia. All subjects were healthy older (age, 60–78 y) men, whose baseline physical examination and screening biochemical tests of renal, hepatic, hematological, and metabolic function (thyroid function and fasting plasma glucose) were unremarkable. A screening preinterventional prostate-specific antigen (PSA) and digital prostatic exam were performed on each individual subject. Subjects also provided fasting serum samples on d 1, 7, 14, 21, and 28 during each interventional month. The latter was used to monitor serum concentrations of GH, IGF-I, LH, prolactin, estradiol (E2), total T, and free T.

Assays. Serum GH concentrations (2000 h to 0800 h) were measured in duplicate by an ultrasensitive (0.005 μg/liter threshold) chemiluminescence-based assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). All samples from an individual subject were analyzed in the same assay. The assay standard was 22-kDa rhGH. The mean intra-assay coefficient of variation (CV) was 4.8%, and the interassay CV was 8.6%. Serum total T and free T concentrations (2000 h to 0800 h) were measured by solid-phase RIA (Coat-a-Count, Diagnostic Products, Los Angeles, CA), with respective intra-assay CV of 6.1% and 3.8% and interassay CV of 7.9% and 4.2%, respectively. E2 (pooled sample) was assayed by a chemiluminescence assay (Automated Chemiluminescence Systems, Bayer Corp., Diagnostics Division, Norwood, MA), with respective intra-assay CV of 5.3% and interassay CV of 6.4%. SHBG (pooled sample) was measured using an assay from Diagnostic Systems Laboratories, Inc. (Webster, TX). The intra-assay CV ranged from 2.9–3.0%, and the interassay CV ranged from 8.9–10%. Serum IGF-I concentrations were assayed by RIA after acid ethanol extraction (Nichols Institute Diagnostics). The intra-assay CV was 2.7%, and the interassay CV was 6.8%. Integrated serum GH concentrations over the 12-h interval 2000 h to 0800 h were calculated by the trapezoidal rule (40). Serum PTH and osteocalcin were quantitated by two-site immunoassay (Nichols Institute Diagnostics). Serum bone alkaline phosphatase was measured by immunoradiometric assay using the Tandem-R-Ostase kit from Hybridtech (San Diego, CA). CV for the latter assays were 4–10% (intra-assay) and 7–15% (interassay).

Muscle biopsy. Muscle biopsies were performed at 0930 h. The dominant vastus lateralis was anesthetized locally using lidocaine. A 6 × 8-mm tissue sample was removed using a Bergstrom needle and snap-frozen in liquid nitrogen.

Skeletal muscle mRNA measured by RT-PCR. For RNA extraction, the frozen muscle sample was pulverized in liquid nitrogen using a mortar and pestle and homogenized for 30 sec at 8000 rpm. Total RNA was extracted using RNA STAT-60 (Tel-Test, Friendswood, TX) and quantified by duplicate absorbance determinations at 260 nm (26, 28).

cDNA was reverse transcribed from 0.5 μg total RNA using 1 μM random hexamers and 100 U Superscript II reverse transcriptase (Life Technologies, Inc., Rockville, MD) in a final volume of 20 μl at 42 C for 50 min, followed by 5 min of heat inactivation at 99 C.

The cDNA was amplified from the 20-μl reverse transcription reaction mixture in the same tube in a final concentration of 1X PCR buffer [Perkin-Elmer Corp., Norwalk, CT], 25 mM Tris-HCl, 50 mM KCl, 1.5 mM MgCl2, 1.0 mM deoxy-NTP, forward and reverse primers (gene of interest), 0.1 μmol of each], 5 U AmpliTaq DNA Polymerase (Perkin-Elmer Corp.), and 0.0225 μCi [32P] deoxy-CTP (Amersham Pharmacia Biotech, Arlington Heights, IL) in a final volume of 50 μl. The linear portion of the amplification curve for each transcript was defined and then used to determine the appropriate number of PCR amplification cycles in the RT-PCR analyses. Curves for IGF-I, AR, and myostatin were generated independently (data not shown). The PCR for IGF-I was carried out using 22-kDa rhGH. The linear portion of the amplification curve for each transcript was defined and then used to determine the appropriate number of PCR amplification cycles in the RT-PCR analyses. Curves for IGF-I, AR, and myostatin were generated independently (data not shown). The PCR for IGF-I was carried out using 22-kDa rhGH. The linear portion of the amplification curve for each transcript was defined and then used to determine the appropriate number of PCR amplification cycles in the RT-PCR analyses. Curves for IGF-I, AR, and myostatin were generated independently (data not shown). The PCR for IGF-I was carried out using 22-kDa rhGH.
dried, and [35S] incorporation was determined by quantitative autoradiography using a PhosphorImager from Molecular Dynamics, Inc. (Sunnyvale, CA). For final analyses, the OD of the transcript of interest was determined in duplicate using SigmaGel 1.05 software (SPSS, Inc. Richmond, CA) and subsequent sequencing of the IGF-I, AR, and myostatin DNA fragments, PCR products were isolated using a 5% polyacrylamide (1:25 bis to acrylamide ratio) gel with 25% glycerol. Samples were run for 3 h at 250 V in 0.5× Tris-borate EDTA buffer. The gel was then stained with ethidium bromide, and the bands were excised under UV illumination. The gel slices were electroeluted for 30 min (Bio-Rad Electro-Eluter 442, Bio-Rad Laboratories, Inc., Hercules, CA). The samples were extracted with phenol-chloroform (2×) and ethanol precipitated. Samples were sequenced at the University of Texas Medical Branch Molecular Core Laboratory with the specific forward and reverse primers from the 3’ to 5’ ends using an ABI Prism (Model 310) Sequencer (PE Applied Biosystems, Foster City, CA). All amplified DNA fragment sequences were compared to confirm identity.

Muscle RNA extracts (for samples being measured) were reverse-transcribed in duplicate and subjected to PCR. Duplicate samples were electrophoresed, and OD was determined from [35S] incorporation into the relevant bands. The arbitrary value for OD was then averaged between duplicate samples. Analysis of duplicate samples minimizes the potential variability in reverse transcription, PCR cycle efficiency, between duplicate samples. Analysis of duplicate samples minimizes the potential variability in reverse transcription, PCR cycle efficiency, and gel loading. The intra-assay variance for the entire set of duplicate samples determined (IGF-I, AR, and myostatin) was 9.7% and gel loading. The intra-assay variance for the entire set of duplicate samples determined (IGF-I, AR, and myostatin) was 9.7%.

**Outpatient testing**

**Body composition.** Body volume and density were estimated by hydrostatic weighing (43) and air-displacement plethysmography (44). For hydrostatic weighing, each subject was weighed in air on an Accu-Weigh beam scale accurate to 0.1 kg and subsequently weighed under water on a Chatillon autopsy scale accurate to 10 g. Residual lung volume was measured using an oxygen dilution technique (45). Body volume was measured using an oxygen dilution technique (45). Body density was also determined using the Bod Pod body composition system (Life Measurement Instruments, Concord, CA). Subjects were instructed to wear close-fitting swimwear, including a swim cap, and to remain in the water for 3 min. Body volume was obtained by calibrating the test tank to the resolution of 5 g and then asked to enter the chamber and sit quietly during the initial measurement of body volume. The body volume trial was repeated, and the thoracic gas volume (VTG) was determined while the subject was in the chamber. The subject’s body volume based on the following equation: body volume (raw) = surface area (SA) + 400 g. The computational procedure of Brozek et al. (46) was used to determine the percentage of total body fat from the body density measurements.

**Strength.** Eccentric and concentric strength of the quadriceps femoris and biceps femoris muscle groups was assessed using the Kin-Com II isokinetic dynamometer (Chattecx Corp., Hixson, TN). Tests were performed at 60°/sec. To ensure testing of the dominant leg, subjects were asked to kick a ball, and the preferred leg was used in further testing. Each subject was seated on the Kin-Com, with the lateral epicondyile of the knee aligned with the axis of the dynamometer and the inferior edge of the force plate directly above the joint. Velcro straps were placed across the hips, thigh, and ankle of each subject for stabilization. Each subject performed three eccentric and three concentric contractions at the velocity of 60°/sec. The eccentric test contraction was followed by the concentric test without any rest. Gravity correction was performed according to the manufacturer’s protocol with the knee at 0° flexion. The dynamometer’s preload and minimal force values were set at 50 and 20 N, respectively.

**Balance.** One-legged stance was used to assess balance. This assessment recorded the amount of time the subject remained standing on one leg with his eyes open and eyes closed. Subjects were instructed to pick a point on the wall ahead, steady themselves and lift the nonsupporting leg when ready. Total time on one leg was recorded. The clock was stopped if the subject put his nonsupporting foot down or moved the supporting leg from the initial location. Left and right legs were alternated. Each test was repeated three times, beginning with the eyes-open test.

**Flexibility.** Hamstring/ lower back flexibility was assessed using a sit-and-reach apparatus. Subjects were asked to sit with their feet against the apparatus, place their hands one on top of the other, and reach as far forward as possible, with knees extended. Positive scores indicated the number of inches the subject could reach past his toes. Negative scores indicated that the subject was a distance away from touching his toes. Three trials were performed.

**Adverse events.** Subjects were examined on d 1, 7, 14, 21, and 28 of each interventional period and asked to report anything unusual, such as skin irritations, itching, sneezing, or fatigue. Subjects were asked to rank the severity of the symptoms they were experiencing as mild, moderate, or severe. If the symptoms were mild to moderate, subjects were provided appropriate treatment and asked whether they wanted to continue participation in the study. Subjects with severe symptoms would be treated and withdrawn from the study. Documentation was maintained in the subject’s chart.

**Statistical analysis.** All values are expressed as the mean (SEM). ANOVA with repeated measures was used to determine mean differences between baseline and each of the three interventions. The primary endpoints were 12-h integrated GH, serum IGF-I, T, free T, and SHBG concentrations; percentage body fat; fat free mass; strength; flexibility; function and muscle gene expression; bone turnover; sexual function; and mood. Sexual function and mood scores were averaged for each 7-d period (25, 40, 41). Whenever a significant interventional effect was observed, mean comparisons were examined by post hoc examination. Bonferroni correction was performed to adjust for multiple comparisons. Significance was set at $P < 0.05$.

**Results**

**Subject characteristics**

The mean age of the subjects was 68.1 ± 2.4 yr; height, 171.5 ± 2.4 cm; weight, 79.3 ± 3.0 kg; body mass index (BMI), 26.71 ± 1.05 kg/m2; and percentage body fat, 30.5 ± 1.4%.

**GH release**

Figure 1 shows the overnight serum GH concentration profiles in one subject based on blood sampling at 10-min intervals over 12 h (2000 h to 0800 h) at baseline (B) and during randomly ordered T, GH, and GHT supplementation. Figure 2 summarizes 12-h integrated (area under the curve) serum GH concentrations at B and during the T, GH, and GHT interventions. ANOVA revealed that GH was greater than B ($P < 0.001$) and GHT was greater than B ($P < 0.001$). GH and GHT effects were not significantly different ($P = 0.877$), but exceeded the effect of T: GH was greater than
T (P = 0.001) and GHT was greater than T (P < 0.001). T administration did not have a significant effect on 12-h integrated serum GH concentration (P = 0.468).

**IGF-I**

Figure 2 also shows the changes in serum IGF-I concentrations, which paralleled those of GH. GH and GHT produced an approximately 70% increase in IGF-I: GH was greater than B (P = 0.01) and GHT was greater than B (P = 0.002). Mean IGF-I during the GH and GHT interventions did not differ (P = 0.498), but exceeded that during T: GH was greater than T (P = 0.04) and GHT was greater than T (P = 0.008). T did not have a significant effect on IGF-I concentrations (P = 0.508).

**Total T**

Administration of T increased total T by 62% above B (P = 0.004), whereas GHT elicited a 75% increase in total T above B (P = 0.016). Both GHT and T significantly increased total T over GH administration: GHT was greater than GH (P = 0.003) and T was greater than GH (P = 0.011; Fig. 3). The response to GH administration was not significantly different from B (P > 0.05).

**Free T**

Figure 3 also shows the changes in free T concentrations, which are similar to changes in total T concentrations. T and GHT elicited an approximate 2-fold increase in free T above B: T was greater than B (P = 0.020) and GHT was greater than B (P = 0.005). The responses to T and GHT were comparable (P = 0.477).

**E2**

Administration of GHT increased serum E2 concentrations by 38% over B. In addition, we found that GH increased E2 above B (P = 0.05) and GHT increased E2 more than GH (P = 0.02; Fig. 4). T and GHT had a greater effect than GH on E2 (P = 0.05 and P = 0.02, respectively).

**SHBG**

GH, GHT, and T interventions resulted in a nonsignificant reduction in SHBG [B = 80.4 ± 12.4 nmol/liter; GH = 66.1 ± 6.8 nmol/liter; GHT = 77.2 ± 16.2 nmol/liter; and T = 71 ± 9.4 nmol/liter (P = 0.33)].

**Muscle gene expression**

Figure 5 shows semiquantitative estimates of muscle IGF-I gene expression, which was stimulated equally by GH (P = 0.05) and GHT (P = 0.05). T alone had no effect on muscle IGF-I gene expression. AR gene expression was invariant of intervention (P > 0.05; Fig. 5). Myostatin gene expression was also unaffected by T or GH supplementation, although the effect of GHT approached statistical significance (P = 0.09).

**Strength, flexibility, and body composition**

Table 1 summarizes quantitation of eccentric and concentric knee extension and knee flexion strength (P > 0.05), hamstring flexibility (P > 0.05), and percentage body fat (P > 0.05). The Bod Pod (see Subjects and Methods) but not hydrostatic weighing estimates identified significant overall increases in fat-free mass (P = 0.03). There was no statistical difference in BMI during the interventional periods compared with B or each other (P > 0.05).

**Function**

T and GHT significantly reduced the time required to complete the 30-m walk compared with B: T was less than B (P = 0.045) and GHT was less than B (P = 0.009) and from each other, and GHT was less than T (P = 0.004). GH alone had no effect (Table 2). The stair-climb time improved significantly over B; GH was less than B (P = 0.022); T was less than B (P = 0.025); and GHT was less than B (P = 0.012). There were no differences among the interventions (P > 0.05).

**Balance**

GH, but not T, enhanced performance in the eyes-closed, nondominant-leg stance (P = 0.047; Fig. 6). The GH effect was significantly different from that of GHT (P = 0.0294).

**Markers of bone remodeling**

Table 3 shows no significant effects of any of the interventions on serum 25-hydroxyvitamin D or bone alkaline phosphatase concentrations, or fasting urinary calcium or
creatinine excretion. There was a significant interventional effect on osteocalcin \((P < 0.0095)\) for all three treatments.

**Sexual function and mood**

Table 4 shows the values for the mood questionnaires \((n = 7;\) three subjects did not complete the questionnaire). There were no significant changes in positive mood attributes (alertness, energy, feelings of well/good), negative mood attributes (irritable, lethargic, sad, angry), or frequency of intercourse.

**Adverse events**

There were no significant changes in fasting blood glucose, glycosylated hemoglobin, total cholesterol, HDL cholesterol, or PSA. No subject presented with polycythemia, sleep apnea, edema, arthralgias, carpal tunnel syndrome, or gynecomastia. One volunteer presented with a mild skin irritation associated with the use of the T transdermal patch. The individual was treated with a topical steroid and continued in the study.

**Discussion**

An aging-associated reduction in the combined anabolic drive achieved by GH and/or T may contribute to diminished well-being, energy, strength, libido, muscle and skeletal mass, and increased abdominal visceral fat accumulation in elderly men \((2–12)\). This inference is supported by many but not all analyses of the individual effects of T or GH supplementation in healthy older men. Some studies report that T supplementation has a salutary effect on total body mass \((22)\), muscle mass \((22, 26)\), strength \((28–30)\), and protein synthesis \((28, 30)\). Likewise, GH administration may exert beneficial effects on body composition \((15–18)\), protein synthesis \((19)\), muscle strength \((15, 27)\), and function \((14, 27)\) in some older individuals. We reasoned that the combined administration of GH and T would exert synergistic anabolic effects on selected biochemical measures, balance, strength, performance, and/or muscle gene expression, and impose few adverse events at near-physiological doses of each. Indeed, supplementation with T and GH, single and combined, induced mid-adult serum concentrations of GH, IGF-I, T, and E2 (reference levels for the mid-adult hormones levels are
Increased muscle strength after androgen or GH supplementation in older men has been demonstrated inconsistently. Wang et al. (25) administered sublingual testosterone cyclodextrin in hypogonadal middle-aged men, and Urban et al. (28) and Tenover (23) injected im testosterone enanthate (100 mg/wk) in older men and reported significantly increased leg strength without exercise. Welle et al. (15) administered rhGH (30 μg/kg three times a week for 3 months) to older (>60 yr) men and observed an increase in muscle strength, but a more extended intervention in men aged 70 yr and older did not improve strength and induced adverse events that required dose reduction in 25% of subjects (16).

The interventional goal was to restore hormone levels to the normal ranges of young adults and, more importantly, alleviate the symptoms of hormone deficiency. The general androgen supplementation to elderly men is a biweekly injection of 200 mg of testosterone enanthate. Although we administered 5.0 mg transdermal T, we restored T to levels similar to most authors (6, 20, 23, 25). However, it must be kept in mind that guidelines for plasma T levels used to determine androgen deficiency are not completely defined, thus making it more difficult to assess biological parameters of androgen action when existing clinical criteria are somewhat arbitrary (35). Various dose regimens for GH have been reported in GH intervention protocols (13, 15, 17, 18), thus providing a challenge when comparing results. However, the GH dosing regimen used in the present study was effective, as indicated by the achievement of IGF-I concentrations within the mid-adult range without serious adverse events.
TABLE 1. Intervention effects on strength, flexibility, and body composition

<table>
<thead>
<tr>
<th>Measurement</th>
<th>B</th>
<th>T</th>
<th>GH</th>
<th>GHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility (in.)</td>
<td>-2.6 (1.7)</td>
<td>-1.8 (1.7)</td>
<td>-2.5 (1.9)</td>
<td>-2.0 (1.4)</td>
</tr>
<tr>
<td>Knee extension concentric</td>
<td>310.4 (15.5)</td>
<td>298.7 (19.2)</td>
<td>311.0 (16.8)</td>
<td>303.2 (26.0)</td>
</tr>
<tr>
<td>Knee extension eccentric</td>
<td>415.7 (24.0)</td>
<td>410.4 (35.9)</td>
<td>409.4 (27.6)</td>
<td>407.3 (32.0)</td>
</tr>
<tr>
<td>Knee flexion concentric</td>
<td>155.7 (14.2)</td>
<td>172.6 (8.7)</td>
<td>176.8 (18.8)</td>
<td>171.5 (11.9)</td>
</tr>
<tr>
<td>Knee flexion eccentric</td>
<td>256.4 (15.7)</td>
<td>264.4 (21.8)</td>
<td>272.7 (28.9)</td>
<td>260.6 (18.5)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.7 (1.05)</td>
<td>26.7 (1.01)</td>
<td>26.9 (1.01)</td>
<td>26.9 (0.91)</td>
</tr>
<tr>
<td>Fat-free mass (kg) (Bod Pod)</td>
<td>54.79 (1.30)</td>
<td>54.94 (1.46)</td>
<td>56.39 (1.07)</td>
<td>57.41 (1.74)</td>
</tr>
<tr>
<td>% Body fat (UWW)</td>
<td>29.10 (1.66)</td>
<td>29.05 (1.48)</td>
<td>27.72 (1.43)</td>
<td>26.98 (1.27)</td>
</tr>
</tbody>
</table>

Data are presented as the mean (SEM); n = 10. No evident interventional effects; ANOVA yielded P > 0.05 for all outcomes. UWW, Underwater weighing.

a ANOVA P = 0.03; no statistical differences among interventions as determined by post hoc testing.

TABLE 2. Interventional effects on functional status

<table>
<thead>
<tr>
<th>Measurement</th>
<th>B</th>
<th>T</th>
<th>GH</th>
<th>GHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-m walk (sec)</td>
<td>6.65 (0.34)</td>
<td>5.89 (0.28)</td>
<td>6.21 (0.69)</td>
<td>5.49 (0.26)</td>
</tr>
<tr>
<td>Stair climb (sec)</td>
<td>32.17 (1.39)</td>
<td>30.44 (1.39)</td>
<td>29.76 (1.24)</td>
<td>29.88 (1.19)</td>
</tr>
</tbody>
</table>

Data are presented as the mean (SEM); n = 10.

a T < B (P = 0.045); GHT < B (P = 0.009); GHT < T (P = 0.004).
b GH < B (P = 0.022); T < B (P = 0.0025); GHT < B (P = 0.012).

Quality of life, as measured by reported mood changes and a sexual-function scale, did not change. This outcome may reflect limited statistical power for this secondary endpoint. However, it is possible that quality of life did not change in this short treatment period, because the subjects in the present study were active, healthy older men and likely had a good health-related quality of life. It has been shown that quality of life in the GHD subjects improves most in the individuals who had the worst initial scores (13). In support of the above, Snyder et al. (21) also observed no psychosocial benefits during 2 yr of transcrrotal T administration in older men. In contrast, Wang et al. (41) reported an increase in positive affect and a decrease in negative affect in middle-aged hypogonadal men after 3 months of treatment with sublingual T. A recent 2-yr GH replacement study found no effect of GH on psychological well-being (49). Thus, further clinical studies will be required to clarify this issue in the older male.

The current data affirm the a priori hypothesis that combined intervention with GH and T for 1 month can enhance certain measures of balance and physical performance, such as a more stable stance (one-legged stance) and a faster stair climb and 30-m walk. In an older individual, such improvements in functional outcomes may be important to quality of life. Whether these effects persist or increase during long-term dual-hormone replacement is not known, and whether fewer falls and fractures would result from improved balance remains to be determined.

We reasoned that the relatively hypogonadal and hyposomatotropin state in the aging male contributes to diminished bone mineral density, because GH and T both maintain bone mass and influence bone remodeling (1–12, 50–56). The present interventional data support (but do not prove) this notion, because short-term administration of GH with or without T significantly increased serum osteocalcin concentrations. On the other hand, serum alkaline phosphatase levels and urinary calcium loss did not change. Moreover, plasma concentrations of GH and IGF-I in older men do not always correlate with bone mineral density or markers of bone turnover (57) particularly over short intervals. In a recent study in the pan-hypopituitary elderly adult, Drake et al. (58) reported that rhGH supplementation increased bone mineral density and serum bone-specific alkaline phosphatase after 6 months. In addition, in other analyses, bone mass improved without major changes in bone-turnover markers (59). Thus, GHT should not be discounted as a possible interventional strategy in aging men until more extended trials are performed.

As complementary direct measures of target-tissue responses to GH and/or T, we examined specific muscle gene expression. Both GH alone and GHT produced an increase in skeletal-muscle mRNA IGF-I content. T slightly aug-

![Fig. 6](https://academic.oup.com/jcem/article-abstract/87/12/5649/2823629/1587269)
TABLE 3. Intervventional effects on markers of bone remodeling

<table>
<thead>
<tr>
<th>Measure</th>
<th>B</th>
<th>T</th>
<th>GH</th>
<th>GHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-Hydroxyvitamin D (ng/ml)</td>
<td>22 (0.92)</td>
<td>23 (1.0)</td>
<td>23 (0.92)</td>
<td>23 (0.64)</td>
</tr>
<tr>
<td>Bone alkaline phosphatase (IU/liter)</td>
<td>10 (1.77)</td>
<td>9.8 (0.87)</td>
<td>9.5 (0.80)</td>
<td>9.4 (0.81)</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>4.8 (0.52)</td>
<td>4.7 (0.33)</td>
<td>5.7 (0.54)</td>
<td>5.5 (0.40)</td>
</tr>
<tr>
<td>Urinary creatinine (g/12 h)</td>
<td>0.80 (0.07)</td>
<td>0.78 (0.06)</td>
<td>0.80 (0.07)</td>
<td>0.84 (0.07)</td>
</tr>
<tr>
<td>Urinary calcium (mg/dl)</td>
<td>12 (3.4)</td>
<td>10 (3.0)</td>
<td>12 (2.2)</td>
<td>12 (2.4)</td>
</tr>
</tbody>
</table>

Values reported are mean (SEM) (n = 10).

TABLE 4. Descriptive characterization of interventional effects on mood and sexual function

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>T</th>
<th>GH</th>
<th>GHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert</td>
<td>5.41 (0.98)</td>
<td>5.6 (1.34)</td>
<td>6.06 (0.57)</td>
<td>5.75 (0.78)</td>
</tr>
<tr>
<td>Energetic</td>
<td>4.62 (0.86)</td>
<td>4.51 (1.50)</td>
<td>5.24 (0.90)</td>
<td>5.36 (0.92)</td>
</tr>
<tr>
<td>Friendly</td>
<td>5.56 (1.31)</td>
<td>5.59 (1.27)</td>
<td>6.10 (0.74)</td>
<td>5.73 (1.15)</td>
</tr>
<tr>
<td>Well/Good</td>
<td>5.56 (1.30)</td>
<td>5.48 (1.42)</td>
<td>5.98 (0.85)</td>
<td>5.87 (0.86)</td>
</tr>
<tr>
<td>Angry</td>
<td>0.50 (0.86)</td>
<td>0.46 (0.59)</td>
<td>0.79 (1.12)</td>
<td>0.65 (0.94)</td>
</tr>
<tr>
<td>Irritable</td>
<td>0.78 (1.29)</td>
<td>0.96 (1.06)</td>
<td>1.63 (1.82)</td>
<td>1.05 (1.08)</td>
</tr>
<tr>
<td>Sad</td>
<td>1.07 (1.36)</td>
<td>0.84 (1.06)</td>
<td>0.84 (1.14)</td>
<td>0.86 (1.02)</td>
</tr>
<tr>
<td>Nervous</td>
<td>0.56 (1.38)</td>
<td>0.46 (0.93)</td>
<td>0.32 (0.46)</td>
<td>0.38 (0.45)</td>
</tr>
<tr>
<td>Tired</td>
<td>2.07 (1.4)</td>
<td>2.64 (1.63)</td>
<td>2.77 (1.29)</td>
<td>2.4 (2.03)</td>
</tr>
<tr>
<td>Frequency of intercourse per week</td>
<td>1.10 (0.80)</td>
<td>1.78 (1.72)</td>
<td>1.75 (1.78)</td>
<td>2.0 (2.0)</td>
</tr>
</tbody>
</table>

n = 7. Values are mean (SD) on a Likert-type scale (see Subjects and Methods).

References

Acknowledgments
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n = 7. Values are mean (SD) on a Likert-type scale (see Subjects and Methods).


