

Low-Dose Recombinant Human Growth Hormone as Adjuvant Therapy to Lifestyle Modifications in the Management of Obesity

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Obese individuals are in a reduced GH/IGF-I state that may be maladaptive. Fifty-nine obese men and premenopausal menstruating women (body mass index, 36.9 ± 5.0 kg/m²) were randomized to a double-blind, placebo-controlled trial of low dose recombinant human GH (rhGH). During the 6-month intervention, subjects self-administered daily rhGH or equivalent volume of placebo at 200 μ g (1.9 ± 0.3 μ g/kg for men, 2.0 ± 0.3 μ g/kg for women); after 1 month, the dose was increased to 400 μ g (3.8 ± 0.5 μ g/kg) in men and 600 μ g (6.0 ± 0.8 μ g/kg) in women. rhGH was then discontinued, and subjects were followed up after 3 months. Forty completed the intervention, and 39 completed the follow-up. Drop-out rates between rhGH vs. placebo groups were not different ($\chi^2 = 1.45$; $P = 0.228$). One subject discontinued the drug due to an rhGH-related side effect. Body weight (BW) decreased with rhGH from $100.4 \pm$

13.2 to 98.0 ± 15.6 kg at 6 months ($P = 0.04$) and was sustained at 98.1 ± 16.6 kg at 9 months ($P = 0.02$). BW loss was entirely due to loss of body fat (BF). Intention to treat analyses demonstrated changes from baseline between rhGH and placebo in BW (-2.16 ± 4.48 vs. -0.04 ± 2.67 kg; $P = 0.03$) and BF (-2.89 ± 3.76 vs. -0.68 ± 2.37 kg; $P = 0.01$). rhGH increased IGF-I from -0.72 to $+0.10$ SD ($P = 0.0001$). rhGH increased high-density lipoprotein cholesterol 19% from 1.11 ± 0.34 to 1.32 ± 0.28 mmol/liter ($P < 0.001$). Neither group had changes in fasting glucose, insulin sensitivity, or resting energy expenditure. In conclusion, in obesity, rhGH normalized IGF-I levels, induced loss of BW from BF, and improved lipid profile without untoward effects on insulin sensitivity. (*J Clin Endocrinol Metab* 89: 695–701, 2004)

AN OPTIMAL GOAL of weight-reducing programs for obesity would be to selectively lose body fat while retaining lean body mass (LBM). At the present time, there are no pharmacological means to achieve this goal. Obese individuals have low basal and stimulatable GH levels and reduced IGF-I levels compared with nonobese individuals (1–5). These abnormalities in the GH/IGF-I axis may improve after sustained weight loss (6, 7). As GH has lipolytic and anabolic properties, it is possible that these obesity-related changes in GH physiology will contribute to the accumulation of adipose tissue mass and therefore may be maladaptive. The precise role of recombinant human GH (rhGH) supplementation in the treatment of obesity has not been defined. Previous studies have used relatively high dose rhGH (2.0–3.5 mg/d) (8–11) compared with current recommendations for adult GH deficiency (0.2–0.7 mg/d) (12–19). Significant proportions of subjects in these studies developed GH-related side effects, such as edema, arthralgia, hypertension, or glucose intolerance. Further studies using lower doses of rhGH were limited due to either the short duration of treatment or the limited number of participants (20, 21). In general, there were no uniform changes in overall

body weight (BW), although body fat (BF) was reduced along with retention of LBM (22–24).

The present study was carried out in obese subjects to test the hypotheses that the low levels of IGF-I are detrimental, and low doses of supplemental rhGH, when used as adjuvant to standard counseling for lifestyle modification, may augment BF loss and preserve LBM without any significant untoward side effects.

Subjects and Methods

Subjects referred to the Obesity Clinic for clinically necessary weight reduction therapy were evaluated. Clinically significant obesity was defined as a body mass index (weight in kilograms divided by height in meters squared) greater than 30 without comorbid illnesses. The protocol was approved by the institutional review board of St. Louis University, and all subjects gave written informed consent.

Inclusion criteria allowed recruitment of men and premenopausal menstruating women between the ages of 20–45 yr with obesity. The age range was set to eliminate confounding age-dependent variables of GH requirements. Subjects were excluded if they reported a history of cardiac, hepatic, renal, or pulmonary disease; diabetes mellitus (by subject report and by screening fasting blood sugar levels ≥ 7.0 mmol/liter); cardiac pacemakers or intracardiac defibrillators; malignancy other than localized skin cancer; appetite suppressants, weight-reducing drugs, or anabolic steroids taken within the past 12 wk; or being pregnant or nursing.

There was a 6-wk screening phase. At wk –6, a clinical history and physical examination were performed. After 2 wk (wk –4), those with stable weight (± 0.9 kg) were entered into the standard weight loss program, which included instruction in diet, lifestyle modification, and exercise. The prescribed diet was calculated to be 500 calories less than their combined basal and exercise caloric needs. At each of the follow-up study visits the subjects met with the dietician for dietary reinforcement.

Abbreviations: BF, Body fat; BW, body weight; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LBM, lean body mass; LDL, low-density lipoprotein; REE, resting energy expenditure; rhGH, recombinant human GH; VLDL, very LDL.

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After 4 wk (wk 0 = baseline), those who demonstrated adherence to the regimen by losing at least 0.9 kg were entered.

The intervention phase consisted of a 6-month, randomized, placebo-controlled, double-blind, comparative trial of low dose rhGH therapy or placebo. Subjects underwent a baseline clinical history, physical examination, waist to hip measurements, and grip strength determination (determined by a Jamar hydraulic hand dynamometer, Sammons Preston, Bolingbrook, IL). Body composition was obtained by dual energy x-ray absorptiometry scan (QDR4500, Hologic, Inc., Bedford, MA); regional body fat distribution in relation to extremity and truncal fat was calculated from these dual energy x-ray absorptiometry measurements (25, 26). According to the manufacturer, the coefficient of variation for body fat is 1.5%. Resting energy expenditure (REE) was determined at the Clinical Laboratories of St. Louis University Hospital after a 12-h fasting state on a Delta Trac Metabolic Cart (VIASYS Healthcare, Yorba Linda, CA), using a canopy for gas exchange. Measurements were considered acceptable when the respiratory quotient fell within the physiological range of 0.67–1.3, at least a 10-min measurement of expired oxygen volume was within 10% of the mean value, and at least a 10-min measurement of expired CO₂ volume was within 6% of the mean value.

Laboratory tests included blood tests for fasting glucose, insulin, IGF-I, IGF-binding protein-3, lipid profile, and a pregnancy test where applicable. Determinations of insulin resistance were calculated by homeostasis model assessment (HOMA) and QUICKI (27). Laboratory determinations were obtained through the Esoterix Center for Clinical Trials (Calabasas Hills, CA). Intra- and interassay coefficients of variation, the sensitivity of the tests, and the age- and gender-specific values for IGF-I used to calculate z-scores were supplied by Esoterix.

Subjects were instructed to self-administer the study drug by nighttime injection. rhGH [somatotropin (rDNA origin) for injection, Genotropin] and identical placebo were prepared by Pfizer, Inc. (New York, NY) in 5.8-mg cartridges, *i.e.* 5 mg/ml. Drug was reconstituted using the Genotropin mixer and injected with an insulin syringe. All subjects started on the study drug equivalent in volume to 200 μ g rhGH/d for the first month (calculated to be $1.9 \pm 0.3 \mu\text{g}/\text{kg}\cdot\text{d}$ for men and $2.0 \pm 0.3 \mu\text{g}/\text{kg}\cdot\text{d}$ for women). The subjects were instructed to inject the equivalent volume using a 0.3-cc insulin syringe. In the second month, the dose was increased to 400 μ g/d for men ($3.8 \pm 0.5 \mu\text{g}/\text{kg}\cdot\text{d}$) and 600 μ g/d ($6.0 \pm 0.8 \mu\text{g}/\text{kg}\cdot\text{d}$) for women. The doses in both groups and the higher dose in women were chosen with regard to previous studies of GH supplementation and in anticipation of the known GH resistance of premenopausal women (19). If there were side effects, the dose was to be decreased to the previous level. No subject required dose adjustment. One subject dropped out after 8 d due to side effects at the starting dose. No other subject required dose adjustment.

Subjects remained on the study drug for 6 months (the intervention phase) and were monitored monthly. At 6 months, baseline tests were repeated. rhGH was then discontinued, and they were reexamined at the end of a 3-month follow-up phase (9 month visit) to determine the retention of benefits.

The study was powered for the primary end point at 6 months of loss of BF, with preservation of LBM. The secondary end point was overall BW loss. The sample size of 20 in each group was calculated using literature estimates with an α error of 0.05 and a power of 80% by two-tailed testing. It was estimated that there would be a 30% drop-out rate during the randomization and intervention phases.

Statistical analysis

Data were analyzed by two processes. The primary analyses were *a priori* evaluations of those who completed the study with paired analyses at 0, 6, and 9 months. The secondary analyses were intention to treat analyses, comparing the baseline values with the last value carried forward in the case of missing values. Results are reported as the mean and SD unless otherwise specified. Parametric group mean data were analyzed by ANOVA for nonpaired data. Paired data were analyzed by ANOVA for repeated measures. When there was a significant difference by ANOVA, *post hoc* analysis was performed using the Newman-Keuls procedure for subgroup analysis. Correlation and regression analyses were performed using Pearson's correlation coefficient. Statistics on proportions were performed by χ^2 analysis. Statistical procedures were performed with the statistical package Statistica for Windows (version

5, Statsoft, Inc., Tulsa, OK). Significance was defined as $P < 0.05$ by two-tailed testing.

Results

Baseline demographics

One hundred seven subjects were assessed for eligibility; 26 were not interested in participation, and 22 did not meet the inclusion criteria. Fifty-nine subjects (44 women and 15 men; body mass index, $36.9 \pm 5.0 \text{ kg}/\text{m}^2$) were enrolled, randomized, and completed the 6-wk screening phase. Thirty were assigned to rhGH (21 women and 9 men), and 29 were assigned to placebo (23 women and 6 men). Forty completed the 6-month intervention phase, and 39 completed the follow-up phase (9 month visit). Of the GH group, 16 women and 7 men completed the 6-month intervention, and 15 women and 7 men completed all aspects of the study. The reasons for dropping out in the GH group were weight gain due to swelling ($n = 1$), did not want the injections or to follow the diet ($n = 4$), started alternate therapy ($n = 1$), and lost to follow-up ($n = 1$). One woman dropped out after the 24-wk intervention due to pregnancy. Of the placebo group, 12 women and 5 men completed all aspects of the study. The reasons for dropping out were did not want the injections or to follow diet ($n = 6$), started alternate therapy ($n = 2$), unrelated rash ($n = 1$), unrelated motor vehicle accident ($n = 1$), and lost to follow-up ($n = 2$). There were no differences in the drop-out rates between the GH and placebo groups ($\chi^2 = 1.45$; $P = 0.228$).

The baseline characteristics of those who were enrolled and randomized and those who completed the protocol are shown in Table 1. There were no differences among those who did not complete the intervention with regard to sex, age, weight, body mass index, percent BF, fasting blood glucose, fasting insulin levels, calculated insulin sensitivity by HOMA and QUICKI, or REE. The baseline characteristics of those enrolled and those completing the intervention were well matched by the randomization process (Table 1). There was a slight difference in baseline characteristics in the group that completed the study between those assigned to rhGH and placebo with regard to triglycerides and very low density lipoprotein (VLDL) cholesterol levels. This was due to a single outlier.

Effects of intervention

BW changes. BW decreased in the GH group during the intervention phase, and this decrease persisted in the retention phase. The primary outcome analyses were *a priori* to be evaluated comparing the values at baseline with those at 6 and 9 months. Those subjects receiving rhGH decreased their BW ($F_{2,74} = 3.28$; $P = 0.04$) from $100.4 \pm 13.2 \text{ kg}$ at baseline to $98.0 \pm 15.6 \text{ kg}$ at 6 months ($P = 0.04$) and sustained a BW of $98.1 \pm 16.6 \text{ kg}$ at 9 months ($P = 0.02$). There were no changes in BW in controls from 0, 6, to 9 months (102.5 ± 13.4 , 101.6 ± 14.1 , and $102.1 \pm 14.2 \text{ kg}$, respectively).

A secondary intention to treat analysis was performed. The last value carried forward, for all subjects enrolled, was analyzed to determine whether those who dropped out during the intervention phase did so because of lack of subject-perceived effect on weight loss. The change in weight in the

TABLE 1. Baseline characteristics

	Enrolled			Completed		
	rhGH	Placebo	<i>P</i> value	rhGH	Placebo	<i>P</i> value
Sex (female/male)	21/9	23/6	0.6	15/7	12/5	0.85
Age (yr)	35.0 ± 6.0	37.6 ± 6.8	0.81	35 ± 6	36 ± 7	0.48
Height (cm)	168 ± 7.0	165.6 ± 7.2	0.3	167.6 ± 7.4	166.9 ± 7.8	0.76
Weight (kg)	102.9 ± 13.7	101.9 ± 13.2	0.34	101.0 ± 13.3	102.5 ± 13.4	0.73
BMI (kg/m ²)	36.6 ± 4.6	37.3 ± 5.4	0.06	35.9 ± 4.0	36.9 ± 5.3	0.5
Waist circumference (cm)	102.8 ± 10.9	104.4 ± 10.0	0.57	100.3 ± 10.1	105.0 ± 8.4	0.13
Hip circumference (cm)	121.8 ± 10.8	124.1 ± 10.9	0.53	121.3 ± 9.1	121.3 ± 9.3	0.78
Pulse (beats/min)	71.5 ± 11.0	75.3 ± 10.9	0.2	71 ± 11	76 ± 13	0.91
Systolic BP (torr)	121.9 ± 11.3	119.9 ± 12.5	0.71	121 ± 12	121 ± 12	0.9
Diastolic BP (torr)	79.0 ± 7.4	78.1 ± 9.8	0.81	79 ± 8	80 ± 11	0.85
DEXA (% fat)	39.1 ± 7.7	42.4 ± 6.9	0.48	38.4 ± 7.8	40.8 ± 7.6	0.32
Grip strength (kg)	35.9 ± 10.5	34.0 ± 14.3	0.29	37.7 ± 11.0	36.6 ± 17.3	0.8
Total cholesterol (mmol/liter)	4.99 ± 0.23	4.80 ± 1.01	0.3	4.71 ± 1.03	4.76 ± 1.14	0.88
LDL cholesterol (mmol/liter)	3.52 ± 1.35	3.08 ± 0.86	0.49	3.23 ± 1.01	3.10 ± 0.75	0.64
HDL cholesterol (mmol/liter)	1.13 ± 0.32	1.14 ± 0.24	0.44	1.11 ± 0.31	1.06 ± 0.21	0.62
VLDL cholesterol (mmol/liter)	0.55 ± 0.20	0.65 ± 0.33	0.08	0.54 ± 0.21	0.72 ± 0.36	0.047
Triglycerides (mmol/liter)	1.65 ± 0.59	1.94 ± 0.98	0.09	1.58 ± 0.63	2.14 ± 1.09	0.049
Fasting glucose (mmol/liter)	4.90 ± 0.55	4.92 ± 0.47	0.96	4.88 ± 0.61	4.94 ± 0.56	0.74
Fasting insulin (pmol/liter)	117 ± 78	88 ± 47	0.1	98 ± 65	91 ± 46	0.74
HOMA	3.64 ± 2.7	2.71 ± 1.53	0.13	3.06 ± 2.34	2.85 ± 1.59	0.75
QUICKI	0.33 ± 0.03	0.34 ± 0.04	0.1	0.34 ± 0.03	0.34 ± 0.04	0.84
IGF-I (μg/liter)	162.6 ± 48.6	146.0 ± 43.4	0.17	167.8 ± 48.6	150.2 ± 48.6	0.27
IGFBP-3 (μg/liter)	2820 ± 730	2800 ± 740	0.54	2800 ± 700	2700 ± 600	0.46
REE (Kcal/24 h)	1721 ± 268	1665 ± 222	0.34	1697 ± 280	1712 ± 221	0.86
% of calculated REE	-8.73 ± 7.04	-8.72 ± 8.50	0.69	-9.33 ± 6.48	-8.16 ± 9.60	0.65

Conversion of SI units to conventional units: cholesterol in mmol/liter /0.02586 = mg/dl; glucose in mmol/liter /0.05551 = mg/dl; triglycerides in mmol/liter /0.01129 = mg/dl; insulin in pmol/liter /7.175 = μU/ml.

GH group (-2.16 ± 4.48 kg) was greater than that in controls (-0.04 ± 2.67 kg; $P = 0.03$).

Body composition changes. BW loss in the GH group was totally due to the loss of BF ($F_{2,74} = 13.5$; $P = 0.0001$; Fig. 1A). Between baseline and 6 months, there was a decrease in BF weight from 37.9 ± 8.8 to 34.5 ± 9.0 kg ($P = 0.0001$); this loss of BF was sustained at 9 months (35.2 ± 9.5 kg; $P = 0.004$). There was a retention of LBM at 0, 6, and 9 months (62.4 ± 12.1 , 63.5 ± 12.7 , and 1.4 ± 10.5 kg, respectively; $P = \text{NS}$). The difference in loss of fat weight greater than that in overall weight may be due to a small nonsignificant change in lean BW. Loss of BF was predominantly due to loss of truncal fat ($F_{2,74} = 16.6$; $P = 0.000001$), which decreased from 19.5 ± 4.4 to 17.4 ± 5.1 kg at 6 months ($P = 0.0002$) and to 18.0 ± 5.1 kg at 9 months ($P = 0.001$). In controls, there were no significant changes in BF at 0, 6, or 9 months (42.0 ± 9.6 , 40.5 ± 10.0 , and 40.7 ± 10.1 kg, respectively) or in LBM (60.5 ± 10 , 61.1 ± 11.0 , and 61.4 ± 10.5 kg, respectively; Fig. 1B). By intention to treat analysis, the change in BF weight in the GH group (-2.89 ± 3.76 kg) was significantly different from that in controls (-0.68 ± 2.37 kg; $P = 0.001$).

GH effects on IGF-I. rhGH increased IGF-I levels ($F_{2,74} = 17.6$; $P = 0.000001$) from 164 ± 45 to 223 ± 65 μg/liter at 6 months, with a return to baseline levels after the drug-free phase to 168 ± 46 μg/liter. IGF-I levels were unchanged in controls. IGF-I levels increased from 0.72 SD (z-score) below the mean to $+0.10$ SD at 6 months in those receiving rhGH (Fig. 2A; $F_{2,76} = 12.7$; $P = 0.00002$). The IGF-I z-scores were significantly different between the groups ($F_{2,76} = 6.5$; $P = 0.003$), with the peak difference at 6 months ($P = 0.0001$). There were no differences between men and women in IGF-I levels ($204 \pm$

60 vs. 229 ± 66 μg/liter; $P = \text{NS}$) or in IGF-I z-scores (0.11 ± 1.42 vs. 0.09 ± 0.98 ; $P = \text{NS}$) attained at 6 months with the doses of rhGH selected in the study. There were no changes in IGF-I levels in controls. The maximum achieved IGF-I z-score was 2.15 SD in the GH-treated group. There was a direct correlation between the IGF-I levels and IGF-I z-score at 6 months with the change in BF ($r = 0.37$; $P = 0.02$; Fig. 2B). This correlation was no longer significant if we eliminated the responses of the two subjects who lost 9.0% and 10.8% of their BF.

Other metabolic effects. Serum cholesterol levels in the GH group increased ($F_{2,74} = 9.7$; $P = 0.0002$) from 0 to 6 to 9 months (4.65 ± 1.01 to 5.07 ± 1.06 ; $P = 0.02$ to 5.12 ± 0.85 mmol/liter; $P = 0.01$, respectively; Fig. 3A). These changes were mostly ascribed to increased high-density lipoprotein (HDL) cholesterol levels. HDL cholesterol increased ($F_{2,74} = 13.0$; $P = 0.00001$) by 19%, from 1.11 ± 0.34 to 1.32 ± 0.28 mmol/liter, at 6 months ($P = 0.001$; Fig. 3B) and decreased at 9 months to 1.19 ± 0.23 mmol/liter ($P = \text{NS}$ vs. baseline). Total cholesterol did not change in controls, but there were changes in HDL cholesterol from 1.06 ± 0.21 to 1.19 ± 0.31 mmol/liter at 6 months ($P = 0.03$) and 1.19 ± 0.34 mmol/liter at 9 months ($P = 0.046$; Fig. 3, A and B). There were no changes in serum low-density lipoprotein (LDL) cholesterol (Fig. 3C) or VLDL cholesterol. The baseline difference in triglycerides between the groups persisted; there were no changes in triglycerides within the groups over time (Fig. 3D).

There were no differences between the groups with regard to pulse, blood pressure, waist or hip circumference, bone mineral density, levels of glucose and insulin, measures of

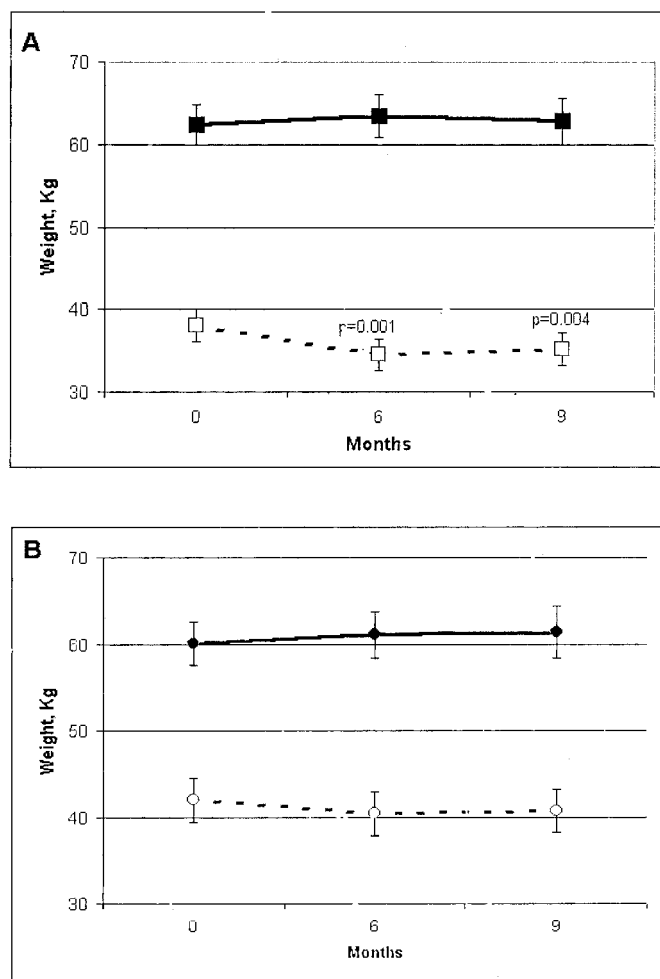


FIG. 1. Weight measurements during the study. LBW and fat weight at baseline, after 6 months of study drug (intervention phase), and after the drug-free period (retention phase) at 9 months are shown for subjects receiving GH (A; ■, lean weight; □, fat weight) and those receiving placebo (B; ●, lean weight; ○, fat weight). Error bars represent the mean \pm SEM.

insulin sensitivity (HOMA and QUICKI), levels of IGF-binding protein-3, or REE (Table 2).

Side effects

One subject stopped rhGH due to an attributable side effect of edema within 8 d of starting the initial 200- μ g dose (no IGF-I levels were obtained). No other subject required dose adjustment or stopped the drug due to known side effects.

Discussion

This study showed that obese individuals are in a low GH state, as determined by low levels of IGF-I. This state may be maladaptive with regard to weight loss and lipid profile. When rhGH is administered at doses sufficient to achieve physiological levels of IGF-I, weight loss could be achieved in obese subjects. The weight loss was entirely due to loss of BF with retention of LBM. There were significant improvements in serum lipids. There were no detrimental changes in

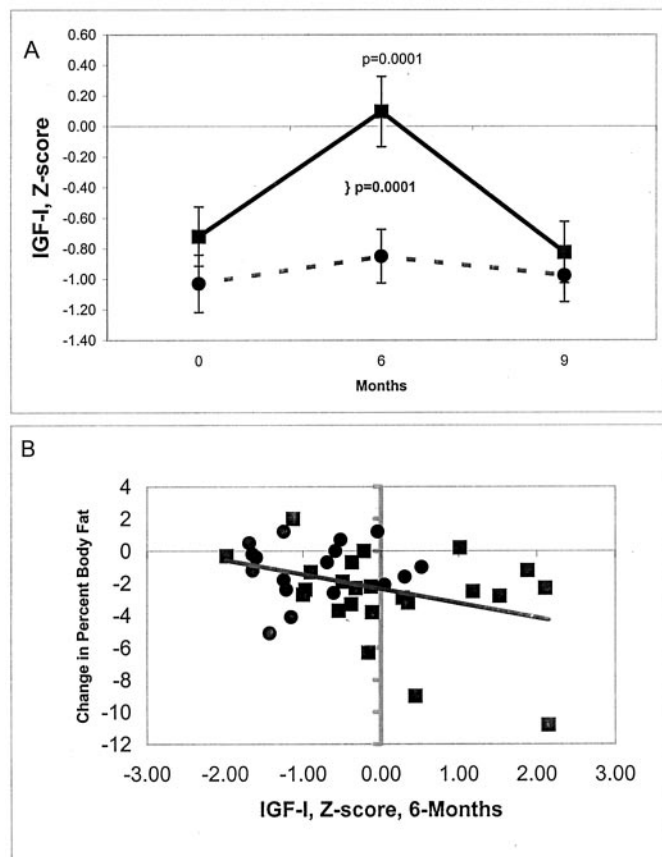


FIG. 2. Effects of rhGH or placebo on serum IGF-I levels and body fat. A, Serum levels of IGF-I z-score at baseline, after 6 months of study drug, and after the drug-free period at 9 months are shown for subjects receiving GH (■) and placebo (●) as the mean \pm SEM. The *P* values refer to changes from baseline. }, Significant difference between the two groups. B, Change in percent body fat 6 months relative to the IGF-I z-score at 6 months for subjects on GH (■) and placebo (●). The fitted line is calculated by the method of least squares ($r = 0.37$; $P = 0.02$).

fasting glucose or insulin levels or in parameters of basal insulin resistance (HOMA and QUICKI).

The rhGH-related weight loss achieved (2.4 kg) was less than the drug-related weight loss observed previously in trials of the approved weight loss medications, such as sibutramine (range, 2.2–3.9 kg) or orlistat (range, 1.76–3.41 kg) (28, 29). The lack of significant weight loss in controls has also been observed in previous trials of appetite suppressants (28, 29). The BW loss was sustained for 3 additional months after discontinuation of the drug. The cause of the weight loss in the GH-treated group is unknown. It could have been due to decreases in appetite or increases in exercise because of improved physical stamina or lack of fatigue, and future studies should be directed at quantifying these possibilities.

In agreement with previous studies, obese individuals had lower REE than would be calculated based on their sex- and age-adjusted body mass (30, 31). There was no significant change in REE with weight loss, possibly reflecting the fact that LBM did not change. This is in contrast to the increased REE with GH supplementation reported in GH-deficient adults (12) and in men with central obesity (23).

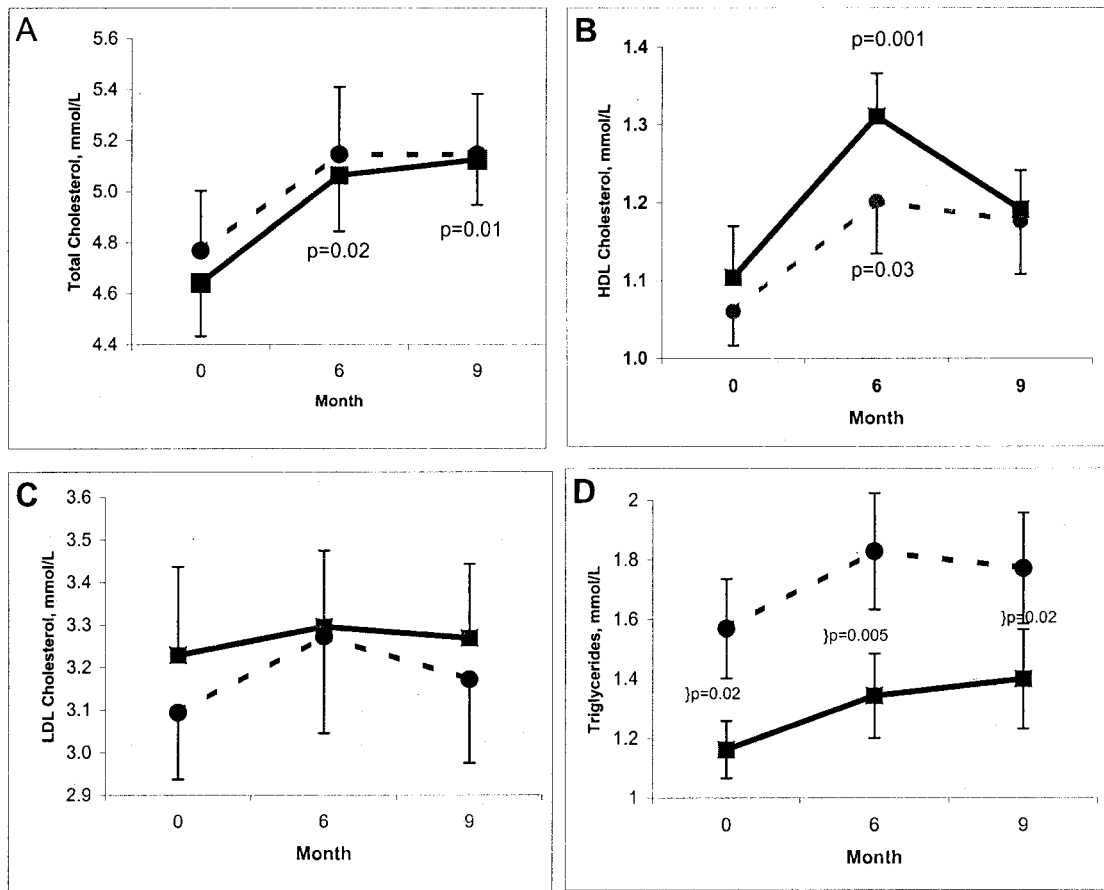


FIG. 3. Changes in cholesterol levels. Serum levels of total cholesterol (A), HDL cholesterol (B), LDL cholesterol (C), and triglycerides (D) were determined at baseline, after the 6-month intervention phase, and 3-month drug-free period, for those on GH (■) and placebo (●). *P* values refer to changes from baseline. }, Significant difference between the two groups.

TABLE 2. Clinical and metabolic effects of GH or placebo

Month	GH			Placebo		
	0	6	9	0	6	9
Pulse (beats/min)	71 ± 11	75 ± 10	75 ± 9	76 ± 13	80 ± 10	79 ± 13
Systolic BP (torr)	121 ± 12	118 ± 13	123 ± 12	121 ± 12	125 ± 13	118 ± 28
Diastolic BP (torr)	79 ± 8	77 ± 10	78 ± 8	80 ± 11	76 ± 12	79 ± 9
Waist (cm)	100.3 ± 10.1	98.5 ± 11.9	99.1 ± 11.7	105.0 ± 8.4	102.5 ± 9.5	103.0 ± 10.1
Hip (cm)	120.5 ± 9.1	118.7 ± 10.9	118.5 ± 10.2	121.3 ± 9.3	119.9 ± 9.5	121.1 ± 9.9
BMD (g/cm ²)	1.25 ± 0.11	1.27 ± 0.11	1.27 ± 0.12	1.22 ± 0.11	1.22 ± 0.10	1.21 ± 0.09
Glucose (mmol/liter)	4.88 ± 0.06	5.22 ± 0.72	5.16 ± 0.78	4.94 ± 0.56	5.11 ± 0.56	5.22 ± 0.50
Insulin (pmol/liter)	100 ± 65	100 ± 57	86 ± 50	93 ± 43	100 ± 57	100 ± 57
HOMA	3.06 ± 2.34	3.25 ± 2.12	2.82 ± 1.82	2.85 ± 1.59	3.27 ± 2.28	3.20 ± 2.03
QUICKI	0.59 ± 0.10	0.58 ± 0.11	0.59 ± 0.10	0.60 ± 0.12	0.58 ± 0.10	0.57 ± 0.08
IGFBP-3 (μg/liter)	2800 ± 70	2900 ± 600	2700 ± 500	2700 ± 600	2600 ± 700	2700 ± 500
REE (Kcal/24 h)	1697 ± 280	1701 ± 259	1701 ± 329	1712 ± 221	1691 ± 278	1748 ± 256
% REE	-9.3 ± 6.5	-8.2 ± 7.8	-8.2 ± 10.2	-8.2 ± 9.6	-9.1 ± 13.7	-5.6 ± 11.4

Conversion of SI units to conventional units: glucose in mmol/liter /0.05551 = mg/dl; insulin in pmol/liter /7.175 = μU/ml.

Obese individuals have hormonal parameters suggestive of a low GH state (1–5). Basal and stimutable GH levels and IGF-I levels are significantly lower than those in nonobese individuals. These abnormalities in GH dynamics may be reversible after achievement of long-term weight loss (6, 7). Metabolic abnormalities associated with obesity simulate those found in subjects with permanent GH deficiency due to hypothalamic or pituitary disease. These abnormalities

include changes in total BW, fat distribution, glucose intolerance, and lipid abnormalities, and they may be associated with a predilection to increased cardiovascular disease (12, 13, 25, 32–41). In individuals with GH deficiency, these abnormalities may be corrected with rhGH supplementation (41). In this study BF and truncal BF improved with normalization of IGF-I levels. The effects of rhGH therapy on the known hyperlipidemias in GH-deficient individuals have

shown variable changes. Most studies show beneficial improvements in either LDL or HDL cholesterol (12, 41). There was a 19% improvement in HDL cholesterol from 43 to 51 mg/dl, which reverted to the baseline once rhGH was discontinued. Although HDL changes are variable, changes of this magnitude in HDL have been reported in treated GH-deficient individuals (13, 40). There were no significant changes in LDL cholesterol, VLDL cholesterol, or serum triglycerides.

Early trials in GH-deficient adults or obese subjects used high dose rhGH comparable to that used for the induction of growth in children (2.0–3.5 mg/d) (8–11). As such, these doses were associated with significant adverse effects, such as edema, arthralgia, carpal tunnel syndrome, and hyperinsulinemia. In addition, insulin resistance with elevated insulin levels induced by high dose GH therapy may be counterproductive, as insulin increases fat storage and stimulates appetite. Low dose rhGH (0.2–0.7 mg/d) (12–19), designed to achieve physiological IGF-I levels, may not cause these side effects. Whereas high dose rhGH is associated with deterioration in insulin sensitivity (12, 42), low dose therapy may improve insulin sensitivity, presumably due to favorable improvements in body composition (34, 43). In the present study fasting glucose and insulin levels and measures of insulin resistance (HOMA and QUICKI) did not deteriorate.

In this study GH dosage was not titrated against IGF-I levels (25). However, in consideration that premenopausal women are relatively GH resistant (19), they were scheduled to receive 600 μ g, whereas men received 400 μ g rhGH daily during the intervention phase. At 6 months, there was no significant difference in IGF-I levels between men and women.

In patients who have childhood- or adult-onset GH deficiency, IGF-I levels are lower than those recorded in this study (10, 14, 18, 19). However, in a study of elderly subject preselected for low GH levels, serum IGF-I levels were comparable to those in the present study (44). GH replacement therapy in these older subjects resulted in changes in body mass and lipids similar to those found in these obese individuals who were not preselected on the basis of low GH or IGF-I. This suggests that the treatable physiological GH deficiency found in selected older subjects is a common feature of young obese individuals.

The high attrition rate was a limitation of this study, but is reported in most weight loss studies (29, 45, 46). We tried to monitor for the drop-outs. There were no baseline differences between those who completed the study and those who did not complete the study. There were no differences in the reasons for drop-out in the GH or placebo groups. We noted that the changes in BW and BF persisted after intention to treat analyses, which suggested that the drop-outs were not due to the subject's perceived ineffectiveness of therapy.

It is unclear from these data whether the changes in BF were linked to the direct biological actions of GH or IGF-I. There are clear biological differences in the actions of GH and IGF-I, as shown in animal knockout models (47). In a trial of Gh vs. IGF-I replacement in GH-deficient children, both hormones increased linear growth, whereas the percent BF remained unchanged after IGF-I alone (48). Similarly, in a

prospective study of weight loss in postmenopausal women, fat weight loss was greater in those treated with GH and IGF-I than in those treated with IGF-I alone (10).

In summary, this study showed that in obese individuals the low GH state with low levels of IGF-I might be maladaptive with regard to weight loss and lipid parameters. When low dose rhGH was administered to obese subjects at doses sufficient to achieve physiological levels of IGF-I, significant BW loss was achieved. The BW loss was entirely due to loss of BF with retention LBM. There was a significant improvement in HDL cholesterol without detrimental side effects on fasting blood glucose, fasting insulin levels, or measures of insulin sensitivity. It is possible that higher rhGH doses would have greater effects on weight and fat losses; however, the incidence of side effects may well be increased. Thus, further studies may be considered on the role and dose of rhGH as an adjuvant to existing behavioral and pharmaceutical weight loss therapies.

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