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Effects of Human Growth Hormone, Insulin-Like Growth Factor I, and Diet and Exercise on Body Composition of Obese Postmenopausal Women*

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ABSTRACT

To determine the effects of GH and insulin-like growth factor I (IGF-I) administration, diet, and exercise on weight loss, body composition, basal metabolic rate (BMR), muscle strength, and psychological status, 33 moderately obese postmenopausal women (67.1 ± 5.2 yr) participated in a 12-week randomized, double blind study. Participants were placed on a diet that provided 500 Cal/day less than that needed for weight maintenance, and they walked 3 days and strength trained 2 days each week. Subjects also self-injected GH (0.025 mg/kg BW·day), IGF-I (0.015 mg/kg BW·day), a combination of these doses of GH and IGF-I, or placebo (P). Twenty-eight women completed the study, as five subjects dropped out due to intolerable side-effects (*e.g.* edema). Weight loss occurred in all groups, with the largest decrease occurring in the GH plus IGF-I group (5.6 ± 1.4 kg). Fat mass significantly decreased in all groups, with the largest losses observed in GH and GH plus IGF-I groups (6.3 ± 1.8 and 8.4 ± 2.8 kg, respectively). Despite weight loss, BMR was maintained in all groups. Muscle strength increased with training for all groups, and depression and anxiety scores decreased in groups receiving IGF-I. These data show that obese postmenopausal women can lose weight and fat without compromising fat free mass, BMR, or gains in muscle strength, and that GH and IGF-I given together may enhance fat loss over either given alone. (*J Clin Endocrinol Metab* **83:** 1477–1484, 1998)

SOMATIC changes in normal aging include loss of lean tissue and bone mass, decreased muscle strength and resting metabolic rate, and increased fat mass (1–3). One possible mechanism underlying these changes is the age-related decline in the activity of the GH/insulin-like growth factor I (IGF-I) axis (4), referred to as the somatopause.

A few studies have examined the combined effects of diet and exercise on body composition in obese elderly women, and these indicate that such individuals are capable of losing body fat with dietary restriction, and that energy restriction coupled with exercise may permit the maintenance of fat-free mass, bone mass, and resting metabolic rate (5–7). As both GH and IGF-I have been shown to have dramatic effects on body composition of normal weight postmenopausal women even in the absence of dietary change (8, 9), it is possible that combining GH and IGF-I therapy with a sound dietary and exercise regimen could provide additional benefit to overweight postmenopausal women. As postmenopausal women are already at an increased risk of lower bone mass and fat-free mass, treatment regimens that minimize these changes while enhancing fat loss would be beneficial. In addition, the stabilization or increase in fat-free mass and resting metabolic rate with a decrease in fat mass are critical to long term maintenance of weight loss and exercise capacity (10).

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Recent studies have reported the effects of GH and IGF-I on body composition in postmenopausal women, in whom both agents increased fat-free mass and decreased fat mass (8, 9). However, 1 yr of GH administration did not promote any sustained effect on whole body muscle or bone accretion (8), and the effects of longer term IGF-I administration on body composition in postmenopausal women have not been determined. Both GH and IGF-I are reported to produce unpleasant and potentially serious adverse effects, such as carnal tunnel syndrome and edema (8, 9, 11).

Administration of GH increases circulating concentrations of IGF-I and IGF-binding protein-3 (IGFBP-3), whereas IGF-I administration increases IGF-I, but has no effect on IGFBP-3 (8, 9, 12). As IGFBP-3 plays an important role in IGF-I action (13), it is possible that administering a combination of IGF-I with GH at relatively low doses could result in a greater action of these two hormones. This action could enhance fat loss while sparing fat-free mass in obese individuals.

The purpose of this study was to determine whether GH and IGF-I, given alone or in combination, were of additive benefit for weight loss, fat loss, maintenance of fat-free mass and resting metabolic rate, gains in muscle strength and maximal oxygen consumption, and improvement in psychological status in moderately obese postmenopausal women participating in a 12-week diet and exercise program.

Subjects and Methods

Subjects

Thirty-four postmenopausal women initially volunteered for this study. Thirty-three (mean age ± SD, 67.1 ± 5.2 yr) actually participated in this 12-week, randomized, double blind diet and exercise study. All

women were 20–40% above ideal body weight, as determined by the 1954 Metropolitan Life Insurance Co. height and weight chart (14). Exclusion criteria included diabetes, uncontrolled hypertension, personal history of cardiovascular disease or cancer, family history of colon cancer, and any other disorder that would prevent safe participation in a diet and exercise program.

Women taking hormone replacement therapy (HRT) were allowed to enroll if they had been on a stable dose for at least 6 months. All participants completed rigorous medical screening before entry into the program, including a physical examination, mammogram, blood and urine analyses, a 12-lead resting electrocardiogram, an endometrial biopsy for women receiving HRT, and a maximal exercise stress test. Written consent to participate was given by all subjects, and the protocol was approved by the Stanford committee for the protection of human subjects.

Diet and exercise program

Before starting the 12-week diet and exercise program, all women completed an 8-day diet and activity record. The diet log was used to highlight potential areas for improvement and to acquaint the women with tracking their dietary intake. The activity records were used in conjunction with the measured basal metabolic rate (BMR) to estimate each woman's daily energy need using energy values previously reported (15). The diet and exercise program was similar to one previously described (7). Briefly, the energy intake was 500 Cal/day less than estimated daily energy needs and subjects performed endurance exercise (walking, three times per week) and weight training (two times per week).

Body composition assessments

Body weight was measured every week for the initial 4 weeks of treatment and every 2 weeks for the remaining 8 weeks. Body weight was measured using a digital scale, with subjects wearing a light weight hospital gown. Measurements of fat-free mass, fat mass, and percent body fat were completed at baseline and after 12 weeks of participation using dual energy x-ray absorptiometry (DXA; Hologic QDR 2000, software version 6.3, Hologic, Waltham, MA). Total body water (TBW) and extracellular fluid (ECF) compartments were measured at baseline and after 4 and 12 weeks of treatment. TBW was determined using deuterium dilution (16, 17), and ECF was measured using the sodium bromide technique (18). Intracellular fluid (ICF) was estimated by subtracting ECF from TBW.

BMR

BMR was measured at baseline and after 12 weeks of treatment. Measurements were made as previously described (7). The reliability of BMR measurements was high (intraclass correlation = 0.96). At least two of the three BMR values matched within 80 Cal, and the closest values were averaged to represent BMR before and after drug treatment.

IGF-I and GH administration

Study drugs were administered under IND 34,291 and IND 36,944. Both GH and IGF-I were provided by Genentech (South San Francisco, CA). Subjects were admitted to the Aging Study Unit, a clinical investigation ward. After completion of the medical screening and baseline records, subjects were randomly assigned by age, height, weight, and estrogen replacement status into four treatment groups. The first group received GH (0.025 mg/kg BW·day; n = 9). The second group received IGF-I (0.015 mg/kg BW·day; n = 7). The third group received both GH and IGF-I at the doses given above (GH+IGF-I; n = 10), and the fourth group received a placebo injection (P; n = 7). Participants were trained to self-administer study drugs sc every morning and evening. Each drug was administered once per day; for those subjects receiving GH or IGF-I only, a single injection of placebo or drug was given at each time point.

Biochemical analyses

Morning fasting measurements of IGF-I and IGFBP-3 in serum were taken at baseline and after 4 and 12 weeks of treatment. IGF-I was assayed by RIA after acid chromatography of samples to separate the IGF peptides from the BPs (19). IGFBP-3 was measured using our previously described RIA (20). Blood samples were permitted to clot and were quickly centrifuged and separated before storage at −20 C. All samples from a given woman were assayed in single assay runs.

Biochemical markers of bone resorption and formation were measured, as we previously validated and reported (21). To assess bone resorption activity, we measured urinary excretion of deoxypyridinolines (Pyrilinks-D, Metra Biosystems, Mountain View, CA) and the carboxyl-terminal telopeptide of type I collagen (Crosslaps, Diagnostic Systems Laboratories, Webster, TX). To estimate bone-forming activity, we measured plasma concentrations of osteocalcin by immunoradiometric assay (Diagnostic Systems Laboratories) and the carboxyl-terminal extension peptide of type I collagen (CICP) by enzyme-linked immunosorbent assay (Metra). Specimens were stored frozen at −80 C and were thawed only at the time of assay. All samples for an individual subject were processed batchwise in a single assay run.

Muscle strength, maximal oxygen uptake, and walking performance

Isotonic muscle strength was determined for all muscle groups at baseline and every 2 weeks during the treatment period using the one repetition-maximum test. Training loads were increased every 2 weeks based on the updated one repetition-maximum values. Maximal oxygen uptake (VO_2max) was measured at baseline and after 12 weeks of treatment, as previously reported (7). To determine possible benefits to activities of daily life, walking performance was determined using timed walk and timed stair climb tests. The timed walk test involved subjects walking at their self-selected pace over a distance of 25 feet, and the number of steps taken and the time to complete this distance were recorded. The timed stair climb test required walking up a set of stairs (12 steps) at a self-selected pace with the option to stop before completing the task due to fatigue. The number of stairs climbed and the time to complete the climb were recorded.

Psychological measures

Subjects were also tested on a brief psychometric battery completed before and after treatment. This battery was designed to test memory function and levels of depression and anxiety. Depression was evaluated using the Geriatric Depression Scale (22), a self-rating measure that is widely used in the assessment of depression in the elderly. Anxiety was tested using the State-Trait Anxiety Inventory. The Trait version State-Trait Anxiety Inventory (23) provides a measure of one's perceptions of anxiety at the time the inventory is administered. Memory testing included tests of name-face recall and word recall used in studies of cognitive interventions for older adults (24).

Statistical analyses

Physiological data were analyzed using the Statistical Analysis System (SAS-PC for Windows, version 6.2, SAS Institute, Cary, NC), and the psychological variables were analyzed using StatView and SuperANOVA for MacIntosh. Physiological measures were analyzed using a 2×4 (time $\times$ treatment) repeated measures ANOVA (with time as the repeated measures factor) to determine any difference among treatment groups over time, with significance set at $P \leq 0.05$. Tukey *post-hoc* tests were used to identify significantly different means among treatments. Psychological measures were analyzed using a $2 \times 2 \times 2$ (time $\times$ GH treatment $\times$ IGF treatment) repeated measures ANOVA (with time as the repeated measures factor) to determine any difference among treatment groups over time, with significance set at $P \leq 0.05$. The results for psychological measures are considered preliminary and hypothesis generating rather than hypothesis testing due to the multiple measures and small number in each condition.

Results

Table 1 contains the descriptive characteristics of the 33 women who initially participated for this study. There were no significant differences in any baseline descriptive char-

TABLE 1. Baseline characteristics of study participants

	GH (n = 9)	IGF-I (n = 7)	GH + IGF-I (n = 10)	Placebo (n = 7)
Age (yr)	69 ± 7	65 ± 5	67 ± 5	67 ± 4
Ht (cm)	161.9 ± 4.6	162.1 ± 3.2	163.8 ± 4.2	162.3 ± 5.0
Wt (kg)	80.5 ± 6.4	81.5 ± 7.0	83.0 ± 8.0	81.7 ± 6.3
Body fat (%)	42.3 ± 4.2	42.8 ± 4.8	42.7 ± 4.0	42.0 ± 5.9
Fat-free mass (kg)	46.1 ± 3.1	46.5 ± 3.4	46.3 ± 4.1	46.8 ± 2.7
Serum IGF-I (ng/mL)	94.0 ± 54.9	78.4 ± 38.6	121.3 ± 32.8	95.6 ± 38.1
VO_2max (mL/kg·min)	18.2 ± 3.4	19.6 ± 2.5	17.3 ± 4.2	18.4 ± 3.7
Body mass index (kg/m^2)	30.7 ± 2.3	31.0 ± 2.5	30.9 ± 3.0	31.1 ± 3.0

Values are the mean ± SD.

acteristics among the treatment groups. All women were considered obese, with body mass index (BMI) values ranging from 26–35 (31 of 33 women had BMI ≥27) and percent body fat ranging from 34–53%. Twenty-four women were taking HRT: 6 of 9 in the GH group, 5 of 7 in the IGF group, 5 of 7 in the P groups, and 8 of 10 in the GH+IGF-I group. There was no difference observed in any measured variable by HRT status; therefore, the data for women taking and those for women not taking HRT were combined.

Of the original 34 volunteers, one was removed from the study for noncompliance, and five did not complete the study because of intolerable side-effects. Two of these women were in the GH group, and the others were assigned to the GH+IGF-I group. All women assigned to IGF-I and P groups completed the study. One GH woman and two of the GH+IGF-I women completed the study at half the dose of study drug. Table 2 lists the adverse experiences of all subjects in each treatment group. The most commonly reported symptom was peripheral edema, which was particularly frequent in women receiving GH.

For the BMR data, analyses were performed on the 27 women who completed the study. Psychological measures were analyzed for the 24 women who completed these tests at baseline and posttreatment. Analyses of body composition, body weight, muscle strength, and blood parameters were performed on the data from the women who participated through the defined time points, with the corresponding subject numbers reported in the subsequent tables and figures.

Fifteen women were prescribed furosemide (20 mg) to treat the discomfort of edema. Eight women taking GH and five women taking GH+IGF-I, but only one woman each in the IGF-I and P groups, were prescribed furosemide.

Changes in body weight, fat, and fat-free masses are presented in Figs. 1 and 2. All groups experienced a significant decrease in body weight ($P = 0.0001$). There was a significant treatment by time interaction ($P = 0.03$), indicating significant differences among groups for weight loss over time. However, *post-hoc* analyses were unable to distinguish where significant differences existed among the groups.

Fat-free mass significantly increased over 12 weeks, with a significant treatment by time interaction ($P = 0.003$). As shown in Fig. 2A, mean increases of 3.6 ± 1.9 and 2.7 ± 2.1 kg were found for the GH and GH+IGF-I groups, respectively, whereas IGF-I and placebo groups showed virtually no change. Fat mass decreased significantly in all treatment groups, and a significant treatment by time interaction was found ($P = 0.002$). For both fat-free mass and fat mass, *post-hoc* tests could not identify the significantly different groups. BMI decreased in all but 3 women, with 10 women showing a posttreatment BMI between 27–29, and 4 women with BMI values less than 27.

Sample volumes for TBW and ECF were insufficient for four women, resulting in final samples sizes of six for the GH, IGF-I, and P groups and five for the GH+IGF-I group. TBW did not change for any group over the course of treatment ($P = 0.29$; Fig. 3A). There were significant changes in ECF (Fig. 3B) from baseline to 12 weeks of treatment ($P = 0.04$), with no differences found among treatment groups. No sig-

TABLE 2. Adverse experiences according to treatment assignment

Adverse event	GH (n = 9)	IGF-I (n = 7)	GH + IGF-I (n = 10)	Placebo (n = 7)
Edema	8	2	6	1
Joint soreness	2	1	0	0
Hand numbness	4	2	3	0
Wrist pain	0	0	2	0
Fatigue/lethargy	5	0	3	1
Breast tenderness	1	1	2	0
Irritation at injection site	1	4	1	0

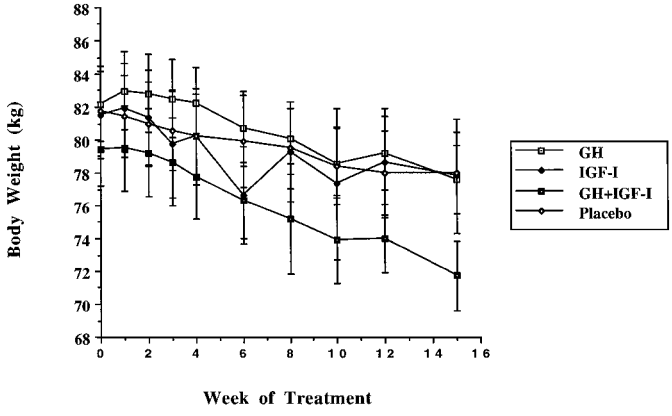

FIG. 1. Changes in body weight (mean ± SEM) in postmenopausal women completing a 12-week diet and exercise study in which GH, IGF-I, GH+IGF-I, or P were administered. Subject number in each group is as follows: GH, n = 7 for weeks 1–8, 12, and 15, n = 6 for week 6; IGF-I, n = 7 for weeks 1–12; GH+IGF-I, n = 5 for weeks 1–6, 12, and 15, n = 3 for week 8, and n = 4 for week 10; and P, n = 7 for weeks 1–12.

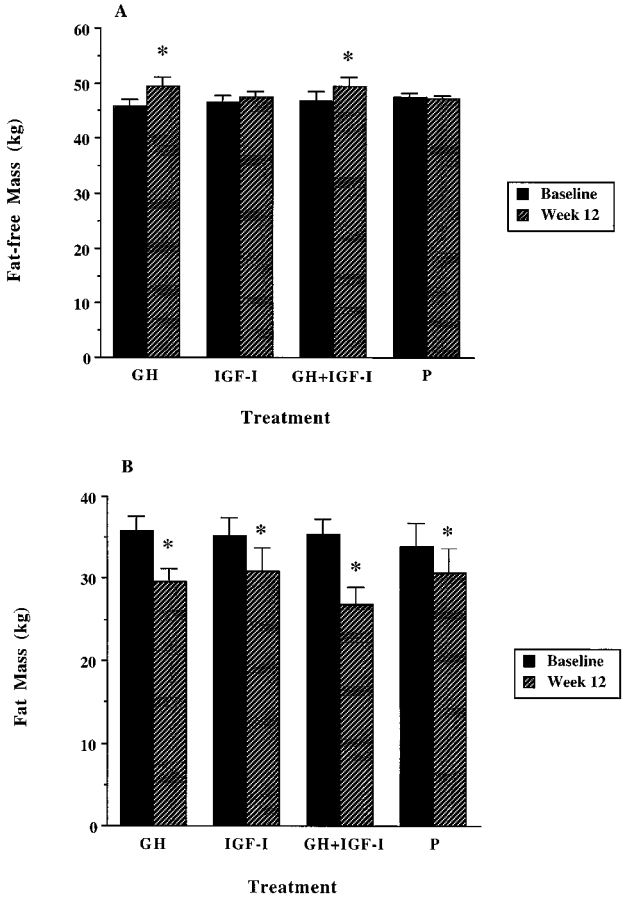

FIG. 2. Levels of fat-free mass (A) and fat mass (B) at baseline and after 12 weeks (Post Treatment) of GH (n = 7), IGF-I (n = 7), GH+IGF-I (n = 6), or P (n = 7) administration in postmenopausal women participating in a 12-week diet and exercise study. Values are the mean ± SEM. *, Significantly different from baseline at $P \leq 0.05$.

nificant changes in ICF (Fig. 3C) were observed over time ($P = 0.62$).

Figure 4 represents the relationship between BMR and fat-free mass for all subjects at baseline and at week 12. There was no significant change in BMR over the course of 12 weeks for any treatment group ($P = 0.71$). Thus, data for all groups were combined.

Serum IGF-I concentrations increased significantly after 4 and 12 weeks of treatment in the drug-treated groups (with values meeting or exceeding those of young subjects), with no changes observed in the P group (Table 3). Compared to baseline, the largest increase occurred at 4 weeks of treatment ($P = 0.0001$), with levels decreasing, but remaining elevated above baseline, after 12 weeks of treatment ($P = 0.01$). Serum concentrations of IGFBP-3 increased for the GH and GH+IGF-I groups after 4 weeks of treatment ($P = 0.008$) and remained elevated above baseline values at week 12 for the GH group only (Table 3).

Treatment effects on bone resorption markers are presented in Table 3. No treatment group demonstrated statistically significant changes over time in either deoxypyridinoline or C-terminal telopeptide (Crosslinks) excretion. However, the GH and GH+IGF-I groups showed trends at

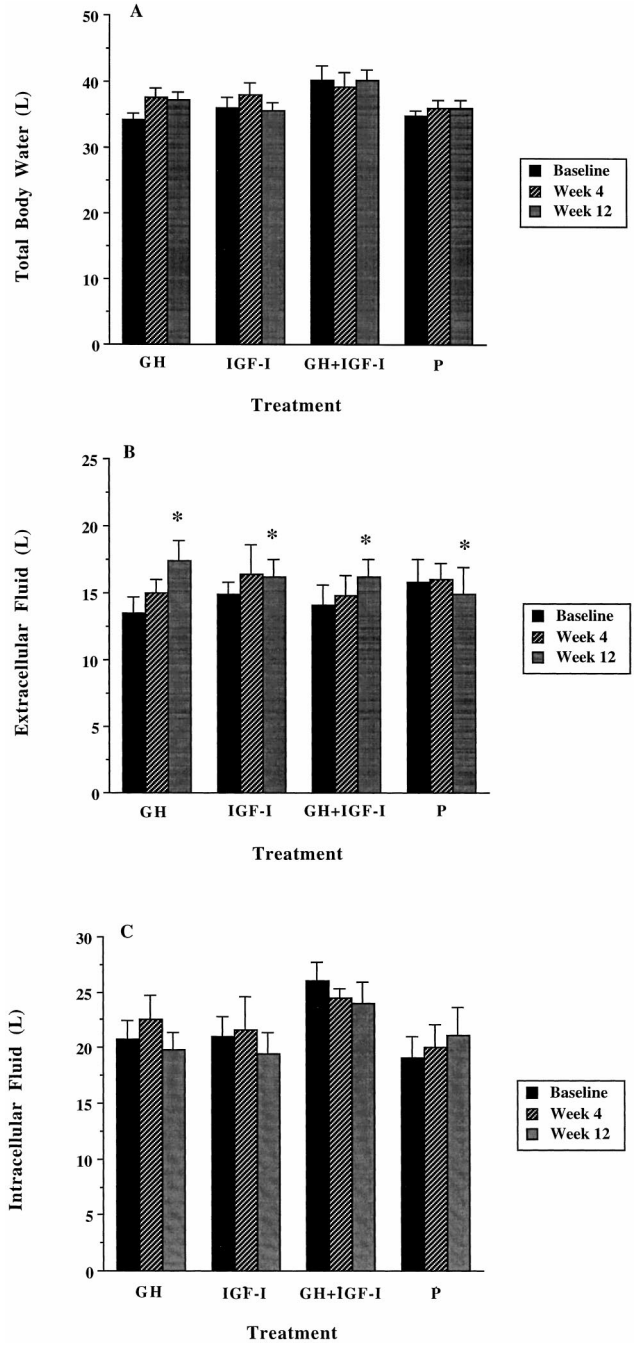

FIG. 3. Changes in TBW (A), ECF (B), and ICF (C) for postmenopausal women participating in a 12-week diet and exercise study in which subjects were administered GH (n = 6), IGF-I (n = 6), GH+IGF-I (n = 5), or P (n = 6). Values are the mean ± SEM. *, Significant at $P \leq 0.05$.

12 weeks ($P = 0.08$) toward increased excretion of the C-terminal telopeptide.

Treatment effects on bone formation markers are also presented in Table 3. Osteocalcin concentrations were significantly higher than baseline in the GH, IGF-I, and GH+IGF-I groups at 4 weeks and for all treatment groups at 12 weeks. The osteocalcin response in subjects receiving GH+IGF-I showed a nonsignificant trend toward being higher (P =

0.09) than in the other groups. No significant changes were observed in CICP activity for any treatment group.

There were no significant changes in VO_2max for any treatment group over time whether the values were expressed in absolute terms or per kg BW. There was a trend toward a faster walking time ($P = 0.10$) and a reduced number of steps taken ($P = 0.0001$) during the timed walk test for all groups, with no differences among the treatment groups. There was no change in timed stair test performance ($P = 0.89$). Progressive increases in maximal strength of all muscle groups were observed in all treatment groups ($P = 0.0001$), with no differences by treatment assignment (data not shown). Strength gains for the biceps curl began to plateau at 6 weeks of treatment, whereas gains for the triceps extension and leg press plateaued by the eighth week of treatment.

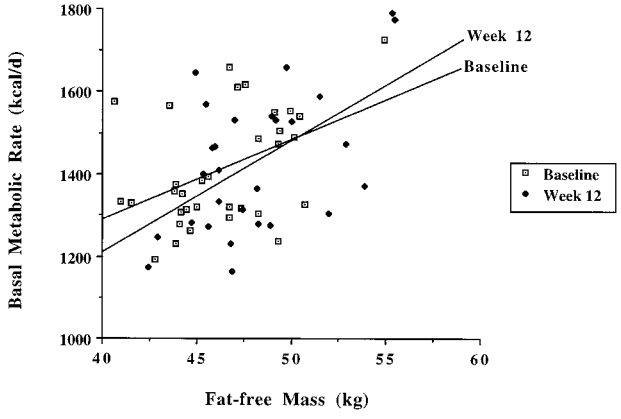

FIG. 4. The relationship between BMR and fat-free mass for 27 postmenopausal women at baseline and after 12 weeks of diet and exercise accompanied by the administration of GH, IGF-I, GH+IGF-I, or P.

As shown in Table 4, there was a significant interaction of IGF-I and time of testing for the depression ($P = 0.02$) and anxiety ($P = 0.04$) measures, such that depression and anxiety scores decreased over time with IGF-I treatment regardless of whether GH was also given. There was also a nonsignificant trend for the IGF-I subjects to show improvement on the list-learning task ($P = 0.09$).

Discussion

The results of this study show that administration of GH alone or in combination with IGF-I caused a greater increase in fat-free mass and a greater reduction in fat mass than those achieved by diet and exercise alone. Administration of GH+IGF-I resulted in significant changes in fat and fat-free masses over 12 weeks of energy deficit, with fat loss averaging 0.7 kg/week, and gains in fat-free mass of 0.2 kg/week. Gains in fat-free mass under circumstances of energy deficit are contrary to the experience of other diet and exercise studies, in which fat-free mass has usually been reported to decrease significantly (25, 26) or, at best, to be maintained (5, 6, 27).

GH treatment alone in the present study led to the smallest change in body weight of all treatments. There were no obvious indications that the women in this group failed to comply with the dietary intervention. They did express frustration with the fact that they did not experience satisfactory weight loss despite adhering to the prescribed regimen. The low dose of IGF-I used alone did not appear to enhance weight or fat loss, or increase fat-free mass compared to the use of diet and exercise alone.

TABLE 3. Changes in serum levels of growth factors and bone markers in postmenopausal women according to treatment assignment

Variable	GH (n = 9)	IGF-I (n = 7)	GH + IGF-I (n = 9)	Placebo (n = 7)
IGF-I (μg/L)				
Baseline	94.0 ± 54.9	78.4 ± 38.7	121.2 ± 32.8	95.6 ± 38.1
Week 4	246.7 ± 125.7[a]	220.1 ± 96.1[a]	520.1 ± 227.3[a]	92.0 ± 48.2
Week 12	170.3 ± 133.4[a,b]	128.3 ± 44.2[a]	209.1 ± 162.1[a,c]	92.5 ± 49.6
IGFBP-3 (μg/L)				
Baseline	2394.7 ± 957.5	2397.3 ± 634.5	2831.3 ± 676.9	2100.4 ± 561.5
Week 4	3284.9 ± 799.9[a]	2227.0 ± 696.5	3531.3 ± 889.4[a]	1912.5 ± 540.7
Week 12	2991.9 ± 1035.5[a,b]	2248.3 ± 536.3	2266.1 ± 1178.8[c]	2217.7 ± 535.7
PYD (nmol/L/mmol/L)				
Baseline	5.4 ± 3.6[d]	5.4 ± 4.0[c]	3.6 ± 1.3[e]	6.1 ± 3.1[e]
Week 12	12.6 ± 14.8[d]	6.8 ± 2.3[c]	11.7 ± 5.3[e]	5.1 ± 2.3[e]
C-Terminal telopeptide (μg/L/mmol/L)				
Baseline	102.3 ± 36.6[b]	84.4 ± 51.5	92.8 ± 65.5[e]	176.5 ± 106.2[c]
Week 12	698.9 ± 1128.2[b]	166.7 ± 91.4	388.3 ± 305.8[e]	160.2 ± 177.5[c]
Osteocalcin (ng/mL)				
Baseline	2.2 ± 2.8[b]	6.0 ± 7.7	1.9 ± 3.3[c]	9.9 ± 12.3
Week 4	3.6 ± 3.8[a,b]	9.9 ± 10.6[a]	19.6 ± 14.7[a,c]	7.4 ± 11.3
Week 12	8.7 ± 8.1[a,d]	8.2 ± 8.1[a]	17.9 ± 20.0[a,e]	14.1 ± 13.2[a,b]
CICP (ng/mL)				
Baseline	85.2 ± 20.8[b]	85.3 ± 31.4	88.6 ± 58.5[c]	99.7 ± 41.9
Week 4	146.9 ± 43.7[b]	94.2 ± 38.9	98.6 ± 30.6[c]	95.1 ± 39.3
Week 12	76.8 ± 55.9[b]	80.4 ± 27.7	78.1 ± 89.5[c]	97.8 ± 26.7[b]

Values are the mean ± SD.
[a] Significantly different at $P \leq 0.05$.
[b] n = 7.
[c] n = 6.
[d] n = 5.
[e] n = 4.

TABLE 4. Changes in psychological measures in subjects according to treatment group

	GH (n = 6)	IGF-I (n = 6)	GH + IGF-I (n = 6)	Placebo (n = 6)
Depression				
Baseline	1.2 ± 1.3	7.5 ± 7.8	6.3 ± 7.0	3.0 ± 2.5
Week 12	5.2 ± 6.6	6.5 ± 7.0[a]	4.3 ± 6.0[a]	3.3 ± 3.1
Change (%)	333.3	−13.3	−31.7	10.0
Anxiety				
Baseline	26.7 ± 4.8	41.5 ± 12.8	30.7 ± 8.6	29.3 ± 7.9
Week 12	31.3 ± 12.3	34.7 ± 11.8[a]	27.2 ± 6.9[a]	28.3 ± 7.0
Change (%)	17.2	−16.4	−11.7	−3.4
Memory for words				
Baseline	7.7 ± 5.4	10.3 ± 2.7	6.3 ± 3.1	6.2 ± 2.9
Week 12	6.3 ± 3.4	11.2 ± 3.0	8.0 ± 4.3	6.0 ± 1.7
Change (%)	−18.2	8.7	27.0	−3.2
Memory for names				
Baseline	6.5 ± 3.4	9.3 ± 2.4	6.2 ± 3.6	7.7 ± 3.8
Week 12	4.2 ± 2.7	9.5 ± 2.3	4.8 ± 3.8	6.5 ± 1.6
Change (%)	−35.3	2.1	−21.3	−14.4

Values are the mean ± SD.
[a] Significantly different from baseline at $P \leq 0.05$.

Despite increases in fat-free mass for the women taking GH and GH+IGF-I in the present study, TBW did not increase significantly. Although these findings appear contradictory due to the obligatory water retention that accompanies a gain in protein (6), lack of statistical significance in the GH group most likely reflects low statistical power. TBW increased by 2.91 L from baseline to week 12 in women assigned to GH treatment, which is consistent with the observed 3.3 ± 2.0-kg increase in fat-free mass in these same women. No significant changes in TBW occurred in those taking GH+IGF-I, as an increase in ECF (2.07 L) was offset by a concomitant decrease in ICF (2.03 L).

Although some of the increased FFM measured by DXA in both the GH and GH+IGF-I groups is due to water retention, some undoubtedly represents true increases in fat-free tissue. Previous results in normal weight elderly women (28) demonstrated that both GH and IGF-I stimulate whole body and muscle protein synthesis. The effects of GH diminished after 4 weeks, whereas the changes occurring with IGF-I were retained. Although muscle protein turnover was not assessed in the present study, increases in TBW reflect at least to some extent the increase in fat-free mass demonstrated by DXA. Although a portion of the observed changes in relative adiposity would have been influenced by fluid balance, the observed loss of adipose mass by DXA is robust over a wide range of hydration states (29).

All women in the present study achieved significant body weight and fat loss without a change in BMR. As failure to maintain BMR appears to predict failure of some long term weight control strategies (10), these findings are promising and differ from most diet and diet plus exercise studies (27, 30). The moderate degree of energy restriction and maintenance of fat-free mass in the present study most likely contributed to these findings. The few published studies of diet and exercise in postmenopausal women (6, 7) have shown BMR to decrease slightly (46–86 Cal/day) with diet and exercise treatments similar to those of the present study. The BMR responses of our participants varied greatly, with the GH group showing a trend toward an increase of 145 Cal/day, the IGF-I group showing no apparent trend, and the P and GH+IGF-I groups showing trends toward decreases of 36 and 80 Cal/day, respectively. However, these trends were less impressive than those reported for premenopausal women on more severe dietary restrictions (decreases of 100–250 Cal/day), and none achieved statistical significance.

Both GH and IGF-I have been previously reported to increase the rate of bone turnover in healthy postmenopausal women, as evidenced by increased activity of both resorption and formation markers (21). In the present study, only statistically nonsignificant trends toward increased resorption activity were observed, whereas bone formation (as indicated by osteocalcin concentrations) increased significantly in all participants, including those exposed only to diet and exercise. Proper interpretation of these findings requires consideration of several issues. First, all markers of bone turnover show a high degree of interindividual variation, so that the relatively small number of participants in whom these measurements were made may have limited statistical power. Second, as we have previously demonstrated, the bone turnover response to GH is considerably blunted in women who are taking HRT (8), and the majority of participants in whom these measurements were obtained in the present study were taking HRT. Third, the failure of CICP (formation) and deoxypyridinoline (resorption) markers to duplicate the results with osteocalcin or the carboxyl-terminal telopeptide markers confirms our previous experience (8, 21), suggesting that osteocalcin and Crosslaps are more robust measures of GH-induced short term increases in bone turnover. Finally, it is of interest that the participants who undertook diet and exercise but did not receive either GH or IGF-I also showed increased osteocalcin concentrations at 12 weeks. Our group has previously shown an exercise-induced rise in osteocalcin in older women (31) performing resistance exercise 3 days/week, and such data support the view that progressive resistance exercise is itself osteotropic.

IGF-I treatment appeared to be associated with a significant reduction in anxiety and depression scores and a trend for improvement of memory scores. These results should be viewed with caution because of the small subject number. No

significant psychological effects of GH could be documented, but scores for the depression scale increased with GH treatment. No literature could be found in a search of the effects of IGF-I on cognition or mood. These preliminary results warrant follow-up study.

As previously reported for GH and IGF-I administration (8, 9), both hormones in the present study produced edema in many women, a finding consistent with the observed increases in ECF. Furosemide was necessary to reduce the fluid retention to tolerable levels. Edema was the primary contributor to women dropping out of this study. It is important to note that if the use of GH or IGF-I is to have any practical value, diuretic therapy may be unavoidable, as lower doses of these agents may not achieve the desired changes in body composition, as illustrated in this and other studies (9).

GH and IGF-I did not affect VO_2max or differentially influence gains in muscle strength. Although aerobic exercise is known to increase VO_2max in postmenopausal women (32), we do not know why our subjects failed to show an increase. Compliance for exercise participation was high (>85% attendance for both walking and resistance training sessions), with all women meeting their training heart rate range for more than 90% of all walking sessions. During the VO_2 max tests all women were encouraged to exercise until volitional exhaustion, and all reached a respiratory exchange ratio of 1.1 or more and met or exceeded the predicted maximal heart rate. The women did appear to improve walking performance, as indicated by faster walking time and fewer steps taken during the timed walk test.

Gains in strength were similar to those reported by others for postmenopausal women undertaking exercise alone (31, 33). The plateau in strength gains reported in both older men and women (33–35) was also observed here, with the most dramatic gains in strength observed before 8 weeks of treatment. Taaffe *et al.* also reported no additive benefit of GH administration on gains in muscle strength in elderly men (35).

In summary, addition of GH and IGF-I to a program of diet and exercise in obese postmenopausal women achieved greater loss of weight and fat than did diet and exercise alone or diet and exercise combined with either GH or IGF-I as single agents. However, GH and IGF-I did not improve aerobic fitness or promote greater gains in muscle strength in obese postmenopausal women than did diet and exercise alone. These results support the contention that a sound diet and exercise program will result in a significant loss of weight and body fat in obese postmenopausal women without compromising fat-free mass, BMR, or gains in muscle strength, which, in turn, should result in successful maintenance of reduced body weight and improved exercise tolerance. GH and IGF-I may play an important adjunctive role in the enhancement of fat loss in obese elderly women.

Acknowledgments

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Erratum

In the article "Immunohistochemical Localization of Gonadotropin and Gonadal Steroid Receptors in Human Pineal Glands," by R. Luboshitzky, M. Dharan, D. Goldman, Y. Hiss, P. Herer, and P. Lavie (*The Journal of Clinical Endocrinology and Metabolism* **82:** 977–981, 1997), an error was found in the *Material and Methods* section of the paper. The antibodies we used, clone ZSL11 and ZMFS1 are directed against gonadotropin hormones (LH and FSH) and are not against their corresponding receptors. The antibodies clone 39.4.1 and clone ID5 are directed against androgen and estrogen receptors, respectively. The authors regret any confusion caused by the mistake.