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

KIMBERLY T. BRILL, ARTHUR L. WELTMAN, ANGELA GENTILI, JAMES T. PATRIE, DAVID A. FRYBURG, JOHN B. HANKS, RANDALL J. URBAN, AND JOHANNES D. VELDHUIS

Departments of Internal Medicine (K.T.B., A.L.W., D.A.F., J.D.V.), Human Services (K.T.B., A.L.W.), Health Evaluation Sciences (J.T.P.), and Surgery (J.B.H.), General Clinical Research Center (K.T.B., A.L.W., J.T.P., J.D.V.), and Center for Biomathematical Technology (J.D.V.), University of Virginia, Charlottesville, Virginia 22908; Department of Geriatrics (A.G.), Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298; and Department of Internal Medicine (R.J.U.), Division of Endocrinology, University of Texas Medical Branch, Galveston, Texas 77555

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/daily); 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 = 363 (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 = 106 (13), T = 129 (13), and GHT = 153 (17) pmol/liter; P < 0.02], and both T and GHT elevated free T: [B = 12 (2.1), 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)

Healthy 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).

Although unproven, an emergent hypothesis is that improved 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, arthralgias, 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 hypogonadotrophic 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 cross-over intervention design comprising the single and combined administration of recombinant human (rh)GH sc (6.25 g/kgd) 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 yr) 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 preintervention prostate-specific antigen (PSA) and digital prostatic exam were normal. To determine gonadal status, morning serum total T concentrations and fasting plasma glucose) were unremarkable. A screening preintervention T repletion at nearly physiological doses. In the latter regard, few interventional studies in older individuals have implemented combined GH and T supplementation.

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**GCRC admissions.** After admission to the GCRC in the evening, subjects received a eucaloric standardized meal (12 kcal/kg) with a macronutrient composition of 55% carbohydrate, 15% protein, and 30% fat. A catheter was placed in a forearm vein at 1800 h. Subjects received the last sc injection (above) and replaced T or placebo patches at 1900 h. Beginning at 2000 h, blood samples were withdrawn every 10 min for 12 h for later analysis of GH and T. At 0800 h the next morning, serum was collected for later measurements of bone turnover markers including PTH, bone specific alkaline phosphate, and osteocalcin. A fasting timed urine specimen was obtained to measure urinary calcium and creatinine on each admission. 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 ng/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 4.4% 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 phosphate was measured by immunoradiometric assay using the Tandem-R-Ostase kit from Hybritech (San Diego, CA). CV for the latter assays were 4–10% (intraassay) 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 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 1× PCR buffer [Perkin-Elmer Corp., Norwalk, CT], 25 mM Tris-HCl, 50 mM KCl, 1.5 mM MgCl₂, 1.0 μM deoxy-NTP, forward and reverse primers (gene of interest, 10 pmol), glyceraldehyde-phosphodehydrogenase, 1.5 pmol) 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 determined and then used to determine the appropriate number of PCR amplification cycles in the RT-PCR analyses. Curves for IGF-I, AR, and myostatin 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).
dried, and [35S] incorporation was determined by quantitative autoradiography using a PhosphoImager 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, VA). All data were 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 of the duplicate samples measured as a unitless ratio (arbitrary units) of the duplicate samples measured to a housekeeping (glycerialdehyde-phosphodehydrogenase) gene measured. The arbitrary value for OD was then averaged of the duplicate samples measured as a unitless ratio (arbitrary units) of the duplicate samples measured.

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.

**Results**

### Subject characteristics

The mean age of the subjects was 68.1 ± 2.4 yr; height, 171.5 ± 2.4 cm; weight, 79.9 ± 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 GH; 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 \((n = 7; \text{three subjects did not complete the questionnaire})\). 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...
Longer interventional intervals of 3 or more months and/or higher doses of GH (14, 15, 17, 18) and T (20–26, 47) alone can decrease total body fat and increase lean body mass in older men (14, 15, 17, 18, 20–26, 47). A recent 6-month trial of combined GH and injected androgen revealed a significant decrease in sc but not visceral fat (48). The present data indicate that combining T and GH administration does not evidently achieve a reduction in total body fat within 1 month.

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 g/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 present analysis of a total of 30 patient-months of supplementation with T, GH, and GHT revealed no significant adverse events or drug-related dropout. This outcome may reflect the small cohort size and/or the dose of androgen (T, 5.0 mg transdermally) and GH (6.25 g/kg sc) selected here. In particular, no subject developed headache, peripheral edema, lethargy, joint swelling or pain, abdominal bloating, hypertension, arthralgia, carpal tunnel syndrome, gynecomastia, glucose intolerance, polycythemia, an HDL reduction, worsening of sleep apnea, a PSA elevation or prostate growth, all of which have been reported otherwise (23, 33, 35–39).

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. Interventional 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 average</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 average</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 average</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 average</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>% 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>
<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>BMI (kg/m²)</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>
</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) a</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) b</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 transcrotal 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 longer-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 hyposomatotropic 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-
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>Anxgy</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).

mented the effect of GH (Fig. 6). Thus, the present data do not exclude longer-term synergy. No treatment effect was observed for the AR gene at 1 month, although parenteral T repletion did alter this endpoint (28). Expression of the myostatin gene further determines skeletal muscle mass (28, 60). Because heightened myostatin levels are associated with muscle wasting (60), we did not predict a tendency for GH and T administration to elevate myostatin mRNA concentrations in thigh muscle (P = 0.09). An analogous response was reported in preliminary studies by Blackman et al. (61) and could indicate increased cellular turnover of this muscle protein.

It should be realized that in the present study a placebo patch and placebo injection condition was not implemented. Rather, all subjects completed B before administration of GH, T, or GHT. However, because the treatment was short (1 month), administered in random order, and the washout between treatment was relatively long (3 months), it is unlikely that either an order effect or a persistent anabolic effect of repeated treatment occurred.

In summary, a short-term, nonpharmacological dose of combined GH and T supplementation in older men elevates serum concentrations of GH, IGF-I, T, and E2, improves selected facets of physical performance, and increases muscle IGF-I gene expression without measurably changing body composition or muscle strength or inducing clinically adverse events. These preliminary outcomes suggest the utility of evaluating the impact and safety of longer-term, midphysiological bihormonal supplementation in older men.

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References


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