0013-7227/01/$03.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 86(8):3604–3610


# Effects of GH and/or Sex Steroid Administration on Abdominal Subcutaneous and Visceral Fat in Healthy Aged Women and Men

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**Aging is associated with reduced GH, IGF-I, and sex steroid axis activity and with increased abdominal fat. We employed a randomized, double-masked, placebo-controlled, noncrossover design to study the effects of 6 months of administration of GH alone (20 μg/kg BW), sex hormone alone (hormone replacement therapy in women, testosterone enanthate in men), or GH + sex hormone on total abdominal area, abdominal sc fat, and visceral fat in 110 healthy women (n = 46) and men (n = 64), 65–88 yr old (mean, 72 yr). GH administration increased IGF-I levels in women ($P = 0.05$) and men ($P = 0.0001$), with the increment in IGF-I levels being higher in men ($P = 0.05$). Sex steroid administration increased levels of estrogen and testosterone in women and men, respectively ($P = 0.05$). In women, neither GH, hormone replacement therapy, nor GH + hormone replacement therapy altered total abdominal area, sc fat, or visceral fat significantly. In contrast, in men, administration of GH and GH + testosterone enanthate decreased total abdominal area by 3.9% and 3.8%, respectively, within group and *vs.* placebo ($P = 0.05$). Within-group comparisons revealed that sc fat decreased by 10% ($P = 0.01$) after GH, and by 14% ($P = 0.0005$) after GH + testosterone enanthate. Compared with placebo, sc fat decreased by 14% ($P = 0.05$) after GH, by 7% ($P = 0.05$) after testosterone enanthate, and by 16% ($P = 0.0005$) after GH + testosterone enanthate. Compared with placebo, visceral fat did not decrease significantly after administration of GH, testosterone enanthate, or GH + testosterone enanthate. These data suggest that in healthy older individuals, GH and/or sex hormone administration elicits a sexually dimorphic response on sc abdominal fat. The generally proportionate reductions we observed in sc and visceral fat, after 6 months of GH administration in healthy aged men, contrast with the disproportionate reduction of visceral fat reported after a similar period of GH treatment of nonelderly GH deficient men and women. Whether longer term administration of GH or testosterone enanthate, alone or in combination, will reduce abdominal fat distribution-related cardiovascular risk in healthy older men remains to be elucidated. (*J Clin Endocrinol Metab* 86: 3604–3610, 2001)**

AGING IS ASSOCIATED with increases in total-body, total-abdominal, and intraabdominal visceral (V) fat (1, 2). Total-body and abdominal obesity are known risk factors for cardiovascular morbidity and mortality (3–6). Age-related increases in total and abdominal fat have been implicated in contributing to augmented cardiovascular risk, at least until 80 yr of age (7). For example, in postmenopausal women, increased abdominal V fat is directly associated with higher fasting levels of glucose, cholesterol, and triglycerides (8), and inversely related to high-density lipoprotein cholesterol levels (9). Moreover, abdominal fat is strongly related to insulin sensitivity and mean arterial blood pressure in aged women and men (10).

It has been speculated that the age-related declines in the activity of the GH/IGF-I and gonadal steroid axes contribute to the above-noted alterations in body fat (11–14). Administration of GH to elderly women and men (15–17) or testosterone (T) to old (18) or middle-aged men (19) has been reported to decrease total-body and/or abdominal fat. Similarly, estrogen administration to postmenopausal women reduced age-related central adiposity (20–23). Nonelderly GH-deficient patients and hypogonadal men, like healthy aged individuals, exhibit increases in total-body fat and abdominal sc and V fat, which are improved after GH administration (24–28) or T treatment (29), respectively.

In the current study, we assessed the effects of 6 months of administration of GH and/or gonadal steroids on abdominal sc and V fat, as measured by magnetic resonance imaging (MRI), in a cohort of 110 healthy women (n = 46) and men (n = 64), 65 yr of age or older.

## Materials and Methods

### *Study population*

Participants were recruited by mailed brochures and newspaper advertisements. All but 3 of our study population were Caucasian. One subject was African-American, and 2 were Asian-American. All participants were 65 yr of age or older and were healthy by history, physical examination, routine serum chemistries (including total cholesterol, high-density lipoprotein- and low-density lipoprotein cholesterol, and triglycerides), urinalysis, and graded treadmill electrocardiogram testing. Subjects were nonsmoking, drank no more than 30 g alcohol/d, and

Abbreviations: BMI, Body mass index; CT, computed tomography; CV, coefficient of variation; HRT, hormone replacement therapy; MRI, magnetic resonance imaging; T, testosterone; TAA, total abdominal area; TE, testosterone enanthate; V, visceral; WHR, waist to hip ratio.

took no medications known to interfere with GH -IGF I axis activity or with gonadal steroid levels. No woman had taken any estrogen or progestogen for at least 3 months before study. Eighteen women reported having taken hormone replacement therapy (HRT) previously. Among women in all treatment groups combined, the mean period of discontinuation of HRT before study participation was 12 ± 3 yr. However, there was variability among treatment groups, with the shortest time interval off HRT being at least 3 yr. Four of the 18 women were actively taking HRT until 3 months before randomization to receive either placebo + placebo (n = 2) or HRT + placebo (n = 2). No man was taking T replacement before entry into the study. Eligible women and men were also selected to have age-related reductions (1 SD below the mean for values in healthy adults, 20–35 yr old) of their circulating IGF-I levels (230 μg/L) and, for men, of serum T (1630 nM/L). The study protocol was approved by the combined Institutional Review Board of the Johns Hopkins Bayview Medical Center and the Intramural Research Program, National Institute on Aging. Written informed consent was obtained from each participant.

### *Study protocol*

The study used a randomized, double-masked, placebo-controlled, double-dummy, noncross-over 2 × 2 factorial design for a total period of 26 wk. Thus, participants received either GH + sex steroid placebo, sex steroid + GH placebo, GH + sex steroid, or GH placebo + sex steroid placebo. Recombinant human GH (Nutropin, Genentech, Inc., South San Francisco, CA) was administered as 20 μg (0.055 U)/kg BW, self-injected sc, 3 times/wk, in the afternoon. This dose was chosen based upon review of the original study by Rudman *et al.* (16), assessing effects of GH in healthy aged men (30 μg = 0.0825 U/kg). HRT was given as 100 μg/d E2 patch (Estraderm, Novartis Pharmaceuticals, East Hanover, NJ) + 2.5 mg medroxyprogesterone acetate (Provera, Pharmacia & Upjohn, Inc., Kalamazoo, MI) for the first 10 d of each month; and T was administered as im injections of 100 mg T enanthate (TE) (Delatestryl Injection, Bio-Technology General Corp., Iselin, NJ) every 2 wk.

At baseline, participants were admitted, on the evening before study, to the General Clinical Research Center at the Johns Hopkins Bayview Medical Center, where they received a standard dinner. After an overnight fast, blood samples were obtained, the following morning, for baseline determinations of serum E2 in women or T in men and IGF-I (women and men). Subsequently, baseline anthropometric measurements were recorded, and an abdominal MRI was performed in the nonfasting state. Subjects were subsequently seen on a weekly basis, as outpatients, for clinical assessments of possible adverse effects; every 4 wk, blood was collected for serial assessments of serum IGF-I, T, and E2. Medication doses, active or placebo, were reduced by the safety monitor, based on clinical symptoms and/or elevations of serum IGF-I more than 350 μg/liter, T more than 28 nM, or E2 more than 55 pM. Participants were advised not to change their level of physical activity or to make dietary alterations during the 26-wk protocol. At wk 26, the baseline investigative procedures were repeated.

### *Anthropometric assessment of body composition*

Weight was measured to the nearest 0.1 kg on a calibrated scale, and height was determined using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$). Waist circumference (cm) was measured as the minimum circumference at the umbilicus, using a tape measure. The waist to hip ratio (WHR), defined as the circumference at the waist divided by the maximum circumference over the ischial tuberosities, was used as an index of central adiposity.

### *Abdominal MRI*

Abdominal MRI examinations were performed on a Resonex RX 5000 0.38T clinical imaging system (Resonex, Sunnyvale, CA) using a multislice spin-echo inversion-recovery pulse sequence set to optimize bright (fat) *vs.* dark (aqueous signal) contrast from adjacent tissue (inversion time = 350 msec; repetition time = 500 msec; echo time = 15 msec; number of acquisition = 4; acquisition matrix = 128 × 256, zero-filled to 2562 image matrix). The participants were nonfasting at the time of examination. Three 1-cm-thick axial images were acquired at the level of the L4–L5 junction at a standard field of view (52 × 52 cm) with a 10% gap. Images were transferred to a Macintosh Computer and analyzed by a single, experienced observer, masked to group assignment, using the public domain NIH Image program (developed at the NIH and available on the Internet at http://rsb.info.nih.gov/nih-image/). Total abdominal area (TAA) was expressed as the area covering the cross-sectional area of the abdomen derived from the mean of 3 slices. The area of sc fat (in pixels) was calculated as the difference between the TAA and an area inside a continuous hand-drawn line demarcating the sc fat from the abdominal wall and paraspinal muscles. Intraabdominal visceral fat was identified using the density plot subroutine in the NIH Image program to plot pixel density across a fat/soft tissue boundary, selecting the signal intensity value at the center of the maximum intensity gradient and using that as the discriminant value. The number of pixels within the abdominal cavity of density equal to the critical value was then automatically counted using the Density Slice subroutine. Fat tissue was defined as previously reported (30). To account for possible changes in fat density between slices, we determined the density for each slice separately. Islands of fat in the abdominal wall and paravertebral muscles were excluded from the analysis. Pixel values were converted into $cm^2$ by applying the formula: $cm^2$ = number of pixels measured*(field of view)2/2562. For each subject, the mean areas, in $cm^2$, of all 3 slices were averaged for further statistical analysis. Repeated measurements of a random sample of 20 images produced an intraobserver coefficient of variation (CV) of 1.6% for sc fat and 6.5% for abdominal V fat, respectively.

### *Hormone assays*

Total serum IGF-I levels were measured by RIA after acid-ethanol extraction (Endocrine Sciences, Inc. Laboratories, Calabasas Hills, CA). Sensitivity of the IGF-I assay was 30 μg/liter, and the intra- and interassay CVs were, respectively, 5.9% and 7.3% at 289 μg/liter, and 4.6% and 6.3% at 591 μg/liter. Serum levels of E2 and T were determined by RIA, (Coat-A-Count, Diagnostic Products, Los Angeles, CA) performed in the laboratory of the Endocrine Section, National Institute on Aging. For E2, the minimum detectable concentration was 7.3 pM; and the interassay CVs were 7.6% at 32 pM, 5.0% at 68 pM, and 5.7% at 182 pM; and intraassay CVs were 9.7% at 31 pM, 9.3% at 66 pM, and 4.3% at 185 pM. For T, minimum detectable concentration was 0.3 nM; and the interassay CVs were 5.9% at 2.6 nM, 3.9% at 10.4 nM, 3.2% at 24.5 nM, and 4.8% at 36.1 nM; and intraassay CVs were 11.2% at 2.1 nM, 6.7% at 10.4 nM, 1.5% at 20.7 nM, and 3.1% at 34.6 nM.

### *Statistical analyses*

Data were analyzed with the SAS statistical software package, version 6.12 (SAS Institute, Inc., Cary, NC). All data are expressed as the mean ± SE. Possible sex differences in baseline measures between groups were assessed by the unpaired *t* test. Significance of changes in circulating hormone levels and MRI areas, after 26 wk of hormone administration (both within groups and *vs.* placebo) were calculated by analysis of covariance adjusted for age, hormone concentration at baseline, and treatment group. The analysis of covariance was performed using the General Linear Models Procedure to control for unequal group size. Relationships between changes in fat areas and anthropometric measures were assessed by linear regression analyses using Pearson's correlation coefficient. Results were considered significant at $P = 0.05$. The frequency of adverse events during the study period was assessed by Fisher's exact test with Bonferroni adjustment.

## Results

We studied 110 healthy elderly women (n = 46) and men (n = 64); mean age, 71 ± 0.4 yr (range, 65–88 yr). As shown in Table 1, at baseline, men were heavier and taller than women and had higher BMIs, waist circumferences, and WHRs. There were no significant baseline differences in anthropometric measures among treatment groups in either women or men. After 26 wk, GH (but not HRT or GH + HRT) decreased waist circumference in women (within group mean difference, −3.0 cm, $P = 0.05$). Similarly, in men, waist

**TABLE 1.** Age, anthropometric parameters and MRI measurements (mean ± SE) at baseline

| Group | N | Age | | Weight (kg)[a] | | Height (cm)[a] | | Waist (cm)[a] | | BMI (kg/m$^2$)[a] | | WHR[a] | | TAA (cm$^2$) | | sc Fat (cm$^2$)[a] | | V fat (cm$^2$)[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Women | | | | | | | | | | | | | | | | | | | |
| Placebo | 11 | 72.2 | 1.5 | 65.9 | 2.3 | 160.3 | 1.9 | 82.7 | 2.5 | 25.5 | 0.6 | 0.81 | 0.03 | 624 | 29 | 295 | 18 | 96 | 10 |
| GH | 12 | 70.2 | 1.2 | 67.5 | 2.0 | 158.7 | 1.4 | 86.2 | 2.0 | 26.8 | 0.8 | 0.82 | 0.02 | 612 | 22 | 274 | 23 | 97 | 12 |
| HRT | 12 | 71.3 | 0.9 | 63.6 | 2.0 | 159.9 | 1.7 | 81.6 | 2.0 | 25.0 | 0.5 | 0.83 | 0.02 | 544 | 16 | 232 | 17 | 83 | 5 |
| GH + HRT | 11 | 71.0 | 1.6 | 61.6 | 3.1 | 157.8 | 1.9 | 78.1 | 3.0 | 24.9 | 1.2 | 0.79 | 0.02 | 532 | 32 | 216[b] | 18 | 64[b] | 9 |
| Men | | | | | | | | | | | | | | | | | | | |
| Placebo | 15 | 70.5 | 1.0 | 88.1 | 2.6 | 178.3 | 1.6 | 99.2 | 1.8 | 27.5 | 0.4 | 0.96 | 0.01 | 623 | 20 | 198 | 10 | 126 | 9 |
| GH | 15 | 71.2 | 1.3 | 82.3 | 2.2 | 174.3 | 1.9 | 97.6 | 1.6 | 27.2 | 0.6 | 0.96 | 0.01 | 623 | 22 | 200 | 12 | 122 | 14 |
| T | 17 | 70.8 | 0.7 | 78.3 | 2.7 | 172.5 | 1.7 | 94.3 | 2.2 | 26.4 | 0.8 | 0.95 | 0.02 | 589 | 30 | 192 | 18 | 115 | 12 |
| GH + T | 17 | 73.6 | 1.5 | 80.6 | 2.2 | 173.1 | 1.3 | 96.9 | 2.3 | 27.0 | 0.8 | 0.97 | 0.02 | 617 | 29 | 207 | 16 | 119 | 11 |

[a] $P < 0.05$ women *vs.* men.
[b] $P < 0.05$ *vs.* placebo.

circumference decreased after treatment with GH alone (mean difference, −1.5 cm, $P = 0.005$) and GH + TE (mean difference, −1.5 cm, $P = 0.01$) but not after TE. In addition, WHR decreased in women after HRT (−0.01, $P = 0.05$) and in men after administration of GH (−0.1, $P = 0.05$) or GH + TE (−0.1, $P = 0.05$). Mean BMI values did not change significantly in any treatment group in either women or men.

At baseline, women and men had similar TAA, whereas sc fat was greater in women, and V fat was greater in men. At baseline, women in the GH + HRT group had less sc fat (216 ± 18 *vs.* 295 ± 18 cm$^2$, $P = 0.01$) and V fat (63 ± 9 *vs.* 96 ± 10 cm$^2$, $P = 0.01$), compared with those in the placebo group.

### *Effects of GH on serum IGF-I levels*

In women treated with GH alone or with GH + HRT, IGF-I levels rose from 107 ± 12 to 191 ± 13 μg/liter ($P = 0.001$) and from 132 ± 12 to 166 ± 17 μg/liter ($P = 0.05$), respectively, with a significantly greater response in women on GH alone ($P = 0.05$). In men, administration of GH alone or GH + T increased IGF-I levels ($P = 0.0001$) from 147 ± 112 to 250 ± 24 μg/liter ($P = 0.0001$) and from 117 ± 10 to 219 ± 12 μg/liter ($P = 0.0001$), respectively, with no significant difference in IGF-I response between the treatment groups. Neither placebo nor sex steroid administration significantly changed IGF-I levels in either sex (data not shown). After GH administration, IGF-I levels were higher in men *vs.* women (187 ± 10 *vs.* 142 ± 9 μg/liter, $P = 0.01$).

### *Effects of sex steroid replacement on serum E2 and T levels*

In women, administration of HRT or GH + HRT increased serum E2 levels similarly, from 7.3 to 31 ± 5.5 pM ($P = 0.005$) and 34 ± 5.1 pM ($P = 0.0001$), respectively. In men, TE increased serum T levels from 15.3 ± 0.8 to 20.2 ± 1.6 nM ($P = 0.005$) and GH + TE increased T levels from 14.6 ± 1.2 to 18.1 ± 0.9 nM ($P = 0.0005$), with no difference, in either sex, between the GH treatment groups with and without sex steroid. Neither placebo nor GH treatment significantly changed sex steroid levels in women or men (data not shown).

### *Effects of interventions on TAA and abdominal fat*

*TAA.* As illustrated in Fig. 1, there were no significant effects of any treatment on TAA in women. In contrast, men exhibited similar decreases in TAA after GH (−24 cm$^2$, $P = 0.05$) and GH + TE (−26 cm$^2$, $P = 0.05$), both within group and as compared with the placebo group. There was no significant change in TAA after TE.

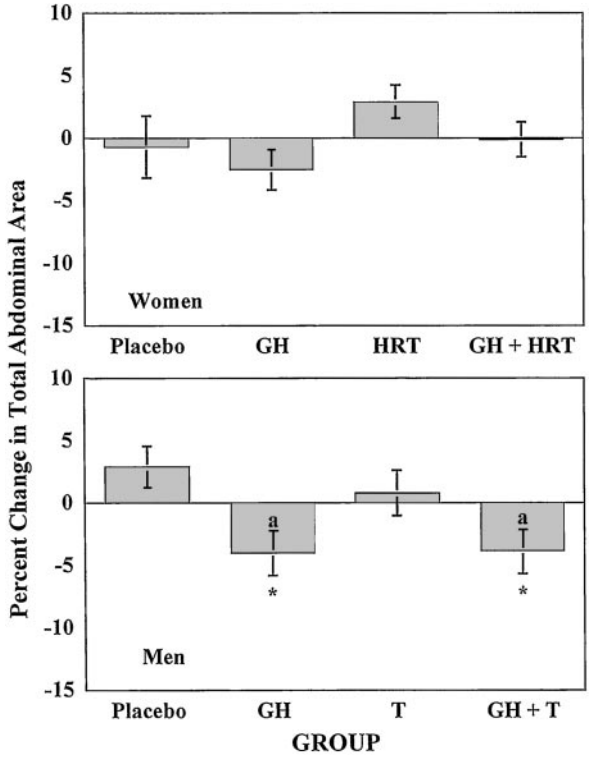


FIG. 1. Effects of hormone administration on TAA in healthy older women and men. Relative changes in areas (± SE) after hormone administration within group, *vs.* baseline; *, $P = 0.05$. Relative changes in areas after hormone administration *vs.* placebo; a, $P = 0.05$.

### *Subcutaneous abdominal fat*

In women, there were no significant changes in sc fat after any treatment (Fig. 2). In men, there were similar within-group decreases in sc fat after GH (−24 cm$^2$, $P = 0.01$) and GH + TE (−26 cm$^2$, $P = 0.0005$) and similar significant decreases *vs.* placebo after GH (−27 cm$^2$, $P = 0.01$), TE (−18 cm$^2$, $P = 0.05$), and GH + TE (−37 cm$^2$, $P = 0.005$).

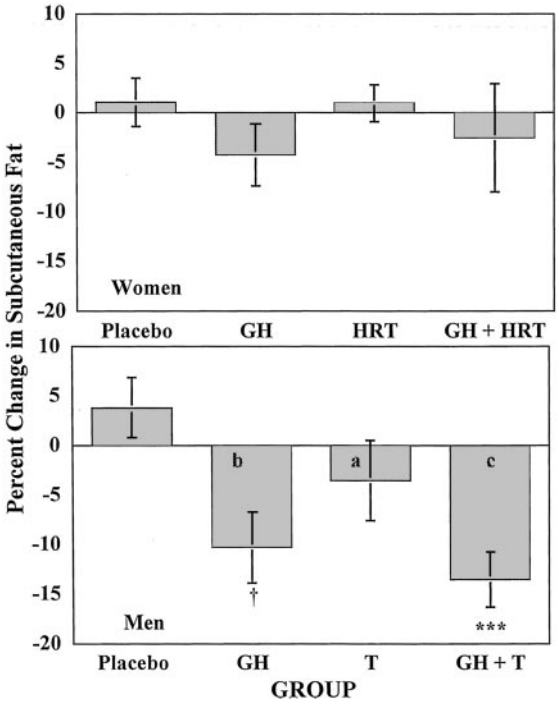


FIG. 2. Effects of hormone administration on sc fat in healthy aged women and men. Relative changes in areas (± SE) after hormone administration within group, *vs.* baseline; ***, $P = 0.005$; †, $P = 0.01$. Relative changes in areas after hormone administration *vs.* placebo; a, $P = 0.05$; b, $P = 0.01$; c, $P = 0.001$.

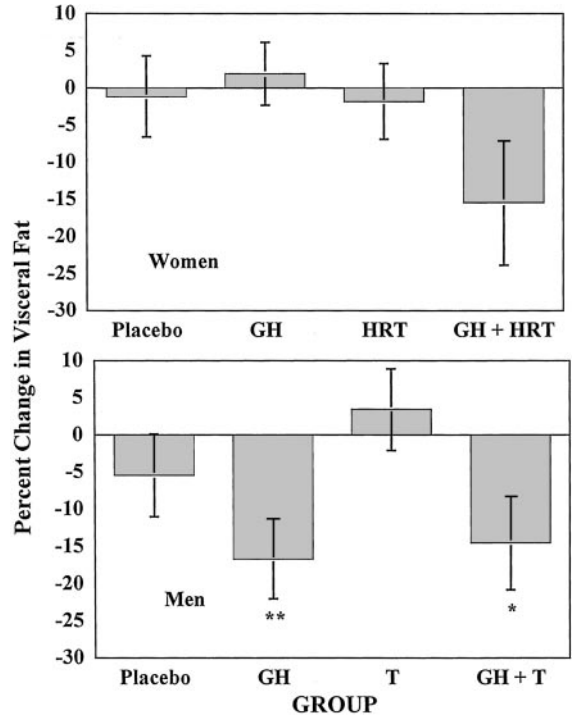


FIG. 3. Effects of hormone administration on V fat in healthy aged women and men. Relative changes in areas (± SE) after hormone administration within group, *vs.* baseline; *, $P = 0.05$; **, $P = 0.005$.

*Abdominal V fat*. In women, there were no significant changes in V fat after any treatment (Fig. 3). In men, there were similar, significant within-group decreases in V fat after GH ($-21$ cm$^2$, $P = 0.01$) and GH + TE ($-20$ cm$^2$, $P = 0.05$); whereas V fat areas did not change significantly, compared with placebo, after any hormone intervention.

### *Correlations of regional fat changes with anthropometric measures*

In men in all treatment groups combined, but not in women, the reduction in waist circumference was directly related to the changes in TAA (r = 0.64, $P = 0.0001$), sc fat (r = 0.51, $P = 0.001$), and V fat (r = 0.40, $P = 0.001$), and the reduction in BMI was directly related to that of sc fat (r = 0.41, $P = 0.01$). There were no other significant correlations between changes in BMI or WHR and any of the regional fat measurements in either sex. In addition, in men, changes in serum levels of IGF-I or T were not significantly related to changes in waist circumference, BMI, or WHR (data not shown).

### *Adverse events of hormone administration*

In women, administration of GH alone or GH + HRT, as compared with placebo, was associated with similar, significantly increased incidences of arthralgias and peripheral edema. By comparison, HRT administration, alone or in combination with GH, led to similar, significantly increased incidences of vaginal bleeding and breast tenderness. Clinical signs of carpal tunnel syndrome did not differ significantly between active and placebo groups. In men, GH alone or in combination with T led to increased incidence of carpal tunnel symptoms and arthralgias. T alone was not associated with significant side effects. Peripheral edema did not differ significantly between active and placebo groups.

## Discussion

The current study, to our knowledge, is the first that compares the effects of administration of GH and sex steroid, alone or in combination, on regional abdominal fat in healthy aged women and men. Prior studies have shown that administration of GH decreases total-body fat by 13–14% in aged men (16, 31) and by 9% in postmenopausal women (15). In comparison, total-body fat decreased by 13% in healthy aged men given T (18), whereas HRT prevented a 1.5–3% increase in body fat in postmenopausal women (23, 32). Because abdominal obesity, especially increased V fat, is a major risk factor for dyslipidemia, insulin resistance, diabetes, and cardiovascular disease (3–6), one potential benefit of GH and/or gonadal HRT in aged individuals is a reduction in the risks of these outcomes.

At baseline, we observed the expected increase in sc fat in women and increase in V fat in men reported in studies using computed tomography (CT) (1) or MRI (33). Our healthy aged men had amounts of sc and V fat similar to those reported in younger GH-deficient men (26, 27), a finding consistent with the observation that GH-deficient patients more than 60 yr old have amounts of truncal fat similar to those in aged matched healthy subjects (34). The latter and our current data are compatible with prior observations that aging and GH deficiency lead to similar effects on abdominal fat.

Waist circumference decreased slightly after GH in women, and after GH and GH + T in men. In women, the anthropometric changes were not mirrored by our negative MRI results. Furthermore, changes in TAA were not related to changes in waist circumference in women; whereas in men, they were directly and significantly related (data not shown). This apparent divergence between anthropometric and MRI findings in women may be attributable to the difference in reliability of the landmarks employed for the two measurements, *i.e.* the umbilicus (waist circumference) *vs.* L4/L5 (MRI), and suggests that in men, the umbilicus (as a topographical landmark) correlates better with L4/5 than in women. Moreover, waist circumference has been reported to correlate fairly closely with MRI-derived measures of sc fat, although the correlation with sc fat has been reported to be lower in women *vs.* men (35).

We found that in men, sc and V fat, as assessed by MRI, decreased by 10–17% after GH or GH + TE, whereas TE alone decreased sc fat by about 7% and did not significantly alter V fat. V fat did not decrease significantly after GH or GH + T. In women, there were no significant changes in sc or V fat after any hormone intervention. In a prior study, treatment of healthy, middle-aged, abdominally obese men with GH was reported to decrease sc fat by 5.4% and V fat by 14.5% fat (36). Similarly, 26 wk of GH treatment of young and middle-aged GH-deficient adults decreased sc fat by 15–27% and V fat by 30–47%, as assessed by either MRI or CT (25–27). The disproportionate reduction in V fat in adult GH-deficient patients treated with GH contrasts with the lesser and proportionate reductions in V and sc fat observed after GH in our older, relatively GH-deficient men, and this suggests that there is an age-related reduction in lipolytic responsivity of V fat to GH and combined GH + T administration. This difference could be related to our use of smaller doses of GH than those employed in some prior studies (25) and, possibly, to delayed responsiveness of V fat to such a hormone intervention. The significant within-group changes observed after GH and GH + T in our men may have resulted from the small group sizes studied and/or the large intragroup variability and, therefore, should not be interpreted as biologically significant. Whether longer-term administration of GH or GH + T to aged men elicits comparable effects on V fat, as observed in patients with adult GH deficiency, remains to be determined. Of note, 6 months of endurance exercise training resulted in disproportionate reductions in V *vs.* sc fat in healthy young men, but similar reductions in V and sc fat (37) in healthy aged men. Analogous data in women have yet to be reported.

Our finding that GH failed to alter abdominal fat significantly in healthy older women is consistent with the reduced response to GH reported in young and middle-aged GH-deficient women (38, 39). The GH doses in our study were calculated based on body weight and were not adjusted for sex. Serum IGF-I levels were significantly lower in our women than in our men, both before and after GH treatment. It is possible that with higher doses or a longer treatment period, we would have seen effects on regional abdominal fat in women similar to those observed in men. Another possible explanation for the reduced response to GH in our women might relate to the timing of the GH injections in our study, in that the injection paradigm employed did not account for the known sexual dimorphism in spontaneous GH secretory profiles in elderly women *vs.* men (40).

Studies of the effects of T on regional abdominal fat have variously shown a 13% reduction in sc fat, but no change in V fat, in young hypogonadal men treated with 100 mg TE/wk for 18 months (29); and a 5.4% reduction in V fat, but no change in sc fat, in abdominally obese men more than 45 yr old, after 8 months treatment with 80 mg T undecanoate twice daily (19). In both studies, the men were younger and received higher doses of T than in our study. In a recent study in which healthy aged men were treated for 3 yr with 6 mg T daily by scrotal patches, a dose comparable with that employed by us (18), leg and arm (but not truncal) fat decreased significantly, suggesting that T exerts a greater effect on peripheral *vs.* central fat depots. Taken together, these data suggest that topographical variations in responsiveness of fat to T administration depend on gonadal status, age, and dose. In our men, GH + TE and GH exerted similar effects on sc fat depots, suggesting that the changes observed in fat were GH-induced. We are unaware of any other published study of the dual *vs.* single effects of GH and/or TE on abdominal fat in aged men.

In women, waist circumference decreased significantly after GH, but not after GH + HRT, suggesting that HRT attenuated the GH-mediated effects on waist circumference. Support for this concept is provided by the observation that GH-deficient women require higher GH replacement doses when cotreated with estrogens (41, 42). Use of HRT has been reported to prevent weight gain in postmenopausal women (21, 22). In one study, using dual-energy x-ray absorptiometry methodology, 6 months of treatment with transdermal estrogens prevented an increase in central adiposity in healthy postmenopausal women (20); whereas in another report, oral HRT reduced central fat in overweight postmenopausal patients with type 2 diabetes mellitus (43). Using MRI methodology in women somewhat older than those in the above studies, we did not detect a significant change in sc or V fat in response to HRT.

There are several possible limitations to the interpretation of our findings. The numbers of individuals in each treatment group, especially for women, were not large. Studies comparing CT and MRI have shown a high correlation between the two methods, but demonstrate CT to have better reproducibility of, and greater absolute areas estimated for, V fat measurements (44, 45). Our use of an average of three contiguous MRI images per subject reduced the average CV to values that were smaller than previously reported for a single MRI image (44, 45). Finally, the MRI image acquisition was weighted to provide maximal signal intensity within fat tissue, which diminished the ability to detect possible changes in lean tissue in the abdominal cross-sectional area.

In the current study, administration, to both women and men, of a fixed dose of 20 $\mu$g GH/kg BW, three times weekly, was associated with an elevated frequency of side effects, similar to that reported previously in studies of older women (15) and men (31) treated with comparable GH doses. It seems likely that use of lower GH doses in older adults, as suggested by Toogood *et al.* (28) would have reduced the frequencies of adverse events.

We studied individuals with a wide range of BMI (19.3–32.4), which increased the variability in our data significantly. Our subjects were selected for unusually good health and were, thus, not representative of a more typical aged population. Although our participants were asked not to change their diet or level of physical activity during the study, the absence of more rigorous control of diet or physical activity during the study is a potential confound.

The current study suggests that administration of GH to healthy somatopausal and gonadopausal men exerts a greater beneficial effect on abdominal fat than does treatment with T, and that there is no additive effect of T with GH. In contrast, in healthy older women, no such beneficial effect is apparent with GH or HRT given alone or together. Because of the association between abdominal obesity and increased risk for coronary artery disease and stroke (46–48) and the epidemiological data showing reduction in fat mass to be associated with lower cardiovascular risk (49), further studies to assess potential beneficial effects of manipulating the GH axis on abdominal fat and the risk of cardiovascular disease in various populations of aged men and women seem warranted.

## Acknowledgments

We gratefully acknowledge the expert assistance of the nursing staff of the Johns Hopkins Bayview Medical Center's General Clinical Research Center. We thank Ms. Stephanie Bosley for her skilled performance of the abdominal MRI scans; Genentech, Inc., and Novartis Pharmaceuticals for their generous provision, respectively, of recombinant human GH and transdermal E2; and Drs. Reubin Andres and Richard Spencer for their constructive critical reviews of this manuscript.

Received February 29, 2000. Accepted April 30, 2001.

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This work was supported in part by NIH Research Grant RO-1-AG11005 (to M.R.B.) and General Clinical Research Center Grant MO-1-RR-02719, from the National Center for Research Resources, NIH. T.M. was supported by the International Fellowship Program of the NIH.

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