The Effects of Growth Hormone and/or Testosterone in Healthy Elderly Men: A Randomized Controlled Trial

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Context: Declines in GH and testosterone (Te) secretion may contribute to the detrimental aging changes of elderly men.

Objective: To assess the effects of near-physiological GH with/without Te administration on lean body mass, total body fat, midthigh muscle cross-section area, muscle strength, aerobic capacity, condition-specific quality of life (Age-Related Hormone Deficiency-Dependent Quality of Life questionnaire), and generic health status (36-Item Short-Form Health Survey) of older men.

Design, Settings, and Participants: A 6-month, randomized, double-blind, placebo-controlled trial was performed on 80 healthy, community-dwelling, older men (age, 65–80 yr).

Interventions: Participants were randomized to receive 1) placebo GH or placebo Te, 2) recombinant human GH (rhGH) and placebo Te (GH), 3) Te and placebo rhGH (Te), or 4) rhGH and Te (GHTe). GH doses were titrated over 8 wk to produce IGF-I levels in the upper half of the age-specific reference range. A fixed dose of Te (5 mg) was given by transdermal patches.

Results: Lean body mass increased with GHTe ($P = 0.008$) and GH ($P = 0.004$), compared with placebo. Total body fat decreased with GHTe only ($P = 0.02$). Midthigh muscle ($P = 0.006$) and aerobic capacity ($P < 0.001$) increased only after GHTe. Muscle strength changes were variable; one of six measures significantly increased with GHTe. Significant treatment group by time interactions indicated an improved Age-Related Hormone Deficiency-Dependent Quality of Life questionnaire score ($P = 0.007$) in the GH and GHTe groups. Bodily pain increased with GH alone, as determined by the Short-Form Health Survey ($P = 0.003$). There were no major adverse effects.

Conclusion: Coadministration of low dose GH with Te resulted in beneficial changes being observed more often than with either GH or Te alone. (*J Clin Endocrinol Metab* **91: 477–484, 2006**)

INCREASES IN POPULATION life expectancy bring additional years of disability (1). Sarcopenia, due to age-associated decreases in skeletal muscle mass and strength (2, 3), is associated with impaired mobility, falls, fractures, and higher mortality rates (4, 5). Aging-associated increases in proportional total body and intraabdominal visceral fat (VF) are risk factors for cardiovascular morbidity and mortality (6, 7). These detrimental aging changes are a challenge to individuals and health care providers.

Age-associated sarcopenia is multifactorial. Hormonal decline may be a factor. GH secretion falls during adulthood; more than 30% of elderly people have circulating IGF-I levels below the young-normal range (8). Testosterone (Te) levels also decline progressively; average levels are 30% lower by age 70 yr (9). In young adults, a deficiency of either GH or Te produces changes similar to the aging phenotype, which reverse after GH and/or Te replacement (10, 11). Thus, aging-associated declines in GH or Te secretion may contribute to detrimental aspects of aging (12, 13).

Several intervention trials have shown that although either GH or Te individually can have anabolic effects in older adults, this may not always translate into functional improvements (13–17). Older people are more sensitive to GH, side effects have been related to circulating IGF-I levels (18), and most GH studies have been hampered by side effects associated with high doses, not tailored to individual responsiveness (19).

There is evidence for synergistic anabolic action between GH and Te (20). mRNA for IGF-I increases after administration of Te to healthy elderly men and decreases in healthy young men after they become hypogonadal (21). This suggests that combining GH and Te may have clinical utility, and indeed, since we embarked on this study, several investigations of this therapeutic approach have been reported (22, 23). We hypothesized that by selecting healthy men with relatively low circulating IGF-I and Te levels and individually tailoring low-dose GH replacement, this combined approach might reverse some of the aging-associated changes without significant adverse effects.

Subjects and Methods

Subjects

Participants were volunteer, healthy, community-dwelling, elderly men (65–80 yr) without significant mobility difficulties or disability, recruited through newspaper articles. The selection and retention of

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participants in the study are illustrated in Fig. 1. Exclusion criteria were clinically significant pulmonary, cardiac, hepatic, renal, neurological, or psychiatric disease; uncontrolled hypertension or diabetes; past or present pituitary disease; receiving corticosteroid treatment; obesity [body mass index (BMI), >30 kg/m^2]; currently evident malignancy; any history of prostate cancer; elevated age-specific level of prostate-specific antigen (PSA; >4.5 ng/ml); or palpable prostate nodule. From volunteers meeting these criteria and whose circulating IGF-I levels were lower than the 50th percentile for the local age-specific reference range [roughly 2 SD below the mean for young adults 30–40 yr (145 ng/ml; 19.0 nmol/ml)], we selected 80 participants with the lowest Te levels, but excluded those with frank Te deficiency (<173 ng/dl; 6.0 nmol/liter). The mean screening Te level of our study participants was 397.6 ± 10 ng/dl. The research ethics committee of Guy's and St. Thomas' Hospitals approved the protocol. Participants provided written informed consent.

Study protocol

The study was a double-blind, randomized, placebo-controlled trial. At baseline (visit 0) participants gave fasting blood samples for routine full blood count, liver function tests, urea and electrolytes, IGF-I, IGF-binding proteins 1 and 3 (IGFBP-1 and IGFBP-3), Te, estradiol, LH, FSH, TSH, SHBG, PSA, glucose, insulin, and C peptide. Participants then had their aerobic capacity (VO$_2$max) and body composition measured, and after a lunch break of about 2 h, their muscle strength measured as described below.

At visit 1 (treatment wk 0), participants were trained to self-administer their treatment, which commenced that day and continued daily for 6 months. We used a dose titration regimen for the administration of GH to minimize possible adverse effects. Consequently, subjects had a regular follow-up on wk 2 (visit 2), wk 4 (visit 3), wk 6 (visit 4), and wk 8 (visit 5) at which time their IGF-I levels were measured, and the GH dose was adjusted according to our predefined protocol (see below). Two more visits were conducted at 3 months (visit 6) and at the end of the study at 6 months (visit 7). At all follow-up visits, subjects were assessed for possible side effects, and blood pressure and percent body fat were measured. All baseline measurements were repeated again at the end of the study at 6 months (visit 7).

Te (5 mg) or placebo was given by transdermal patches (Watson Laboratories, Inc., Salt Lake City, UT). Active recombinant human GH (rhGH) or placebo (Norditropin Simplex, Novo Nordisk, Copenhagen, Denmark) was given by sc injection at bedtime. Treatment group allocation was determined by randomization into four groups to receive 1) placebo rhGH injections and placebo Te patches (group Pl; n = 20), 2) rhGH injections and placebo Te (group GH; n = 18), 3) Te and placebo rhGH injections (group Te; n = 23), or 4), rhGH and Te (group GHTe; n = 19). Randomization using computer-generated preallocated study numbers was performed by a dispensing pharmacist who was not otherwise involved in the study.
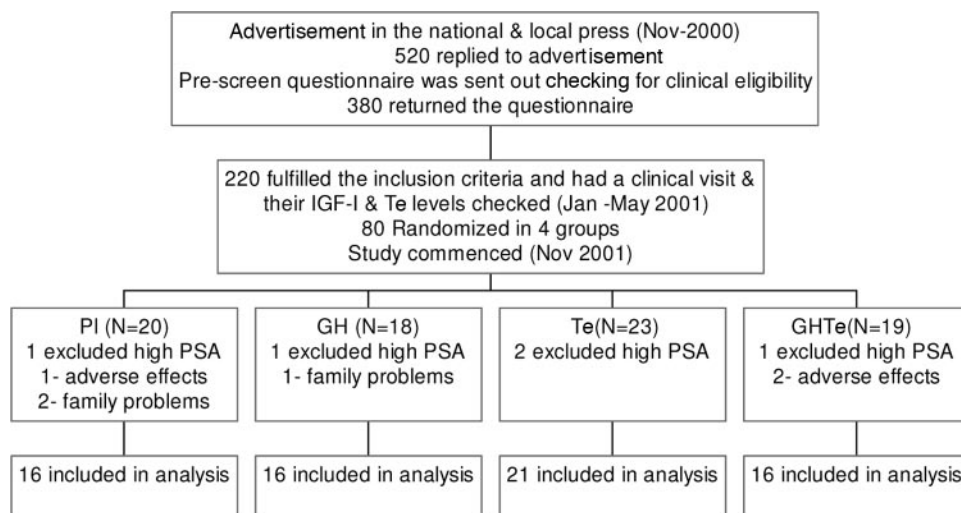
Titration of rhGH doses

The active or placebo rhGH starting dose was 0.1 mg/d. Incremental dose adjustments to 0.2, 0.4, 0.8, and a maximum of 1.2 mg/d were made at the 2-weekly (visits 2–5), according to participants' circulating IGF-I levels and a predefined protocol; the target range was 141–252 ng/ml, equivalent to the upper half of the age-specific reference range or close to the mean for young adults 30–40 yr old. Doses producing IGF-I levels just above target were left unaltered if well tolerated. Doses were reduced if the participant reported probable side effects, or if the IGF-I level was above 380 ng/ml (equivalent to the 75th percentile of the young adult range; conversion: nanograms per milliliter to nanomoles per liter, multiply by 0.131).

Blindness of the treatment

Every reasonable attempt was made to ensure true double-blind conditions throughout. Adjustment of GH and placebo doses were made by our endocrine nurse specialist (ENS), who checked the IGF-I levels of the subjects at each visit, and she adjusted the dose of GH according to a predefined protocol. She was blinded to the treatments and, indeed, increased the placebo dose when IGF-I values failed to rise, but did not exceed a predefined upper dose limit. She also reduced the GH or placebo dose when possible adverse effects were reported. When any additional specialized advice was needed, she consulted a second doctor who was not involved in the study. Placebo rhGH vials and placebo Te patches were indistinguishable from the active treatment and were provided by the same manufacturer. To secure and maintain blindness, treatment drugs were dispensed for each subject in identical packages by the Department of Pharmacy. Subjects picked up their supplies after each study visit in a quantity sufficient to last until their next visit. The medical doctor responsible for the outcome measurements at baseline and at the 6-month visit (M.G.G.) was not involved in this part of the study and was blind to treatment groups throughout.

Assessment of adverse events and treatment side effects

At visits 2–7, participants completed a questionnaire delivered by the ENS, recording all possible adverse events and likely treatment side effects based on previous studies. An independent endocrinologist with access to IGF-I levels and questionnaires, but not otherwise involved with the study, agreed on dose amendments or withdrawal from the study with the ENS. PSA and hemoglobin measurements were repeated after 3 (visit 6) and 6 months (visit 7).

Assays

IGF-I was measured by a two-site chemiluminescence immunoassay on a Advantage analyzer (Nichols Institute, San Juan Capistrano, CA)

FIG. 1. Selection and retention of participants in the study.

and IGFBP-3 by a commercial DSL 6600 ACTIVE IGFBP-3 (immunora-diometric assay) coated tube assay kit. The intraassay coefficient of variation (CV) was less than 5.2% for IGF-I and less than 3.9% for IGFBP-3. The interassay CVs were less than 7.4% and 1.9% for IGF-I and IGFBP-3, respectively. Total Te, estradiol, FSH, LH, TSH, free T_4, free T_3, and PSA were all measured on the ADVIA Centaur analyzer (Bayer, Tarrytown, NY). The intraassay CV for Te was 5.2%, and that for estradiol was 12.1%; the interassay CVs were 6.0% and 6.1%, respectively. SHBG was measured by an immunometric assay on an Immulite ana-lyzer (Diagnostic Products Corp., Los Angeles, CA). Free Te (FTe) was calculated from the formula: FTe (pmol/liter) = 6.11 − [2.38 × log (SHBG nmol/liter)] × Te (nmol/liter) result × 10. Glucose was mea-sured by an oxygen rate method employing an oxygen electrode (Beck-man Coulter, Fullerton, CA). The intraassay CVs ranged from 1.2–6.1%.

Outcome measures

Body composition. Weight was measured using a Tanita (Arlington Heights, IL) electronic scale, height by a standing stadiometer, and waist/hip ratios were calculated from the mean of three tape measure-ments. Total body fat (FBM), lean body mass (LBM), and percent body fat were calculated from dual-energy x-ray absorptiometry scans (QDR-4500W scanner, Hologic, Inc., Waltham, MA) (24). Midthigh muscle cross-sectional area (CSA), cross-sectional abdominal VF, and sc fat (SC) were measured by computed tomography (Philips-Tomoscan AV, Phil-ips Electronic Instruments, Mahway, NJ). One-slice scans in the middle abdomen through the L4/L5 disc space and in the thigh midway be-tween the anterior superior iliac spine to the superior border of the patella were performed (24).

Cardio-respiratory fitness (VO_2max). VO_2max was measured using a step-wise maximal exercise test on an electromagnetically braked bicycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) using a computerized open-loop gas analyzer system (Medical Graphics Corp., St. Paul, MN), as described (25). The peak VO_2max was recorded with participants exercising to exhaustion.

Muscle strength. Strength was measured isokinetically (concentric knee flexion/extension at angular velocities of 60, 90, and 180°/sec) using a Kin-Com model 125E (Chattecx, Chattanooga, TN) isokinetic dynamom-eter. Peak torque was calculated using Kin-Com computer software. In addition, the isometric peak force values were obtained for the knee extensors at an angle of 90° and hand grip. The best of the three maximal efforts was used as the peak force.

Patient-reported outcomes. Patient-reported outcomes were assessed with the specially developed condition-specific Age-Related Hormone Defi-ciency-Dependent Quality of Life questionnaire (A-RHDQoL) (26), the generic health-status measure Short-Form 36 (SF-36) (27), and the ge-neric Well-Being Questionnaire (W-BQ12) (28), and sexual dysfunction was measured by the Arizona Sexual Experience questionnaire (29).

Statistical analyses

Power calculations indicated that group sizes of 19 and 13 would be needed to detect mean differences over 6 months of 2.5% in LBM and 20% in muscle strength, respectively (α = 0.05; β = 0.90). Baseline differences between groups were analyzed by one-way ANOVA, em-ploying the Bonferroni correction. Differences between treatment groups in changes of outcome measures after 6 months of treatment

were analyzed by analysis of covariance (ANCOVA) adjusting for the value of the dependent variable at baseline and age. Each treatment group was compared with placebo and with each other. Differences in final rhGH doses were assessed by Mann-Whitney *U* test. Linear re-gression analysis assessed relationships between variables. $P < 0.05$ was considered significant after a Bonferroni correction. Results are ex-pressed as the mean ± SEM. These data were analyzed using the Stata 6.0 computer program (Stata Corp., College Station, TX).

A mixed model, repeated measures ANOVA was conducted on each of the following: A-RHDQoL average weighted impact score, the SF-36 (eight subscales), W-BQ12 (three subscales), and the Arizona Sexual Experience questionnaire total score, both with and without covariates: BMI, Te, and IGF-I levels (at baseline and end point) and age. Planned orthogonal contrasts were conducted: 1) placebo *vs.* the three treatment groups, 2) GHTe *vs.* GH and Te groups, and 3) GH *vs.* Te group. These analyses were performed using SPSS for Windows, release 9.0 (SPSS, Inc., Chicago, IL).

Results

There were no differences between groups in baseline body composition, hormonal, or clinical measures (Table 1). We intended an intention to treat approach to statistical analysis, including all available data from all participants. Eleven participants did not complete the study. Five were excluded soon after commencement because their baseline visit PSA levels met the revised exclusion criterion (above the revised local age-specific reference range of 4.5 ng/ml). They had been initially included when at screening their PSA levels were below the age-specific upper normal limit of 6 ng/ml, the criterion initially adopted, but subsequently re-vised down to the more cautious lower level. Three were withdrawn because of adverse events, and three withdrew themselves for personal reasons. Outcome data were not available for these six participants. Thus, analysis of the remaining 69 participants is both an intention to treat and a per-protocol analysis (Pl, n = 16; GH, n = 16; Te, n = 21; GHTe, n = 16; Fig. 1). The significant changes reported for hormone profile, body composition, muscle strength, and VO_2max represent changes for each treatment group from baseline compared with changes in the placebo group.

Hormone profile

IGF-I levels increased significantly from 102.9 ± 6.4 to 193.4 ± 10.6 ng/ml in the GH group ($P < 0.0001$) and from 102.4 ± 6.8 to 209.5 ± 15 ng/ml in the GHTe group ($P < 0.0001$), reaching the target IGF-I levels with similar final rhGH doses (GH, 0.54 ± 0.06 mg/d: GHTe, 0.52 ± 0.06 mg/d; $P = 0.80$; Fig. 2A). IGFBP-3 also increased from 3297.2 ± 128.8 to 3688.3 ± 174.5 ng/ml ($P < 0.0001$) and from 3482.8 ± 175.1 to 3941.9 ± 186.6 ng/ml in both GH and GHTe groups,

TABLE 1. Baseline characteristics of the participants

	Pl (n = 20)	GH (n = 18)	Te (n = 23)	GHTe (n = 19)	All (n = 80)	P
Age (yr)	69.5 (0.7)	70.7 (0.7)	70.3 (0.6)	70.3 (0.6)	70.2 (0.3)	0.81
Weight (kg)	81.2 (9.3)	76.9 (9.3)	79.3 (11)	80.8 (11)	79.7 (1.1)	0.52
BMI (kg/m²)	26.7 (0.5)	25.6 (0.6)	26.9 (0.7)	26.2 (0.7)	26.5 (0.3)	0.53
IGF-I (ng/ml)	100.7 (6.1)	102.2 (5.3)	109.1 (6.2)	102.4 (6.7)	103.8 (3.0)	0.77
IGFBP-3 (ng/ml)	3114 (221)	3297 (128)	3272 (155)	3482 (175)	3268 (84)	0.73
Te (ng/dl)	432 (31)	487 (39)	498 (36)	495 (41)	478 (18)	0.54
FTe (pg/ml)	107 (7.9)	115 (8.3)	115 (6.8)	123 (11.2)	114 (4)	0.38

All values are presented as mean (SE). The *P* value is for the overall comparison between groups. To convert Te to nmol/liter, multiply values by 0.0347. To convert IGF-I to nmol/liter, multiply values by 0.131. To convert FTe to pmol/liter, multiply values by 3.47. Pl, Placebo.
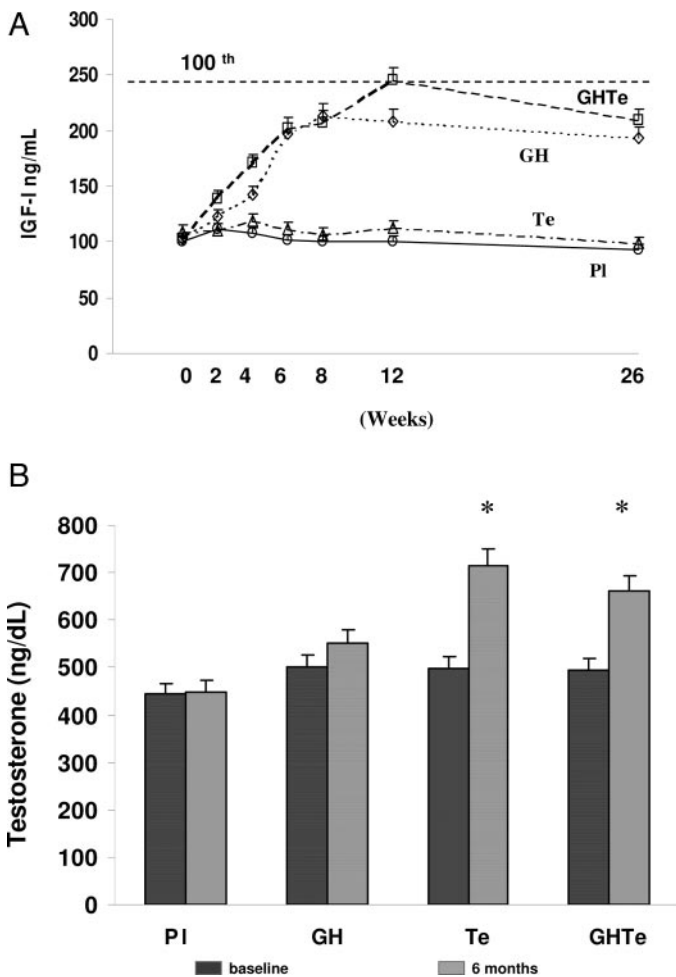
FIG. 2. A, The effects of placebo (Pl), GH, Te, and combined GH and Te on IGF-I levels during the study. B, The effects of placebo, GH, Te, and combined GH and Te on Te levels from 0–6 months (■, 0 months; ▨, 6 months). *, $P < 0.05$.

respectively. Mean Te levels increased from 498.5 ± 34.5 to 714.6 ± 95.1 ng/dl in the Te group ($P = 0.029$) and from 495.6 ± 37.4 to 659.9 ± 80.6 ng/dl in the GHTe group ($P = 0.05$; Fig. 2B). FTe levels increased significantly only in the Te group ($P = 0.019$). No changes in Te or FTe occurred in the Pl or GH groups or in estradiol levels in any group. LH and FSH were suppressed in the Te and GHTe groups ($P < 0.003$).

Outcome measures

Body composition. Compared with placebo, no significant changes in BMI or waist/hip ratio were noted in any group, but LBM increased by 2.0 ± 0.5 kg in the GH group ($P = 0.004$) and by 1.8 ± 0.5 kg in the GHTe group ($P = 0.007$; Fig. 3A). *Post hoc* analysis revealed that the mean increase in the GHTe group was significantly greater than that in the Te group ($P = 0.031$), but not to that in the GH group. FBM decreased significantly by 1.8 ± 0.4 kg ($P = 0.02$) with GHTe, but not with GH (1.4 ± 0.5 kg; $P = 0.09$) or Te alone ($P = 0.86$; Fig. 3B). Statistically insignificant decreases in SC and VF were observed in the GH and GHTe groups (data not shown). A significant increase in midthigh muscle CSA occurred only with GHTe ($7.0 \pm 3.0\%$; $P = 0.006$; Fig. 3C).

Muscle strength. Of all measures, the only significant change in strength was an increase in concentric knee flexion at 120°/sec in the GHTe group ($P = 0.038$). Otherwise, all groups had nonsignificant reductions in muscle strength over 6 months of about 5–10% for extension and somewhat less for flexion (Table 2).

VO₂max. VO₂max increased, compared with that in the placebo group, in the GHTe group from 24 ± 0.9 to 29.5 ± 1.2 ml/kg·min ($P < 0.001$; Fig. 3D). The VO₂max failed to increase significantly after GH from 25.8 ± 0.9 to 27.1 ± 1.1 and Te from 23.6 ± 1 to 24.4 ± 1 ml/kg·min. The *post hoc* analysis indicted that the mean increase in VO₂max in the GHTe group was significantly greater that that in the Te ($P = 0.001$) or GH ($P = 0.008$) group.

Patient-reported outcomes. A significant group-by-time effect was found for the A-RHDQoL average weighted impact score [$F(3,63) = 4.39$; $P = 0.007$; analysis without covariates], with planned contrasts showing that 1) placebo differed from the three treatment groups [$t(63) = -2.08$; $P = 0.04$]; 2) GHTe did not differ significantly from the GH or Te group; and 3) GH differed from the Te group [$t(63) = 2.17$; $P = 0.03$]. The Te group reported a worsening of the negative impact of age-related hormone deficiency on quality of life at the end point, but the GH and GHTe groups showed an improvement (Table 3). The overall group by time interaction was considerably reduced by the introduction of covariates, but was still significant ($P = 0.038$). A significant group by time effect was also found for SF-36 bodily pain [$F(3,59) = 5.27$; $P = 0.003$; significance unaffected by covariates]; planned contrasts showed that GH differed from Te [$t(59) = -3.43$; $P = 0.001$], because bodily pain worsened considerably in the GH-only group by the end point, but improved slightly in the Te and GHTe groups. There were no other significant group by time effects on patient-reported outcomes.

Adverse events

Fifteen of 36 (41%) participants receiving rhGH experienced adverse events probably related to rhGH. One withdrew with carpal tunnel syndrome (GHTe group). Other symptoms were mild and resolved within a few days of rhGH dose reduction. Of 39 participants receiving Te, almost 30% experienced skin irritation; one withdrew (GHTe group). One placebo-treated participant withdrew due to insomnia. There was no increase in the prevalence of impaired glucose tolerance (fasting glucose, >6.1 nmol/liter). No participant developed diabetes. PSA did not increase during the study. No participant developed polycythemia.

Relationship between hormonal changes and outcome measures

At baseline, a negative correlation was found between VF area and Te levels ($r = -0.23$; $P = 0.033$), but no significant correlations were found between Te or IGF-I levels and any other baseline measures. At the end point, changes in IGF-I correlated positively with changes in LBM ($r = 0.53$; $P < 0.001$) and VO₂max ($r = 0.44$; $P < 0.001$) and negatively with changes in total fat mass ($r = -0.34$; $P = 0.003$). No correlation was found between changes in VO₂max and LBM.
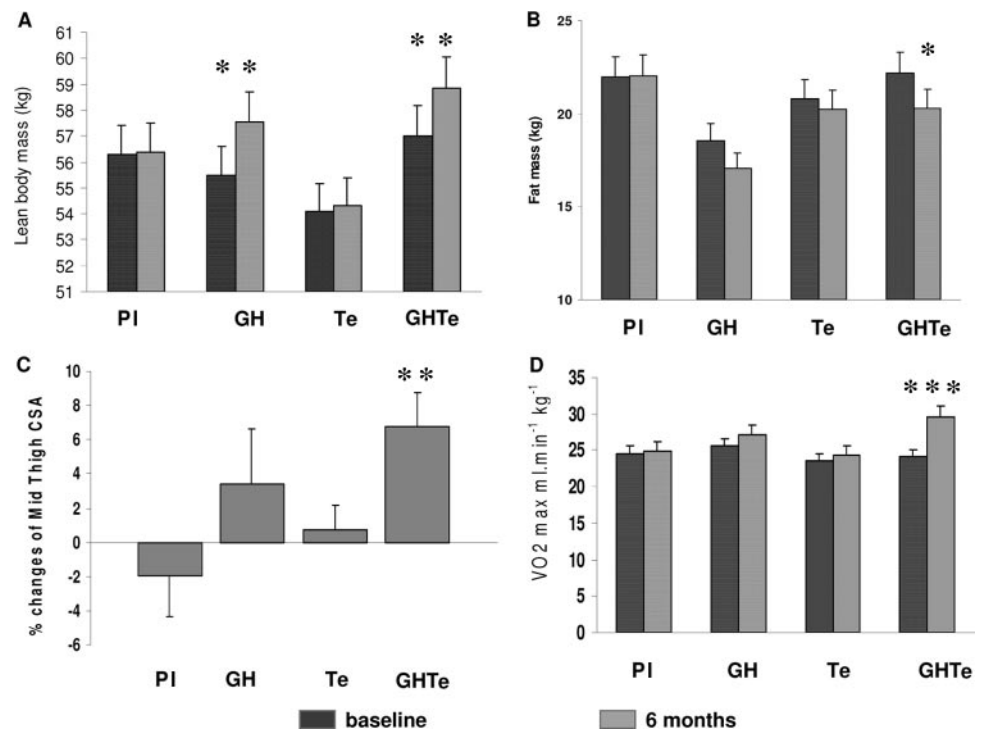
FIG. 3. The effects of placebo, GH, Te, and combined GH and Te on LBM (A), fat mass (B), percent change from 0 to 6 months in the midthigh CSA (C), and VO$_2$max (D). In A, B, and D: ■, baseline; ▨, 6 months. *, $P < 0.02$; **, $P < 0.01$; ***$P < 0.001$.

Discussion

The results show that 6-month administration of rhGH and Te, in contrast to either given alone, has beneficial effects on body composition and cardio-respiratory fitness for healthy elderly men selected for age-relative low IGF-I and Te levels. Furthermore, this is the first double-blind, placebo-controlled trial to show that such effects can be produced by individually adjusted, physiological supplementation of GH with Te. We selected volunteers with relatively low age-specific IGF-I levels and successfully increased these to the upper half of the age-specific reference range using a novel dose titration regimen rather than a weight-based regimen for rhGH administration. There were two reasons for this: firstly, to avoid short-term side effects, and secondly, to assess the effectiveness of a near-physiological rhGH replacement dose. This approach produced fewer side effects than previous studies using traditional weight-based rhGH regimens (13).

LBM increased similarly in both GH and GHTe groups. The 28% greater total fat mass decrease with GHTe than GH alone suggests synergy between GH and Te. These effects resemble those of rhGH given alone at higher doses (13, 14) or combined with Te (22, 23), the smaller body compositional changes being consistent with lower rhGH doses and the titration period reducing the total exposure to target rhGH doses.

The absence of significant LBM or fat changes on Te alone differs from previous studies of elderly or hypogonadal men (16, 17, 30). Te levels achieved in our study compare to Te levels reported in similar studies in which Te was administered in the form of weekly im injections (11, 21). In both of these studies, significant changes in LBM have been reported. The anabolic effect of Te on LBM has been shown recently in a series of studies to be highly dose and Te

concentration dependent (31). A lower weekly concentration of administered Te achieved with transdermal patches, compared with the spikes and troughs seen with weekly injections of Te, could explain this discrepancy. In addition, higher baseline Te values or shorter duration may have contributed. Convenience regarding the administration of the treatment and a more physiological sex hormone profile associated with administration by patches influenced our choice of patches instead of im Te in this study.

Midthigh muscle CSA increased most (7%) in the GHTe group. Skeletal muscle mass increased in GH-deficient (GHD) adults given rhGH (32) and in hypogonadal men given Te (30), but this study is the first to show this effect with computed tomography scanning in healthy elderly men.

As expected in ageing men, we observed small decreases in muscle strength over time. Previous studies of healthy elderly men given GH or Te have demonstrated insignificant or marginal increases (14, 16, 22, 33, 34), and demonstrable strength increases in treated adult GHD patients take up to 12–24 months (35). It has been argued that differences in the methods employed to measure isokinetic muscle strength may well explain the contradictory results of similar studies (36). Indeed, when isokinetic muscle strength was measured by one repetition maximum exercise, an increase in muscle strength was noticed in hypogonadal men (11) and in healthy elderly men after Te and GH plus Te administration (17, 21, 22). Conversely, when muscle strength was measured using an open kinematic chain exercise dynamometer, muscle strength failed to increase (16, 30). In our study, muscle strength was measured with an open kinematic chain exercise dynamometer (Kin-Com); thus, the single finding of significantly increased knee flexion strength with the more potent GH and Te combination after a shorter treatment duration is an important positive finding.

TABLE 2. Effects of treatment on muscle strength

Peak torque (Nm)	Pl (n = 16)	GH (n = 16)	Te (n = 21)	GHTe (n = 16)
Knee extension at 60°·sec^{-1}				
Baseline	116.8 (8.1)	121.8 (8)	115.6 (4.7)	134 (6)
End	107 (6)	111.7 (9.2)	107.2 (4.9)	127.3 (5.9)
Change	−9.81	−10.07	−8.45 (4.2)	−6.7 (5.1)
P value		0.84	0.80	0.19
Knee extension at 90°·sec^{-1}				
Baseline	104.1 (7.5)	114.8 (8.5)	108.5 (4.9)	123.8 (8)
End	94.8 (4.5)	101.6 (8.2)	99.8 (5)	116.8 (4.4)
Change	−9.25 (4.1)	−13.2 (6.6)	−9.1 (4.6)	−7 (4.9)
P value		0.82	0.6	0.05
Knee extension at 120°·sec^{-1}				
Baseline	98.6 (6.5)	107.6 (7.2)	97.7 (4.6)	108.5 (4.5)
End	89.6 (4.1)	98.8 (7.8)	92.2 (4.4)	102.9 (4.3)
Change	−9.06 (4.2)	−8.7 (5.2)	−5.4 (4.4)	−5.5 (4.5)
P value		0.44	0.43	0.12
Knee flexion at 60°·sec^{-1}				
Baseline	67.6 (6.04)	74.9 (3.8)	68.05 (3.1)	77.3 (4.3)
End	66.8 (6.1)	72.5 (5.7)	63.8 (2.8)	76.2 (5.9)
Change	−0.8 (3.8)	−2.3 (3.4)	−4.2 (2.4)	−1 (4.05)
P value		0.97	0.53	0.69
Knee flexion at 90°·sec^{-1}				
Baseline	68.5 (6.2)	78.5 (4.3)	69.2 (3.3)	81.4 (4.3)
End	70.4 (5.1)	74 (5.2)	62.4 (3.2)	82 (5.2)
Change	1.9 (3.3)	−4.5 (2.6)	−6.08 (2.4)	0.5 (4)
P value		0.39	0.05	0.63
Knee flexion at 120°·sec^{-1}				
Baseline	73.8 (6.8)	80.7 (4.9)	73.09 (3.3)	80.8 (3.9)
End	70.6 (4.9)	76.1 (4.8)	66.6 (2.8)	84.8 (5.4)
Change	−3.1 (4.7)	−4.5 (2.3)	−6.4 (2.9)	4.06 (3.6)
P value		0.82	0.44	0.03
Isometric knee (N)				
Baseline	418.6 (27.1)	448.1 (33.4)	433.1 (16.8)	483 (20.5)
End	408.2 (23.6)	442.2 (35.8)	427.5 (24.6)	476 (22.5)
Change	10.4 (17.6)	5.9 (24.5)	5.6 (22.2)	6.6 (19.4)
P value		0.59	0.58	0.33
Hand grip				
Baseline	37.4 (1.6)	37.4 (1.7)	34.6 (1.1)	38.1 (2.1)
End	36.7 (1.6)	37.3 (1.8)	35.3 (1.1)	38.1 (2)
Change		−0.08 (0.5)	0.6 (0.7)	−0.03 (0.8)
P value		0.92	0.13	0.92

n, Number of participants who completed 6 months; Nm, newton meter; N, newton. All values are presented as mean (SE). P values represent changes in each treatment group when compared to placebo (Pl).

Improved cardiovascular fitness (VO$_2$max), observed only in the GHTe group, accords with the findings of a similar study (22). Increased muscle mass probably contributed to this. The smaller LBM and CSA increases with GH alone were not associated with significant strength or fitness gains, but this may also have been due to the relatively short treatment period. Discordance of muscle mass, strength, and fitness gains has also been noted in treated adult GHD patients (33, 37). Increased fiber size was associated with gains in submaximal aerobic capacity and improved walking ability, but not strength (38). Different physiological roles of fiber types may be a factor; in untreated GHD adults, correlations existed between proportional total type I fiber CSA and VO$_2$max and between proportional total type II fiber CSA and strength (39). Thus, differing treatment effects on fiber types may explain some of these findings.

Aging is associated with a progressive decline of physical activity and VO$_2$max (37). Although exercise can increase both muscle mass and strength in elderly people, the dropout rate from exercise programs is high. The therapeutic achievement of increased VO$_2$max is a very important result. In suitable elderly subjects, it may be possible to ameliorate the ageing/disuse muscle strength decline by restoring exercise capacity.

Although one participant withdrew from the study because of carpal tunnel syndrome, other rhGH side effects were minor and reversed within days of dose reduction. None of the rhGH-treated participants developed impaired glucose tolerance or diabetes, in contrast with the high incidence of diabetes reported in a similar study using higher doses of rhGH (22). Lower rhGH doses might improve insulin sensitivity by dissolving VF without first going through a phase of insulin resistance (40). PSA and hemoglobin remained unchanged in Te-treated individuals.

Most patient-reported outcomes showed no significant change, although caution is prudent when interpreting results from small samples. Although those in the Te group reported a worsening negative impact of age-related hormone deficiency on quality of life over time, both GH groups indicated improvements despite increased bodily pain in the GH-only group.

The main limitation of this study was its short duration,

TABLE 3. Patient-reported outcomes [raw cell means (SD)]

	Pl		GH		Te		GHTe	
	Baseline	End	Baseline	End	Baseline	End	Baseline	End
A-RHDQoL								
AWI	−3.0 (1.5)	−2.2 (1.8)	−3.0 (1.8)	−2.6 (1.5)	−2.7 (1.4)	−3.1 (2.1)	−2.2 (1.1)	−1.6 (1.0)
SF-36								
Bodily pain	76.5 (19.2)	71.9 (21.1)	84.2 (18.2)	64.5 (24.7)	75.2 (20.1)	77.5 (22.1)	80.1 (20.4)	82.3 (21.6)
General health	66.3 (14.5)	68.9 (13.4)	77.6 (11.5)	77.6 (11.3)	72.5 (15.1)	68.3 (24.0)	75.8 (10.5)	77.6 (15.0)
Mental health	76.3 (15.6)	78.9 (14.4)	83.9 (13.9)	85.1 (11.9)	79.6 (14.9)	81.5 (13.5)	81.7 (13.4)	80.8 (13.9)
Physical functioning	76.7 (20.7)	74.3 (15.1)	83.3 (13.1)	81.7 (12.9)	76.7 (19.6)	73.3 (24.6)	83.8 (13.7)	81.0 (16.2)
Role-emotional	82.2 (33.0)	82.2 (27.8)	91.1 (19.8)	88.9 (20.6)	91.2 (18.7)	93.0 (17.8)	91.1 (19.8)	91.1 (19.8)
Role-physical	70.0 (36.8)	78.3 (31.1)	60.0 (44.1)	68.3 (44.8)	73.8 (33.0)	81.0 (30.5)	70.0 (30.2)	86.7 (26.5)
Social functioning	88.4 (18.7)	91.1 (11.4)	88.3 (17.3)	86.7 (16.0)	84.5 (24.3)	85.7 (25.4)	87.5 (14.2)	88.3 (19.7)
Vitality	54.3 (15.2)	51.3 (15.1)	69.0 (15.4)	68.3 (13.7)	63.6 (14.2)	63.8 (16.8)	63.3 (13.3)	64.0 (15.1)
W-BQ12								
Negative well-being	1.4 (1.6)	1.1 (1.5)	0.7 (1.3)	0.9 (1.3)	1.0 (1.2)	1.2 (1.8)	1.0 (1.3)	0.9 (1.2)
Energy	6.6 (1.5)	7.0 (1.7)	8.5 (1.6)	8.5 (1.7)	7.5 (2.2)	7.3 (2.7)	7.9 (1.5)	7.6 (2.0)
Positive well-being	7.5 (2.5)	7.9 (2.2)	8.6 (2.3)	8.7 (2.6)	7.7 (3.4)	7.6 (3.8)	9.1 (2.1)	8.0 (2.7)
ASEX								
ASEX score	19.4 (3.7)	19.6 (3.9)	19.5 (5.7)	19.0 (5.1)	18.7 (5.3)	18.5 (5.9)	18.1 (4.4)	18.7 (5.3)

Maximum score range: A-RHDQoL average weighted impact score (AWI): −9 to +9 (maximum negative to maximum positive perceived impact of age-related hormone deficiency on QoL). SF-36 subscales: 0–100 (poor to good health status). W-BQ12: subscale range 0–12 (higher scores indicating increased mood of the subscale label). ASEX score: 5–30, higher score indicating more sexual dysfunction.

because studies in adults with GHD suggest that the benefits of GH replacement accrue over a number of years. Neither rhGH nor Te yet has an established clinical role in older men without frank deficiency, but our study suggests that combining an individually tailored physiological low-dose GH administration with a standard Te dose may be feasible, safe, effective, and clinically useful. Additional longer-term trials with the power to define surrogate end points of frailty, such as falls or dependency, are needed. The maintenance of true double-blind conditions in a study such as this is always difficult, but we believe that the steps we took to maintain such conditions were successful.

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