Growth Hormone and Sex Steroid Administration in Healthy Aged Women and Men

A Randomized Controlled Trial

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Context Hormone administration to elderly individuals can increase lean body mass (LBM) and decrease fat, but interactive effects of growth hormone (GH) and sex steroids and their influence on strength and endurance are unknown.

Objective To evaluate the effects of recombinant human GH and/or sex steroids on body composition, strength, endurance, and adverse outcomes in aged persons.

Design, Setting, and Participants A 26-week randomized, double-blind, placebo-controlled parallel-group trial in healthy, ambulatory, community-dwelling US women (n=57) and men (n=74) aged 65 to 88 years recruited between June 1992 and July 1998.

Interventions Participants were randomized to receive GH (starting dose, 30 µg/kg, reduced to 20 µg/kg, subcutaneously 3 times/wk) + sex steroids (women: transdermal estradiol, 100 µg/d, plus oral medroxyprogesterone acetate, 10 mg/d, during the last 10 days of each 28-day cycle [HRT]; men: testosterone enanthate, biweekly intramuscular injections of 100 mg) (n=35); GH + placebo sex steroid (n=30); sex steroid + placebo GH (n=35); or placebo GH + placebo sex steroid (n=31) in a 2×2 factorial design.

Main Outcome Measures Lean body mass, fat mass, muscle strength, maximum oxygen uptake ($\dot{V}O_2$max) during treadmill test, and adverse effects.

Results In women, LBM increased by 0.4 kg with placebo, 1.2 kg with HRT (P=.09), 1.0 kg with GH (P=.001), and 2.1 kg with GH+HRT (P<.001). Fat mass decreased significantly in the GH and GH+HRT groups. In men, LBM increased by 0.1 kg with placebo, 1.4 kg with testosterone (P=.06), 3.1 kg with GH (P<.001), and 4.3 kg with GH+testosterone (P<.001). Fat mass decreased significantly with GH and GH+testosterone. Women's strength decreased in the placebo group and increased nonsignificantly with HRT (P=.09), GH (P=.29), and GH+HRT (P=.14). Men's strength also did not increase significantly except for a marginally significant increase of 13.5 kg with GH+testosterone (P=.05). Women's $\dot{V}O_2$max declined by 0.4 mL/min/kg in the placebo and HRT groups but increased with GH (P=.07) and GH+HRT (P=.06). Men's $\dot{V}O_2$max declined by 1.2 mL/min/kg with placebo and by 0.4 mL/min/kg with testosterone (P=.49) but increased with GH (P=.11) and with GH+testosterone (P<.001). Changes in strength (r=0.355; P<.001) and in $\dot{V}O_2$max (r=0.320; P=.002) were directly related to changes in LBM. Edema was significantly more common in women taking GH (39% vs 0%) and GH+HRT (38% vs 0%). Carpal tunnel symptoms were more common in men taking GH+testosterone (32% vs 0%) and arthralgias were more common in men taking GH (41% vs 0%). Diabetes or glucose intolerance occurred in 18 GH-treated men vs 7 not receiving GH (P=.006).

Conclusions In this study, GH with or without sex steroids in healthy, aged women and men increased LBM and decreased fat mass. Sex steroid + GH increased muscle strength marginally and $\dot{V}O_2$max in men, but women had no significant change in strength or cardiovascular endurance. Because adverse effects were frequent (importantly, diabetes and glucose intolerance), GH interventions in the elderly should be confined to controlled studies.

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THE EXTENT TO WHICH REduced function of the growth hormone (GH) and insulin-like growth factor I (IGF-I) axis in aged women and men,[1,2] estrogen deficiency in postmenopausal women,[3] and decreases in testosterone[4] in older men contribute to decrements in skeletal muscle mass and strength[5] and increases in total and intra-abdominal fat[6] remains uncertain. The latter may be precursors of clinical conditions such as musculoskeletal frailty with reduced physical function,[7] insulin resistance, type 2 diabetes, and cardiovascular disease.[8]

In nonelderly GH-deficient adults, sarcopenia, central obesity, and other features resembling the aging phenotype are improved by long-term hormone replacement with recombinant

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human GH (rhGH).[9] A study[10] in which 6 months of rhGH treatment increased lean body mass (LBM) and reduced body fat in healthy aged men stimulated widespread interest in whether GH treatment might attenuate physical and functional concomitants of aging. Subsequent studies have confirmed that short-term GH replacement in older persons improves body composition,[2] but studies have not demonstrated gains in muscle strength or cardiovascular endurance. In older adults GH administration commonly produces adverse effects, including carpal tunnel syndrome, peripheral edema, arthralgias, and glucose intolerance.[11,12]

Despite the paucity of efficacy and safety data, there is extensive off-label prescription of GH for healthy older persons to reverse effects of the "somatopause,"[13] with little emphasis given to actual and potential adverse effects.[14]

Hormone replacement therapy (HRT) in healthy postmenopausal women decreases abdominal visceral fat and improves plasma lipid profiles.[15] Although epidemiologic studies suggested that HRT reduces coronary artery disease (CAD) risk, a recent controlled trial calls this into question.[16] In comparison, testosterone treatment improves body composition and muscle strength in nonelderly hypogonadal men[17] and body composition in older men.[18]

Changes in body composition and function during aging may result in part from the interactive effects of decreases in both GH and sex steroids.[19] We previously demonstrated in this population that GH and testosterone did not improve bone mineral density[20] or decrease visceral fat but reduced subcutaneous fat.[21] However, the most important issues clinically—effects on muscle strength, cardiovascular endurance, LBM, and total body fat, as well as adverse effects—have not been assessed. We evaluated the effects of 26 weeks of rhGH and gonadal steroid administration, alone and in combination, on body composition, muscle strength, cardiovascular endurance, and adverse effects in healthy older women and men.

METHODS

Study Subjects

Ambulatory, community-dwelling US women and men, ranging in age from 65 to 88 years, were recruited by mailings and advertisements between June 1992 and July 1998. All were healthy as verified by screening history and physical examination, routine blood studies, and urinalysis. No participant had diabetes, depression, untreated thyroid disease, symptomatic or occult CAD demonstrated by graded treadmill exercise test, liver or renal disease, or cancer other than basal cell skin cancer. Participants did not smoke, drank less than 30 g/d of alcohol, and took no medications interfering with the GH or gonadal steroid axes. Volunteers were selected to have serum IGF-I levels of 230 ng/mL or lower (≥1 SD below the mean for healthy adults aged 20-35 years). Women were postmenopausal (follicle-stimulating hormone levels, ≥30 U/L; estradiol [E_2] levels, ≤30 pg/mL [≤110 pmol/L]) and had not used HRT for at least 3 months before the study. Eighteen women had taken HRT previously, of whom 4 discontinued HRT 3 months before randomization. Men had screening serum testosterone levels of 470 ng/dL (16.3 nmol/L) or lower. No man had previously taken testosterone replacement. The protocol was approved by the combined institutional review board of the Johns Hopkins Bayview Medical Center (JHBMC) and the Intramural Research Program, National Institute on Aging. Written informed consent was obtained from each participant.

Study Protocol

The 26-week study used a randomized, double-blind, placebo-controlled, parallel-group 2×2 factorial design. Volunteers were randomized to receive rhGH plus placebo sex steroid (GH); sex steroid plus placebo rhGH (HRT for women, testosterone for men); rhGH plus sex steroid(s) (GH+HRT for women, GH+testosterone for men); or placebo rhGH plus placebo sex steroid(s) (placebo). Randomization was completed using the "RAND" function in Excel (Microsoft Corp, Redmond, Wash). There was no stratification or blocking.

At baseline, participants were admitted to the General Clinical Research Center at JHBMC at 6 PM on day 1. Height was measured using a standing stadiometer and weight with a calibrated clinical scale. At 8 AM on day 2, after an overnight fast, blood was collected for measurements of serum IGF-I, E_2 in women (to confirm menopause), and testosterone in men. On days 2 and 3, the primary outcome measurements of muscle strength, $\dot{V}O_2$max, and body composition were assessed as described below. Participants were instructed in self-administration of study medications and discharged on the afternoon of day 3.

Participants were advised to maintain their usual level of physical activity and to consume their customary diets during the 26-week protocol. Physical activity patterns were assessed using the Physical Activity Scale for the Elderly (PASE),[22] and 3-day diet histories were obtained by a nutritionist. At week 26, all baseline procedures were repeated.

Administration of Hormones

On the day of discharge, women received the first of 6 one-month supplies of 100 µg/d of estradiol or placebo transdermal patches (Estraderm; Novartis, Basel, Switzerland), plus 10 mg of medroxyprogesterone acetate (Provera; Pharmacia & Upjohn, Peapack, NJ) or placebo tablets. Women applied a new patch twice weekly and took medroxyprogesterone 10 mg/d or placebo for the last 10 days of each 28-day cycle. A nurse not involved in assessment of end points or adverse effects administered testosterone to men as biweekly intramuscular injections of 100 mg of testosterone enanthate in oil (Delatestryl Injection; Bio-Technology General Corp, Iselin, NJ) or the same volume of sterile saline placebo. Men and women were also given their first subcutaneous injections of GH (Nutropin; Genentech Inc, South San Francisco, Calif) or saline placebo at the time of discharge. All participants self-administered GH or pla-

cebo injections 3 times per week (Monday, Wednesday, and Friday) 1 hour before bedtime.

During year 1 the starting dose of GH was 30 µg/kg,[10] after which it was reduced to 20 µg/kg due to the high frequency of adverse effects observed. In women, 2 in the placebo, 2 in the HRT, 4 in the GH, and 3 in the GH+HRT groups started with injection volumes corresponding to 30 µg/kg. In men, 3 in the placebo, 2 in the testosterone, 3 in the GH, and 4 in the GH+testosterone groups started with injection volumes corresponding to 30 µg/kg. In addition, 2 women and 6 men treated with GH alone, 1 woman in the GH+HRT group, and 4 men in the GH+testosterone group required GH dose reductions. Mean daily GH doses were, for women in the GH and GH+HRT groups, respectively, 9.3 (2.2) and 10.0 (1.5) µg/kg/d, and for men in the GH and GH+testosterone groups, respectively, 9.2 (2.1) and 8.8 (1.8) µg/kg/d. Doses did not differ significantly within (women, $P=.23$; men, $P=.81$) or between ($P=.54$) sexes.

Assays

Serum IGF-I levels were measured by radioimmunoassay (normal range, 250-750 ng/mL) after acid-ethanol extraction (Endocrine Sciences Laboratories, Calabasas Hills, Calif), with a sensitivity of 30 ng/mL, and intra-assay and interassay coefficients of variation, respectively, of 5.9% and 7.3% at 289 ng/mL and 4.6% and 6.3% at 591 ng/mL.

Serum levels of E_2 and testosterone were measured in duplicate by radioimmunoassay using commercial kits (Diagnostic Products Corporation, Los Angeles, Calif). The E_2 assay (normal range, 49-199 pg/mL [182-730 pmol/L]) sensitivity was 20 pg/mL (73 pmol/L), with intra-assay coefficients of variation of 8.3%, 2.5%, and 5.3%, respectively, at mean E_2 concentrations of 48 pg/mL (176 pmol/L), 119 pg/mL (437 pmol/L), and 187 pg/mL (686 pmol/L) and interassay coefficients of variation of 8.9%, 6.0%, and 6.8%, respectively, at mean E_2 levels of 29 pg/mL (106 pmol/L), 99 pg/mL (363 pmol/L), and 186 pg/mL (683 pmol/L). The testosterone assay (normal range, 288-1210 ng/dL [10-42 nmol/L]) sensitivity was 10 ng/dL (0.35 nmol/L), with intra-assay coefficients of variation of 11.7%, 6.7%, 1.5%, and 3.1% at mean testosterone concentrations of 60 ng/dL (2.08 nmol/L), 300 ng/dL (10.4 nmol/L), 596 ng/dL (20.7 nmol/L), and 997 ng/dL (34.6 nmol/L), respectively. Interassay coefficients of variation were 9.5%, 5.8%, 5.7%, and 1.4% at mean testosterone concentrations of 75 ng/dL (2.6 nmol/L), 294 ng/dL (10.2 nmol/L), 703 ng/dL (24.4 nmol/L), and 1032 ng/dL (35.8 nmol/L), respectively.

Glucose was measured using a routine glucose oxidase method in the JHBMC clinical laboratory.

Body Composition, Muscle Strength, and $\dot{V}O_2$max

Lean body mass and total fat mass were measured by dual-energy x-ray absorptiometry (DXA) (Lunar model DPX-L; Lunar Radiation, Madison, Wis) using a previously validated 3-compartment model[23] that excludes bone from the LBM compartment. Total body scans were analyzed using Lunar software version 3.65u. The scanner was calibrated daily according to the manufacturer's recommendations. The variability of the DXA scanner for both LBM and fat mass in our laboratory was approximately 1%.[24]

Muscle strength was assessed by a standard 1-repetition maximum (1-RM) procedure[25] using 4 upper body (bench press, upright row, arm curl, and arm extension) and 2 lower body (leg press and leg curl) stations on an exercise machine (Universal Fitness, West Point, Miss). Participants were familiarized with each exercise by performing several repetitions using unloaded equipment, after which a 1-RM weight was estimated by adding 2.5-lb (1.125-kg) increments until a full-range lift could not be completed. The highest weight lifted was the 1-RM. Participants rested as needed between attempts and were monitored continuously with electrocardiography (ECG). Most individuals reached 1-RM in 3 to 4 attempts so that progressive fatigue was not a confounding factor. Total body strength was calculated as the sum of all 6 1-RM values.

Cardiovascular endurance (maximum aerobic capacity [$\dot{V}O_2$max]) was assessed as maximum oxygen uptake during a symptom-limited graded treadmill test using a modified Bruce protocol.[26] The test was performed to maximal volitional fatigue, claudication, or cardiac end points such as angina, significant ST depression, high-grade arrhythmias, or hypotension. Maximal oxygen uptake, ventilation, CO_2 production, and anaerobic threshold were determined using a commercial metabolic analysis system (Medical Graphics CardiO$_2$, St Paul, Minn). Data were expressed as milliliter of oxygen consumed per kilogram of body weight. The ECG was monitored continuously, and blood pressure, heart rate, and a 12-lead ECG were recorded during exercise.

Assessment of Adverse Effects

Participants were seen weekly for assessment of adverse effects and measurement of body weight, temperature, blood pressure, and pulse. Every 4 weeks the same physician or nurse practitioner conducted a detailed assessment including a structured questionnaire seeking symptoms of carpal tunnel syndrome, joint pain, and headaches or visual changes and a physical examination assessing the optic fundi, peripheral sensation in the hands, joint swelling or tenderness, and dependent edema. For reporting purposes, we defined edema as swelling of a lower extremity, with evident pitting on moderate digital pressure, with or without symptoms; carpal tunnel symptoms as complaints of numbness or paresthesia of hands on more than 2 occasions with no precipitating event; and arthralgia as new or increased joint pain, stiffness, or tenderness. Blood was collected after an overnight fast for serum glucose, IGF-I, testosterone (1 week after most recent biweekly injection), E_2, and hematocrit determinations. Glucose intolerance and diabetes were defined using revised American Diabetes Association criteria.[27] Active medication doses were reduced in 25% decrements by an

unblinded safety monitor, based on adverse effects and/or elevations of serum IGF-I higher than 350 ng/mL, testosterone higher than 807 ng/dL (28 nmol/L), or E_2 higher than 55 pg/mL (202 pmol/L). For each dose reduction, a similar reduction was instituted for a participant taking the corresponding placebo.

Serum prostate-specific antigen (PSA) levels were determined at baseline and follow-up in the clinical laboratory of the JHBMC by monoclonal radioimmunoassay (Tandem-R; Hybritech Inc, San Diego, Calif). Men also completed a prostate symptom questionnaire (International Prostate Symptom Scale).[28]

Statistical Analysis

Power analyses indicated that a group size of 20 would detect a 25% difference at the .05 level in muscle strength and a 12% difference in $\dot{V}O_2$max. Additional analyses revealed that group sizes of 10 would detect 10% changes in body composition end points at the .01 level.

Data were analyzed using SAS statistical software versions 6.12 and 8.2 (SAS Institute Inc, Cary, NC). All data are expressed as the mean (SE) values. Primary analyses were by intention to treat, carrying forward the last recorded data points for each variable from the 6 individuals (4.7%) who dropped out.

Sex differences for each variable at baseline or after 26 weeks were assessed by 1-way analysis of variance. Significance of changes (26-week minus baseline values) in LBM, total body fat, muscle strength, and $\dot{V}O_2$max were calculated by 1-way analysis of covariance adjusted for age, value of the dependent variable at baseline, and treatment group. Each treatment group was compared with the placebo group; the method of Dunnett[29] was used to control for multiple comparisons. Separate models were analyzed for men and women.

To investigate relationships between hormones and other outcome measures we calculated Pearson correlation coefficients between variables at baseline and, in separate analyses, between changes in variables. Relationships were assessed in women and men together when slopes of regressions in each sex showed no significant differences. Adverse event frequencies were compared between treatment and placebo groups separately for women and men by Fisher exact test in all participants randomized. Differences between cumulative average rhGH doses per day in the groups receiving GH were assessed by Mann-Whitney *U* tests comparing men vs women and individuals of each sex receiving GH alone vs GH+sex steroid. $P \leq .05$ was considered significant.

RESULTS

Participant Characteristics

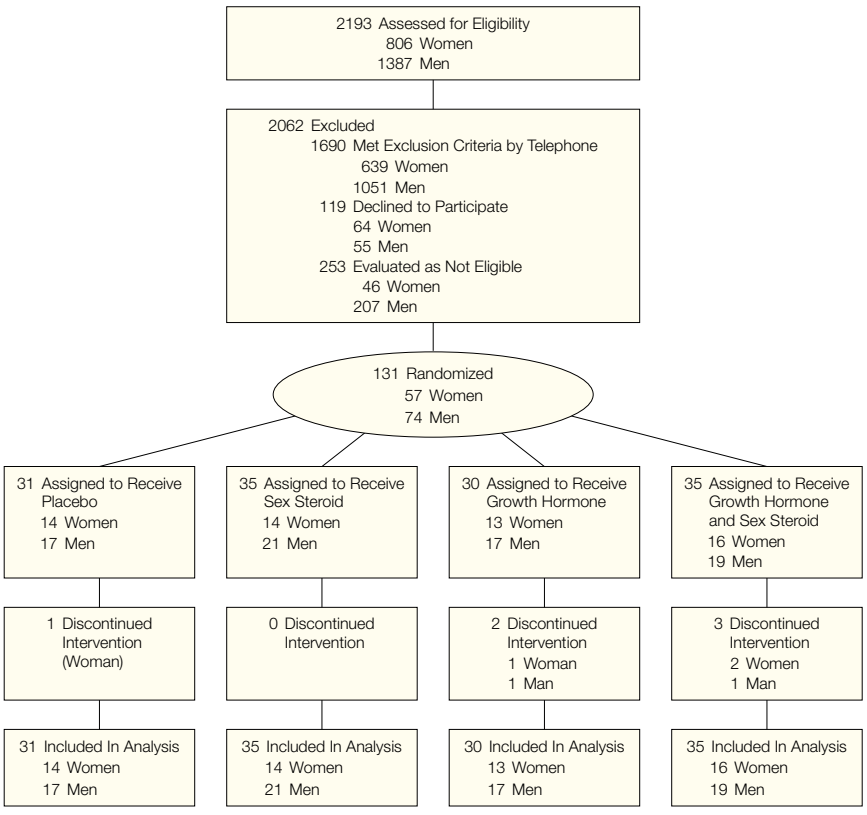
The study population included 57 women and 74 men aged 65 through 88 years (mean [SE], 72 [0.4] years). Four women and 2 men discontinued before 26 weeks (dropout rate, 4.7%): 2 women (both in the GH+HRT group) due to adverse effects consistent with estrogen use (vaginal bleeding, breast tenderness), 2 women (1 each in the placebo and GH groups) for reasons unrelated to adverse effects, and both men (1 each in the GH and GH+testosterone groups) due to GH-related adverse effects (arthralgias, carpal tunnel symptoms, and edema) (FIGURE 1). Mean baseline ages did not differ by sex, but weight, body mass index, and IGF-I levels were higher in men (TABLE 1). Within-sex group characteristics did not differ significantly (Table 1).

Three-day diet histories and self-reported physical activity (PASE) did not differ before or after treatment in either sex (data not shown).

Levels of IGF-I and Sex Steroids

Levels of IGF-I increased in women and men given GH ($P<.001$), with no significant differences between the GH and GH+sex steroid–treated women ($P=.72$) or men ($P=.18$). Levels of IGF-I were higher in GH-treated (mean

Figure 1. Flow of Patients Through the Study



[SE], 244 [5] vs 192 [4] ng/mL; $P<.001$) and non-GH–treated (138 [3] vs 109 [3] ng/mL; $P=.001$) men vs women. Neither placebo nor sex steroids significantly changed IGF-I levels in either sex (FIGURE 2A and 2B).

In women, serum E_2 levels increased after administration of HRT ($P<.001$) and GH+HRT ($P<.001$). In men, serum testosterone levels increased after administration of testosterone ($P<.001$) and GH+testosterone ($P=.002$), respectively. There were no effects of coadministration of GH in women ($P=.97$) or men ($P=.44$) on levels attained. Neither placebo nor GH treatment significantly changed sex steroid levels in either sex (Figure 2C and 2D).

Body Composition

Lean body mass was greater ($P<.001$) in men than in women at baseline and after 26 weeks (TABLE 2). At baseline, there were no significant group differences in LBM in women, whereas in men baseline LBM in the testosterone group was significantly lower than that in the placebo group ($P=.003$). In women, compared with placebo LBM increased significantly with GH and GH+HRT but not HRT, with no significant differences between GH-treated groups. In men, LBM increased significantly with GH and GH+testosterone with a trend toward a significant increase after testosterone ($P=.06$). The increase with GH+testosterone was greater than that for testosterone ($P<.001$) but not significantly greater than with GH alone ($P=.06$). In a secondary "as-treated" analysis of individuals completing 26 weeks, LBM increased significantly with testosterone by 2.9% ($P=.04$).

Total fat mass was greater in women than in men at 26 weeks ($P=.02$) but not at baseline ($P=.08$) (Table 2). At baseline, there were no significant within-sex group differences in fat mass. In women, fat mass decreased similarly with GH and GH+HRT but not HRT. In men, fat mass decreased significantly with GH and GH+testosterone but not testosterone. The decrease with GH+testosterone was greater than that for testosterone ($P=.001$) and was marginally greater than for GH ($P=.05$). In a secondary as-treated analysis of individuals completing 26 weeks, decrease in fat was greater with GH+testosterone than with testosterone ($P<.001$) or GH ($P=.04$).

Muscle Strength

Before and after treatment, strength (TABLE 3) was greater in men than in women ($P<.001$), with no significant group differences at baseline in either sex. At 26 weeks, women's strength did not change significantly in any treatment group, whereas in GH+testosterone–treated men, the increase in strength of 6.8% was marginally significant.

Aerobic Capacity

Before and after treatment, mean values for $\dot{V}O_2$max (TABLE 4) were higher in men than in women ($P<.001$), with no baseline within-sex group differences. In women $\dot{V}O_2$max did not increase, whereas it increased by 8.3% in GH+testosterone–treated men.

Serum Hormone Levels, Body Composition, and Aerobic Capacity

At baseline, in all women and men combined, LBM ($r=0.261$, $P=.003$) and strength ($r=0.306$, $P<.001$), but not fat mass ($r=0.010$, $P=.91$) or $\dot{V}O_2$max ($r=0.088$, $P=.33$), were directly related to IGF-I levels. Strength ($r=0.893$, $P<.001$) and absolute $\dot{V}O_2$max ($r=0.845$, $P<.001$) were also directly related to LBM. After 26 weeks, changes in LBM ($r=0.404$, $P<.001$) and in strength ($r=0.196$, $P=.04$), but not changes in $\dot{V}O_2$max ($r=0.083$, $P=.36$), were directly related to changes in IGF-I. Changes in fat mass ($r=-0.347$, $P=.001$) were inversely related to changes in IGF-I. Changes in strength ($r=0.255$, $P=.005$) and in $\dot{V}O_2$max ($r=0.324$, $P<.001$) were directly related to changes in LBM (FIGURE 3). These baseline and posttreatment relationships were similar in women and men, with no significant sex differences in slopes of corresponding regression equations (data not shown). In men, baseline and posttreatment relationships of testosterone with LBM, fat mass, strength, or $\dot{V}O_2$max were not significant (data not shown).

Adverse Effects

Peripheral edema, carpal tunnel symptoms, and arthralgias occurred in 24% to 46% of GH-treated participants (TABLE 5). Edema and arthralgias were more common in GH-treated women. In men, carpal tunnel symptoms were more frequent in the GH+testosterone group and arthralgias in the GH group. No man taking GH+testosterone re-

Table 1. Baseline Characteristics by Treatment Group*

	Women					Men				
	Placebo (n = 14)	HRT (n = 14)	GH (n = 13)	GH + HRT (n = 16)	All (n = 57)	Placebo (n = 17)	Testosterone (n = 21)	GH (n = 17)	GH + Testosterone (n = 19)	All (n = 74)
Age, y	72 (1.3)	71 (0.9)	70 (1.1)	71 (1.3)	71 (0.6)	70 (1.1)	70 (0.7)	71 (1.3)	73 (1.4)	72 (0.6)
Weight, kg	67.1 (2.1)	65.5 (2.7)	66.1 (2.3)	60.6 (2.5)	65.1 (2.0)	86.8 (2.4)	78.9 (2.3)	83.2 (2.0)	80.9 (2.0)	82.3 (1.1)
Body mass index†	26.1 (0.7)	25.5 (0.7)	26.3 (0.9)	24.4 (1.0)	25.5 (0.8)	27.2 (0.4)	26.6 (0.7)	27.4 (0.6)	27.1 (0.7)	27.0 (0.3)
IGF-I, ng/mL	110 (12)	122 (13)	105 (10)	136 (15)	115 (6)	131 (8)	132 (8)	146 (10)	117 (10)	133 (6)
Testosterone, ng/dL‡						392 (23)	409 (20)	421 (14)	375 (23)	398 (9)

*All data are presented as mean (SE). HRT indicates hormone replacement therapy; GH, growth hormone; and IGF-I, insulinlike growth factor I. Values were significantly different ($P<.001$) between women and men for weight, body mass index, and IGF-I.
†Body mass index is calculated as the weight in kilograms divided by the square of height in meters.
‡To convert testosterone to nmol/L, multiply values by 0.0347. Estradiol levels are not reported for women because the assay's sensitivity (20 pg/mL) was higher than serum estradiol levels in many women.

ported arthralgias, in contrast to 7 (41%) receiving GH. Testosterone administration did not significantly increase these adverse effects.

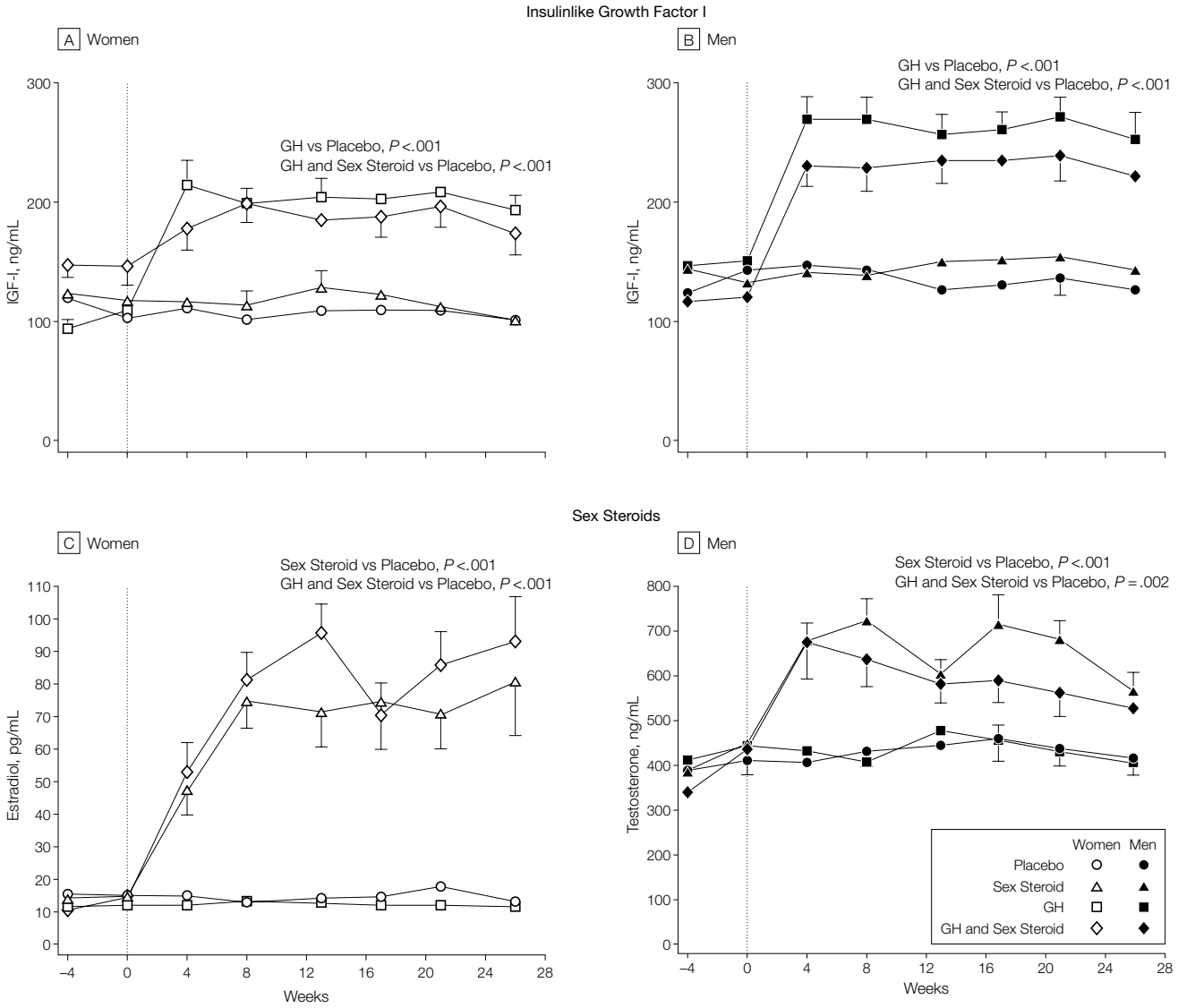
Weight changes of more than 3 kg or changes in mean body weight did not differ significantly in any treatment group (data not shown).

In individuals taking GH without or with sex steroid, the number per participant of arthralgias, edema, and carpal tunnel symptoms in women ($r=0.529$, $P<.001$) and in men ($r=0.412$, $P<.001$) were directly related to mean IGF-I levels during treatment. Occurrence of these adverse effects was similarly correlated with the maximum level of IGF-I and significantly but less strongly with changes in IGF-I levels (data not shown).

Vaginal bleeding occurred in 29% of women receiving HRT ($P=.04$), 65% of women receiving GH+HRT ($P<.001$), 6% receiving GH ($P=.48$), and none in the placebo group.

There were no significant increases in the incidence of headaches or changes in the optic fundi. In men there were no significant increases in gynecomastia (Table 5), symptoms of prostatism, or ex-

Figure 2. Effects of 26 Weeks of Hormone or Placebo Administration



Effects of administration of growth hormone (GH), hormone replacement therapy, and/or placebo to women (A and C) and GH, testosterone, and/or placebo to men (B and D) 65 years or older and sequential serum levels of insulinlike growth factor I (IGF-I) (A and B), estradiol (C), and testosterone (D). Values are presented as mean (SE). To convert estradiol to pmol/L, multiply data by 3.67; to convert testosterone to nmol/L, multiply data by 0.0347. Curves were compared using repeated measures analysis of variance with *P* value estimates shown in the plots calculated for multiple comparisons using a post hoc Scheffé analysis. The time point (–4) before 0 weeks (baseline) represents the screening visit.

cessive daytime sleepiness. Uncommonly reported (<5%) adverse effects included hematochezia; foot, hand, or testis swelling; new heart murmurs; urinary frequency; and transient erectile dysfunction. One woman (placebo group) had a basal cell skin cancer and 1 man (testosterone group) was diagnosed as having a dysplastic junctional nevus, which were resected surgically.

Blood Pressure and Pulse Rates

Systolic and diastolic blood pressures and mean pulse rates did not change significantly in any treatment group (data not shown).

Blood Glucose and Diabetes

As illustrated in TABLE 6, at baseline none of the women or men met the revised[27] ADA criteria for diabetes mellitus, but 3 men did so for fasting glucose intolerance. Sex steroid administration did not increase rates of fasting glucose intolerance or diabetes in women or men. However, diabetes developed in 5 men receiving GH and 1 man not taking GH ($P = .06$), and diabetes or fasting glucose intolerance occurred in 18 GH-treated men vs 7 not receiving GH ($P = .006$). Fasting glucose returned to normal values 2 to 6 weeks after discontinuation of treatment in diabetic men.

Hematocrit

In men, there were no significant increases in hematocrit in any hormone-treated group. No man developed hematocrit values higher than 55%. In men receiving testosterone, there were no significant relationships between maximum value or maximum change

Table 2. Effects of Treatments on Lean Body Mass and Fat Mass as Demonstrated by DXA*

	Women				Men			
	Placebo (n = 14)	HRT (n = 14)	GH (n = 13)	GH + HRT (n = 16)	Placebo (n = 17)	Testosterone (n = 21)	GH (n = 17)	GH + Testosterone (n = 19)
Total lean body mass, kg								
Baseline	35.7 (1.0)	36.7 (1.1)	36.8 (1.0)	35.8 (0.8)	57.0 (1.6)	51.5 (1.0)	54.4 (1.2)	52.7 (0.8)
26 Weeks	36.1 (1.1)	37.9 (1.0)	37.8 (0.9)	37.9 (0.8)	57.0 (1.4)	53.0 (1.1)	57.5 (1.3)	57.1 (1.0)
Change	0.4	1.2	1.0	2.1	0.1	1.4	3.1	4.3
P value for change vs placebo		.09	.001	<.001		.06	<.001	<.001
Total body fat mass, kg								
Baseline	28.4 (1.2)	25.7 (1.7)	27.8 (1.5)	22.6 (1.7)	25.0 (1.1)	23.3 (1.7)	24.4 (1.4)	23.9 (1.6)
26 Weeks	28.1 (1.3)	25.1 (1.4)	25.3 (1.4)	20.8 (1.6)	25.0 (1.3)	22.2 (1.7)	21.1 (1.4)	19.0 (1.3)
Change	−0.02	−0.59	−2.44	−2.10	0.1	−1.2	−3.2	−4.8
P value for change vs placebo		.69	.001	.006		.12	<.001	<.001

*DXA indicates dual-energy absorptiometry; HRT, hormone replacement therapy; and GH, growth hormone. All mass values are reported as mean (SE). Baseline and week 26 data are crude values; change and *P* values are adjusted for age and initial value using the method of Dunnett.[29]

Table 3. Effects of Hormone Administration on Total Body Strength*

	Women				Men			
	Placebo (n = 13)	HRT (n = 13)	GH (n = 12)	GH + HRT (n = 13)	Placebo (n = 16)	Testosterone (n = 19)	GH (n = 15)	GH + Testosterone (n = 18)
Baseline	108.0 (7.5)	111.8 (4.5)	107.1 (5.3)	101.6 (4.7)	209.8 (6.8)	189.5 (6.8)	202.4 (9.9)	198.5 (8.3)
26 Weeks	104.9 (6.6)	115.9 (4.8)	109.2 (5.7)	105.4 (5.6)	212.8 (7.0)	197.0 (6.2)	212.5 (11.7)	211.6 (7.9)
Change	−3.1	4.2	2.3	3.6	3.5	6.2	10.3	13.5
P value vs placebo		.09	.29	.14		.86	.28	.05

*Strength, reported as mean (SE), was measured in kilograms on 1-repetition maximum testing. HRT indicates hormone replacement therapy; GH, growth hormone. Baseline and week 26 data are crude values; change and *P* values are adjusted for age and initial value using the method of Dunnett.[29]

Table 4. Effects of Hormone Treatments on Maximal Oxygen Capacity ($\dot{V}O_2$max) by Graded Treadmill Exercise Testing*

	Women				Men			
	Placebo (n = 14)	HRT (n = 14)	GH (n = 12)	GH + HRT (n = 16)	Placebo (n = 17)	Testosterone (n = 21)	GH (n = 17)	GH + Testosterone (n = 18)
Baseline	21.4 (1.2)	22.9 (1.0)	23.1 (1.7)	21.7 (0.8)	28.1 (1.4)	26.5 (0.6)	28.2 (1.2)	26.9 (1.4)
26 Weeks	21.1 (0.9)	22.3 (0.9)	24.4 (1.6)	23.2 (0.7)	26.8 (1.4)	26.4 (0.9)	28.4 (1.4)	29.0 (1.4)
Change	−0.4	−0.4	1.4	1.3	−1.2	−0.4	0.3	2.3
P value vs placebo		>.99	.07	.06		.49	.11	<.001

*$\dot{V}O_2$max is reported as mean (SE) milliliters per minute per kilogram of body weight. HRT indicates hormone replacement therapy; GH, growth hormone. Baseline and week 26 data are crude values; change and *P* values are adjusted for age and initial value using the method of Dunnett.[29]

in hematocrit and measures of testosterone (data not shown).

Prostate

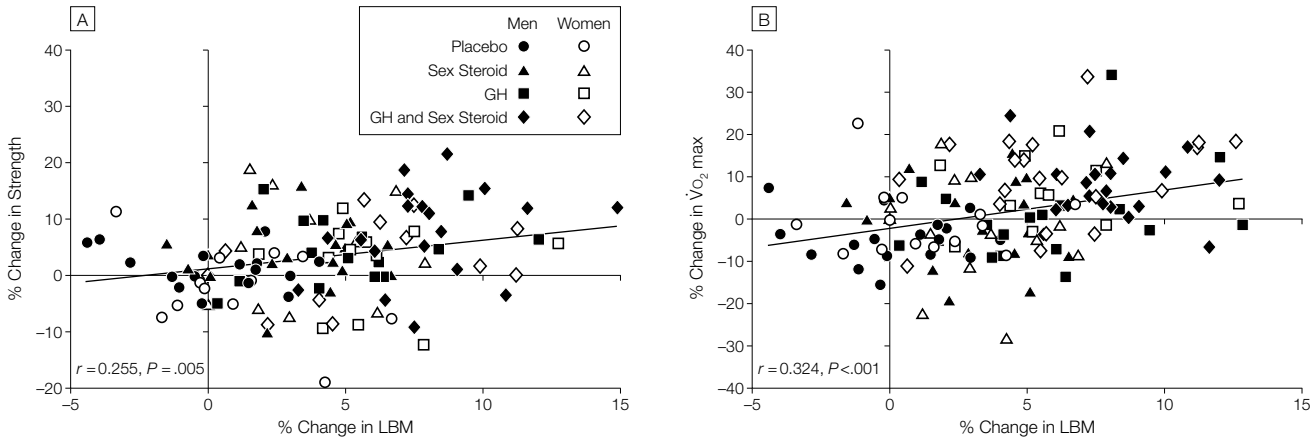
Mean serum PSA levels did not change significantly in any treatment group (data not shown). After testosterone administration, 2 men exhibited increases in PSA greater than 1.0 ng/mL, but neither had prostate carcinoma on fine needle biopsy. There were no significant changes in International Prostate Symptom Scale scores or increased complaints of prostatism symptoms in any group.

COMMENT

During 26 weeks of GH and/or sex steroid treatment, IGF-I, E_2, and testosterone levels increased into the midnormal range for young women and men. In both sexes, GH increased LBM and decreased fat mass. Among men taking GH+testosterone, strength increased marginally and $\dot{V}O_2$max increased significantly. Changes in muscle strength and $\dot{V}O_2$max were directly related to changes in LBM. In men, GH elicited greater responses in IGF-I and body composition than in women. GH+testosterone elicited greater increases in LBM and $\dot{V}O_2$max and decreases in fat than did testosterone alone, and GH+testosterone produced marginally greater responses than did GH alone. In women, changes were similar after GH+HRT or GH alone. To our knowledge, these findings are novel.

Like others,[10,30] we found that GH significantly increased IGF-I in elderly individuals and that IGF-I increased more in older men than in older women, a sex difference also observed after GH administration in nonelderly GH-deficient adults.[9,31] In the women in our study, HRT did not significantly affect IGF-I, consistent with prior reports using similar doses of transdermal estrogens.[32] In contrast, previous studies have shown that oral[33] or high-dose transdermal[34] estrogen decreases IGF-I. In the men in our study, IGF-I increased similarly with GH and GH+testosterone, but not with testosterone alone. Data from prior studies[21,35] suggest that the age-related decline in testosterone in men contributes to reduction in GH secre-

Figure 3. Bivariate Plots of the Relationships of Changes in Lean Body Mass (LBM) With Changes in Total Body Strength and $\dot{V}O_2$max During 26 Weeks of Hormone or Placebo Administration



r and *P* values were calculated by linear regression for the combined groups of women and men. GH indicates growth hormone. $\dot{V}O_2$max is measured as milliliters per minute per kilogram of body weight.

Table 5. Common Adverse Effects During 26 Weeks of Treatment*

	Women							Men						
	Placebo (n = 14), No. (%)	HRT (n = 14)		GH (n = 13)		GH + HRT (n = 16)		Placebo (n = 17), No. (%)	Testosterone (n = 21)		GH (n = 17)		GH + Testosterone (n = 19)	
		No. (%)	*P* Value	No. (%)	*P* Value	No. (%)	*P* Value		No. (%)	*P* Value	No. (%)	*P* Value	No. (%)	*P* Value
Edema	0	4 (29)	.10	5 (39)	.02	6 (38)	.02	2 (12)	2 (10)	>.99	5 (30)	.40	4 (21)	.66
Carpal tunnel symptoms	1 (7)	3 (21)	.60	5 (38)	.08	4 (25)	.34	0	2 (10)	.49	4 (24)	.10	6 (32)	.02
Arthralgias	1 (7)	1 (7)	>.99	6 (46)	.06	5 (31)	.18	0	2 (10)	.49	7 (41)	.007	0	>.99
Mastodynia	0	6 (43)	.02	0	>.99	7 (44)	.007							
Gynecomastia								0	0	>.99	2 (12)	.49	2 (11)	.49
Headaches	0	1 (7)	>.99	3 (23)	.10	3 (19)	.23	0	1 (5)	>.99	0	>.99	0	>.99

*HRT indicates hormone replacement therapy; GH, growth hormone. *P* values (vs placebo) were calculated with the Fisher exact test.

Table 6. Rates of Fasting Glucose Intolerance and Diabetes by Treatment Group*

	Women				Men			
Glucose Classification†	Placebo	HRT	GH	GH + HRT	Placebo	Testosterone	GH‡	GH + Testosterone‡
Normal (<110 mg/dL)								
Baseline	14	14	13	16	17	18	17	19
Follow-up	12	12	11	14	14	17	8	10
Impaired (110-126 mg/dL)								
Baseline	0	0	0	0	0	3	0	0
Follow-up	2	2	2	2	3	3	7	6
Diabetes (>126 mg/dL)								
Baseline	0	0	0	0	0	0	0	0
Follow-up	0	0	0	0	0	1	2	3

*All values were measured at 4-week intervals. HRT indicates hormone replacement therapy; GH, growth hormone.
†Glucose classification defined by American Diabetes Association criteria.[27] To convert glucose to mmol/L, multiply values by 0.0555. Impaired glucose tolerance and diabetes were defined as ≥2 measurements meeting the criteria.
‡For diabetes, combined GH and GH+testosterone groups vs combined placebo and testosterone groups, $P = .06$; for diabetes or impaired fasting glucose, combined GH and GH+testosterone groups vs combined placebo and testosterone groups, $P = .006$.

tion and that the latter can be partially reversed by testosterone in doses higher than those we used. Growth hormone alone did not significantly alter sex steroids in either sex, suggesting that the GH doses used did not stimulate sex steroid production by the senescent gonad.

We found greater GH-mediated responses in LBM and fat in aged men than in women, consistent with prior reports in GH-deficient younger adults.[9] In women, HRT treatment did not increase LBM or decrease fat significantly. The effects of HRT on body composition are controversial, although previous studies suggest that postmenopausal progestin can reduce tissue responsiveness to estrogens during HRT.[36,37] Low-dose testosterone did not elicit significant increases in LBM or decreases in fat in aged men in our study, in contrast to significant changes reported using higher doses of parenteral or transdermal testosterone.[18,38] The effects of GH+testosterone on LBM and fat appeared additive, suggesting that they resulted from submaximal responses mediated by similar mechanisms,[39] or that the mechanisms differed but were complementary.[40]

In the men in our study, the magnitudes of the increases in LBM and decreases in fat following GH+testosterone treatment were similar to those reported after 6 months of exercise training 3 times per week[41] and greater than those observed after training once per week.[42] This finding is noteworthy because participants reported no changes in their dietary or physical activity patterns, as confirmed by dietary histories and PASE surveys. Body composition changes observed could be of clinical significance if they were associated with proportional improvements in strength, performance, and cardiac risk factors. However, GH- and/or sex steroid–mediated increases in LBM demonstrated on DXA must be interpreted with caution because they may reflect changes in cell mass or extracellular water. Isotopic studies reveal that decreased LBM in nonelderly GH-deficient adults results from reductions in cell mass and extracellular water, and that both components increase after GH replacement.[9] We are unaware of analogous studies in somatopausal elderly individuals. The observed correlations of increases in strength and $\dot{V}O_2$max with changes in LBM suggest that, in the current study, GH produced increases in functional muscle mass.

We observed a 6.8% increase in strength in men treated with GH+testosterone, which was of marginal statistical significance. Most[30,43] but not all[44] previous studies reported no effect of GH on strength in aged individuals, consistent with our findings after GH alone. Although one epidemiologic study suggested that grip strength is greater in women taking HRT,[45] most prior cohort[46] or intervention[47] studies are consistent with ours in finding no increases in strength in HRT users. Treatment of andropausal elderly men with higher doses of testosterone increased grip strength[48] and leg strength in some[49] but not other[18] studies. Our observation that men treated with GH+testosterone exhibited the greatest increases in both strength and LBM is consistent with the finding that changes in strength were directly related to changes in LBM. An increase of the magnitude observed would be expected after 6 to 8 weeks of regular resistance exercise[41,42] and is potentially clinically significant. However, functional significance of strength is better assessed by performance-based testing. Significant relationships of IGF-I with such measures have been reported in elderly women,[50] but to date these outcomes have not been found to change in aged individuals after GH administration.[30]

Cardiovascular endurance capacity increased significantly only in men after GH+testosterone treatment. Our observation of a direct relationship of $\dot{V}O_2$max with LBM is consistent with the interpretation that increments in $\dot{V}O_2$max were partly due to increased muscle tissue and its consequent effect on oxygen consumption, rather than to enhanced cardiac output.

Participants treated with GH exhibited soft tissue adverse effects similar to those reported in acromegaly, including edema, arthralgias, and carpal tunnel symptoms. These effects were more common in men than in women, consistent with men's greater responsiveness to GH.[9] Symptoms occurred more often in individuals with greater increases in IGF-I consistent with prior reports in elderly[11,12,30] and middle-aged GH-deficient[51] adults. We, like other authors,[51] noted spontaneous reductions over time in symptoms in some affected individuals. Older age may increase susceptibility to these adverse GH effects.[13] Moreover, such symptoms might presage accelerated osteoarthritis or clinically significant carpal tunnel syndrome. Coadministration of sex steroid with GH did not

increase incidence of soft tissue adverse effects.

Studies of GH treatment have reported headaches in adult GH-deficient patients and benign intracranial hypertension with papilledema in children.[52] We observed no increases in headaches or fundoscopic changes in GH-treated individuals. Despite a significant incidence of dependent edema, we detected no weight gain or increased blood pressure after GH administration. Treatment with GH has been associated with increases in plasma renin activity[53] but not in plasma aldosterone[54] or blood pressure.[9] Whether aging predisposes to hormone-induced edema is unknown.

Diabetes and glucose intolerance developed significantly more often after GH treatment in men, as others have reported.[11] In nonelderly GH-deficient adults, short-term GH treatment reduces insulin sensitivity, despite favorable changes in body composition,[55] whereas longer-term GH therapy[56] improves fasting glucose. We are unaware of analogous reports in aged adults. We found no effect of testosterone or HRT on glucose tolerance or diabetes, although testosterone replacement may improve insulin sensitivity in middle-aged men with low normal testosterone levels and obesity,[57] probably by decreasing central body fat. Postmenopausal HRT exerts little effect on glucose tolerance.[58]

A recent study highlights concerns regarding neoplasia risk after long-term GH treatment in adults,[59] possibly related to the influence of elevated IGF-I levels. Menopausal HRT is associated with small but significant increases in breast cancer risk[16]; estrogen use, unopposed by progestogens, increases rates of endometrial cancer.[60] Whether testosterone treatment of older men stimulates prostate cancer growth is unknown. Although we observed no increase in PSA in hormone-treated men, no prospective trials, including this one, have been large enough to define risk of neoplasia for GH or testosterone replacement in elderly persons.

Using a standardized questionnaire[28] we, like others,[61] found no worsening of benign prostatic hyperplasia symptoms in hormone-treated men. We observed no increases in hematocrit above the normal range. Polycythemia is uncommon after testosterone replacement,[62] tending to occur with high concentrations of testosterone and in men with preexisting hypoxia. About 10% of men receiving GH or GH+testosterone, but not testosterone alone, developed mild gynecomastia, consistent with prior findings.[11]

This study has several limitations. The number of participants, particularly women, was relatively small to determine definitively the possible positive and adverse effects. Participants were in good health relative to their age-matched peers, with potential for treatment-related "ceiling" effects on various outcomes. We did not assess performance-based outcomes and so could not determine whether changes in strength led to significant functional changes. Our study was 6 months long, which may be too short to detect temporally biphasic or other effects. We administered GH and testosterone using a nonphysiologic paradigm, and testosterone in doses lower than those used to treat hypogonadal men. Finally, we did not assess clinical outcomes during or after the study. However, this study demonstrated significant positive and adverse effects, and hence its clinical implications persist despite its limitations.

Our findings suggest that GH and sex steroid supplementation in a selected group of healthy aged women and men can exert potentially beneficial effects on body composition, and possibly improve muscle strength and cardiovascular endurance capacity in men. However, GH supplementation may lead to various adverse effects, most importantly diabetes and glucose intolerance. The beneficial effects of GH appeared to be augmented by coadministration of testosterone but not HRT. These data support the rationale for further, larger-scale investigations of the efficacy, safety, and clinical and functional utility of more physiologic hormone replacement. However, at this time, GH interventions in elderly individuals should be confined to controlled research studies.

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