Growth Hormone Treatment of Abdominally Obese Men Reduces Abdominal Fat Mass, Improves Glucose and Lipoprotein Metabolism, and Reduces Diastolic Blood Pressure*

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ABSTRACT

The most central findings in both GH deficiency in adults and the metabolic syndrome are abdominal/visceral obesity and insulin resistance. Abdominal obesity is associated with blunted GH secretion and low serum insulin-like growth factor-I concentrations. GH treatment in GH-deficient adults has demonstrated favorable effects on most of the features of GH deficiency in adults, but it is not known whether GH can improve some of the metabolic aberrations observed in abdominal/visceral obesity.

Thirty men, 48–66 yr old, with abdominal/visceral obesity were treated with recombinant human GH (rhGH) in a 9-month randomized, double-blind, placebo-controlled trial. The daily dose of rhGH was 9.5 μ g/kg. Body fat was assessed from total body potassium, and abdominal sc and visceral adipose tissue was measured using computed tomography. The glucose disposal rate (GDR) was measured during an euglycemic, hyperinsulinemic glucose clamp.

S TRIKING similarities exist between the metabolic syndrome (1, 2) (also labeled syndrome X or primary insulin resistance syndrome) and untreated GH deficiency in adults (3). The most central findings in both these syndromes are abdominal/visceral obesity and insulin resistance (1, 4–6). Other features common to both conditions are high triglyceride (TG) and low high-density lipoprotein cholesterol concentrations, an increased prevalence of hypertension, elevated levels of plasma fibrinogen and plasminogen activator inhibitor (PAI)-1 activity, premature atherosclerosis, and increased mortality from cardiovascular diseases (1, 4, 7–11).

The metabolic syndrome is associated with multiple endocrine abnormalities. They include increased cortisol secretion, blunted secretion of gonadotrophins and sex steroids, and abnormalities in the GH/insulin-like growth factor I (IGF-I) axis (12–14). With increased adiposity, GH In response to the rhGH treatment, total body fat and abdominal sc and visceral adipose tissue decreased by 9.2 ± 2.4%, 6.1 ± 3.2%, and 18.1 ± 7.6%, respectively. After an initial decrease in the GDR at 6 weeks, the GDR increased in the rhGH-treated group as compared with the placebo-treated one (P < 0.05). The mean serum concentrations of total cholesterol (P < 0.01) and triglyceride (P < 0.05) decreased, whereas blood glucose and serum insulin concentrations were unaffected by the rhGH treatment. Furthermore, diastolic blood pressure decreased and systolic blood pressure was unchanged in response to rhGH treatment.

This trial has demonstrated that GH can favorably affect some of the multiple perturbations associated with abdominal/visceral obesity. This includes a reduction in abdominal/visceral obesity, an improved insulin sensitivity, and favorable effects on lipoprotein metabolism and diastolic blood pressure. (*J Clin Endocrinol Metab* 82: 727–734, 1997)

secretion is blunted with a decrease in the mass of GH secreted per burst but without any major impact on GH secretory burst frequency (15). The serum IGF-I concentration is primarily GH dependent and influences GH secretion through a negative feedback system (16). The serum levels of IGF-I are inversely related to the percentage of body fat (BF) (15). In addition, we have shown previously that the low serum IGF-I concentration in obesity is predominantly related to the amount of visceral adipose tissue and not to the amount of sc fat mass (13). These findings, together with other endocrine disturbances in central obesity, suggest that the low GH secretion that is observed is secondary to a central disturbance of the neuroendocrine regulation, including the GH/IGF-I axis.

Replacement therapy with recombinant human GH (rhGH) has demonstrated favorable effects on most of the features of GH deficiency in adults (17). Whether rhGH treatment can improve the metabolic abnormalities observed in abdominal/visceral obesity has never been investigated. In the present study, a randomized, double-blind, placebo-controlled design was used to evaluate the effects of 9 months of rhGH administration in patients with abdominal/visceral obesity.

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Subjects and Methods

Patients

Thirty men (48–66 yr old) were studied (Table 1). They were recruited by advertisements in a local newspaper. The criteria for inclusion in the study were age, approximately 50–65 yr old, with a body mass index of 25–35 kg/m², a serum IGF-I concentration less than 160 μ g/L (low to normal) (18), and a waist-to-hip ratio of more that 0.95. The criteria for exclusion were overt diabetes mellitus, previous cardiovascular event, or heart disease.

In the rhGH-treated group, two patients were receiving treatment for hypertension with both atenolol (100 mg per day) and nifedipine (40 mg per day) and one patient had slight asthma treated with salmeterol and terbutaline inhalations. In the placebo-treated group, one patient had a slight depressive disorder and was receiving paroxetin (10 mg per day). These medications were kept stable during the study period.

Study design

This study was a 9-month, randomized, double-blind, placebo-controlled trial of the administration of rhGH. Informed consent was obtained from each patient before the study. The study was approved by the Ethics Committee at the University of Göteborg and by the Swedish Medical Products Agency, Uppsala, Sweden.

Treatment

The daily dose of rhGH was 9.5 μ g/kg (0.20 IU/kg BW/week) administered sc before bedtime. The dose was reduced by half in the event of side effects. The average dose reduction during the 9-month study was therefore 0.17 mg per day (range -1.7 to 0). The placebo vials contained the same vehicle as the rhGH vials, and both preparations were visually indistinguishable. Compliance, assessed by counting the returned empty vials and expressing that number as a percentage of the vials needed for the treatment period, was 87.3% (range 32–100).

Study protocol

The patients were studied as outpatients before and after 6 weeks, 6 months, and 9 months of treatment. Physical and laboratory examinations were performed on all visits. The euglycemic hyperinsulinemic clamp, adipose tissue needle aspiration, and measurement of blood pressure and heart rate were performed at baseline, at 6 weeks, and after 9 months of treatment. Body weight was measured in the morning to the nearest 0.1 kg wearing indoor clothing, and body height was measured barefoot to the nearest 0.01 m. The body mass index was calculated as body weight in kilograms divided by height in meters squared. Waist circumference was measured in the standing position with a flexible plastic tape midway between the lower rib margin and the iliac crest, and the hip girth was measured at the widest part of the hip. Systolic and diastolic blood pressure were measured after 5 min supine rest using the sphygmomanometric cuff method. This measurement was repeated after 1 min, and the mean value was used.

Total body potassium was measured by counting the emission of 1.46 MeV γ -radiation from the naturally occurring ⁴⁰K isotope in a highsensitive 3π whole-body counter with a coefficient of variation (CV) of 2.2%. Fat-free mass (FFM) was estimated by assuming a potassium content of 64.7 mmol/kg FFM (19) and BF was calculated as body weight-FFM. A 5-scan computed tomography technique was used

TABLE 1. (Clinical o	characteristics	of the c	ohort (of 30	men	treated	
with GH or j	placebo f	or 9 months						

Patient characteristics	GH	Placebo
Number of men	16	14
Mean age (range); yr	58.3 (48-66)	57.9 (52-63)
Treated hypertension; no.	2	0
Present smokers: no.	5	2
Body height; m	1.80 ± 0.02^a	1.77 ± 0.02
Body weight; kg	101.7 ± 2.4	96.2 ± 2.6
Waist hip ratio	1.01 ± 0.01	1.03 ± 0.02

^{*a*} Plus-minus values are means \pm SEM.

(Philips Tomoscan 350, Mahway, NJ) to measure abdominal adipose tissue. The five levels were derived from two scanograms and included one scan at the level of the midthigh with the lower edge of the symphysis as a reference point. The other four levels were the lower edge of the symphysis, L4–5 lumbar disc, L3–4 lumbar disc, and a scan at the level of the liver and spleen. The tissue areas and anatomic boundaries were determined as described previously (20). The total volume of visceral adipose tissue was determined from the 5-scan model with a CV of 1.2%. Sagittal diameter and abdominal sc and visceral adipose tissue areas were determined at the level of L4–5. The total radiation exposure with the computed tomography technique was 250 mrem.

A euglycemic, hyperinsulinemic glucose clamp was performed after an overnight fast, as previously described (14). The glucose disposal rate (GDR) was measured for 20 min in steady-state conditions, which were reached after 100 min. The insulin concentrations during steady state were 214 \pm 10 µIU/mL before treatment, 226 \pm 12 µIU/mL at 6 weeks, and 213 \pm 11 µIU/mL at 9 months. During the clamp, in steady-state conditions, an sc abdominal adipose tissue biopsy was obtained by needle aspiration for the determination of lipoprotein lipase (LPL) activity. The biopsies were frozen immediately in liquid nitrogen and stored at -80° C until assay.

Analytic methods

Total LPL activity in adipose tissue was determined as described previously (21). The amount of TG in the tissue was measured after extraction (22). Activity was expressed in milliunits [1 mU = 1 nmol free fatty acids (FFA) released per min] per gram of adipose tissue and per gram of TG. The within-assay CV was 4.3%.

Blood samples were drawn in the morning after an overnight fast. The serum concentration of IGF-I was determined by a hydrochloric acidethanol extraction RIA using authentic IGF-I for labeling (Nichols Institute Diagnostics, San Juan Capistrano, CA) with within-assay CV of 2.5% and 4.2% at serum concentrations of 125 μ g/L and 345 μ g/L, respectively. The sp score for IGF-I was then calculated from the predicted IGF-I values, adjusted for age and sex values obtained from the normal population (18).

The IGF-binding protein-3 concentration in serum was determined by RIA (Nichols Institute Diagnostics) with a total CV of 6.2% and 5.7% at serum concentrations of 2.05 mg/L and 3.49 mg/L, respectively.

Serum cholesterol and TG concentrations were determined with enzymatic methods (Boehringer, Mannheim, Germany). The within-assay CV for total cholesterol and TG determinations was 0.9% and 1.1%, respectively.

Fibrinogen was measured according to a syneresis method (23) with a total CV of 4% at 2.5 g/L. PAI-1 activity was measured using a Spectralyse (pL) PAI kit (Biopool Stabilyte, Umeå, Sweden) with a total CV of 10% at concentrations of 10–40 IU/mL.

Serum insulin was determined by an RIA (Phadebas, Pharmacia, Uppsala, Sweden) and blood glucose was measured by the glucose-6phosphate dehydrogenase method (Kebo Lab, Stockholm, Sweden). Hemoglobin A1c was determined by high-pressure liquid chromatography (Waters, Millipore AB, Sweden) and C-peptide was determined by an RIA (Byk-Sangtec Diagnostica, Dictzenback, Germany). FFA levels were determined using an enzymatic colorimetric method (NEFAC; Wako, Neuss, Germany), whereas sex hormone-binding globulin (SHBG) was measured by an immunoradiometric assay (Farmos, Diagnostica, Åbo, Finland) and total testosterone by an RIA (ICM, Biomedical, Costa Mesa, CA).

Statistical methods

All the descriptive statistical results are presented as the means and SEM. Comparisons between baseline values of the two groups were performed using Student's *t* test for independent groups. Comparisons between the rhGH- and placebo-treated groups, with data obtained at all time points, were made by using a two-way ANOVA for repeated measurements. Correlations were sought by calculating the Pearson linear r. Pearson's χ -square test was used to test the independence of frequency of hypertension and smoking between the two treatment groups. Before statistical analysis, logarithmic transformation of data with skewed distribution was performed. A two-tailed probability value less than 0.05 was considered significant.

Results

The two groups were matched with regard to age, body height, body weight, and waist-to-hip ratio and did not differ significantly in terms of the number of subjects with medically treated hypertension ([Chi]-square = 1.87; P = 0.17) and current smokers ([Chi]-square = 1.2; P = 0.27) (Table 1). At baseline, the two groups did not differ significantly in terms of body composition, glucose metabolism, serum lipids, or any other variable studied.

Side effects

No drop-outs occurred during the study. Side effects were observed in eight subjects in the rhGH-treated group and were mainly a result of fluid retention. Five had peripheral edema, two subjects experienced muscle stiffness and arthralgia, one developed mild carpal tunnel syndrome, and one subject experienced increased perspiration. These side effects appeared during the first 6 weeks of treatment and subsided in four patients in response to a reduction in dose implemented within 4 months after the start of treatment; in three patients, the side effects subsided spontaneously. One man from the rhGH-treated group, with medically treated hypertension, was taken off the treatment after 8 months when he experienced an intracerebral hemorrhage. Three subjects in the placebo group experienced slight and transient peripheral edema.

An intention-to-treat analysis was performed using the carry-forward principle. Similar results were obtained, except in diastolic blood pressure, which no longer gained significance between the two treatment groups (P = 0.2). This was an effect of an increment in diastolic blood pressure from 80 mmHg at baseline to 100 mmHg at 6 weeks in the man in the rhGH group who was taken off treatment at 8 months.

Body composition

The patients' mean overall body mass index and FFM did not change, whereas the mean total BF decreased by 9.2 \pm 2.4% during rhGH treatment, in comparison with placebo treatment (Fig. 1). Waist circumference and sagittal diameter decreased in response to rhGH, whereas no change occurred in the placebo group. Moreover, abdominal sc and visceral adipose tissue area at the level of L4–5 decreased in response to rhGH by $6.1 \pm 3.2\%$ and $18.1 \pm 7.6\%$, respectively (Figs. 1 and 2 and Table 2). The corresponding values in the placebo group were $+2.0 \pm 2.8\%$ and $-3.2 \pm 7.6\%$, respectively. Moreover, the volume of visceral adipose tissue decreased in the rhGH-treated group by 17.9 \pm 3.5%, whereas no change was observed in the placebo-treated group ($-0.2 \pm 4.2\%$) (Fig. 1). Thus, the percentage of visceral adipose tissue of the total adipose tissue at the level of L4-5 decreased by $14.5 \pm 3.8\%$, whereas the percentage of sc adipose tissue of the total adipose tissue at the level of L4-5 increased by 5.4 \pm 1.7% in the rhGH-treated group.

Glucose metabolism

No significant effects were elicited by rhGH treatment on blood glucose, serum insulin, and hemoglobin A1c (Table 3 and Fig. 3). The serum concentration of C-peptide increased in the rhGH-treated group because of a transient increase at



FIG. 1. Mean total BF calculated from total body potassium, abdominal sc adipose tissue (AT) area at the level of L4-L5, and total volume of visceral AT assessed with computed tomography during 9 months of treatment with rhGH or placebo in 30 men with abdominal/visceral obesity. The *horizontal bars* indicate the SE for the mean values shown and *P* values denote the differences between the two groups by two-way ANOVA for repeated measurements.

6 weeks, but the C-peptide level was similar in the two groups at 9 months.

At baseline, the GDR did not differ between the rhGH- and the placebo-treated groups ($5.6 \pm 0.7 vs. 7.2 \pm 0.7$; P = 0.15). In the rhGH-treated group, the GDR showed an initial decrease after 6 weeks of treatment followed by an increment, whereas the placebo-treated group demonstrated a slight reduction over time (Fig. 3). The average increase in GDR in response to 9 months of rhGH was $1.2 \pm 0.7 mg/kg\cdotmin$ compared with baseline, whereas in the group receiving placebo, a slight decrease of $0.4 \pm 0.6 mg/kg\cdotmin$ occurred.

decreased from 2.09 \pm 0.29 to 1.78 \pm 0.23 mmol/L in response to rhGH treatment. The corresponding changes in the placebo group were from 5.4 \pm 0.3 to 5.5 \pm 0.2 mmol/L and from 1.65 \pm 0.13 to 2.05 \pm 0.26 mmol/L, respectively. A transient increase in total cholesterol was seen in both treatment groups between 6 weeks and 6 months, and a transient increase was observed in serum TG between baseline and 6 weeks in the rhGH-treated group.

The mean total LPL activity in sc abdominal tissue did not change during rhGH treatment in comparison with placebo treatment. However, between 6 weeks and 9 months, LPL activity tended to increase in the rhGH-treated group as compared with the placebo-treated group (P = 0.06). Similar results were obtained when LPL activity was expressed in mU/g TG.

The plasma concentration of fibrinogen increased in response to rhGH, whereas PAI-1 activity was unaffected by rhGH treatment as compared with placebo.

Blood pressure and heart rate

Diastolic blood pressure decreased from 75 \pm 2 to 70 \pm 2 mmHg in the rhGH-treated group. The corresponding values in the placebo group were from 73 \pm 2 to 74 \pm 2 mmHg (P < 0.05). No significant effects on systolic blood pressure or heart rate were observed in the two treatment groups.

Serum IGF-I, IGF-binding protein-3, testosterone, and SHBG (Table 4)

Before treatment, the serum IGF-I concentration was low to normal in both treatment groups. At 6 weeks, the serum IGF-I concentration reached an average of 3.30 ± 0.35 sp above the predicted mean in the rhGH-treated group, whereas at 9 months, the mean serum IGF-I concentration was 1.89 ± 0.48 sp above the predicted mean. Serum concentrations of testosterone and SHBG were not affected significantly by rhGH treatment.

Discussion

We have shown that 9 months of rhGH treatment in middle-aged men with abdominal/visceral obesity reduced total BF and resulted in a specific and marked decrease in both abdominal sc and visceral adipose tissue. The improvement in insulin sensitivity assessed with the euglycemic glucose clamp technique and the reduction in serum concentrations of total cholesterol and TG was more marked with the rhGH treatment than with the placebo treatment. Furthermore, diastolic blood pressure decreased.

The men who were studied were moderately obese, with a preponderance of abdominal and/or visceral localization of BF, as judged from comparisons with randomly selected men of a comparable age from the same city (24). As a group, they had slight to moderate metabolic changes known to be associated with abdominal/visceral obesity with moderate insulin resistance, as judged from the GDR values obtained during the euglycemic glucose clamp, although none had overt diabetes.

Although we used a lower daily rhGH dose than previously reported in trials involving healthy adults (25–27), the

FIG. 2. Abdominal sc and visceral adipose tissue determined with computed tomography at the level of L4-5 in one man before (A) and after (B) 9 months of rhGH treatment. The scan shows the reduction in both visceral and sc adipose tissue (shown as the *dark gray* area in the figure).

This difference between the two groups still was found after correcting the GDR for the amount of FFM.

In the rhGH-treated group, an inverse correlation was found between the change in GDR and the change in serum TG concentration (r = -0.58; P < 0.05), but no significant correlations were found between the change in GDR and changes in serum IGF-I concentration (r = -0.24), serum insulin concentration (r = -0.27), LPL activity (r = 0.09), diastolic blood pressure (r = -0.30), total BF (r = -0.06), and volume of visceral adipose tissue (r = -0.11).

Total cholesterol, TG, LPL activity, plasma fibrinogen, and PAI-1 activity (Table 3)

The mean total cholesterol concentration decreased from 6.1 \pm 0.2 to 5.4 \pm 0.3 mmol/L, and the TG concentration



Variable	Baseline	6 weeks	6 months	9 months	P^a
BMI; kg/m ²					
GH	31.4 ± 0.7	31.6 ± 0.7	31.3 ± 0.7	31.1 ± 0.8	0.2
Placebo	30.5 ± 0.8	30.6 ± 0.7	30.5 ± 0.8	30.7 ± 0.8	
FFM; kg					
GH	67.5 ± 1.8	69.7 ± 1.9	71.1 ± 1.8	69.5 ± 2.2	0.4
Placebo	64.6 ± 1.4	65.2 ± 1.4	66.4 ± 1.3	65.3 ± 1.4	
Waist; cm					
GH	111.8 ± 1.8	110.8 ± 1.8	107.6 ± 1.7	109.8 ± 1.9	0.002
Placebo	109.5 ± 2.5	109.4 ± 2.4	109.3 ± 2.3	111.0 ± 2.3	
Sagittal diameter; cm					
ĞH	26.1 ± 0.5	25.9 ± 0.5	25.2 ± 0.5	25.0 ± 0.6	0.03
Placebo	25.5 ± 0.7	25.3 ± 0.8	24.6 ± 0.9	25.5 ± 0.8	
Visceral AT; cm ²					
GH	126 ± 15	121 ± 19	98 ± 14	99 ± 15	0.04
Placebo	163 ± 16	147 ± 13	142 ± 12	150 ± 13	

TABLE 2. Measurements of body mass index (BMI), FFM, waist circumference, sagittal diameter and abdominal visceral adipose tissue (AT) area at the level of L4-5 in 30 men during 9 months of rhGH or placebo treatment

All values are expressed as the mean (SEM).

^a P-values denote the differences between the two groups by two-way ANOVA for repeated measurements.

TABLE 3. Measurements of glycosylated hemoglobin (HbA1c), C-peptide, total cholesterol, TG, LPL activity expressed as mU per gram of adipose tissue (AT), plasma fibrinogen and PAI-1 in 30 men during 9 months of rhGH or placebo treatment

Variable	Baseline	6 weeks	6 months	9 months	P^a
HbA1c; %					
GH	5.2 ± 0.1	5.2 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	0.8
Placebo	4.9 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	5.1 ± 0.2	
C-peptide; ng/L					
GH	1.11 ± 0.10	1.60 ± 0.13	1.30 ± 0.17	1.18 ± 0.07	0.02
Placebo	1.28 ± 0.27	1.30 ± 0.27	1.28 ± 0.32	1.42 ± 0.30	
Total cholesterol; mmol/L					
GH	6.1 ± 0.2	5.7 ± 0.2	6.1 ± 0.2	5.4 ± 0.3	0.006
Placebo	5.4 ± 0.3	5.6 ± 0.2	6.1 ± 0.3	5.5 ± 0.2	
TG; mmol/L					
GH	2.09 ± 0.29	2.60 ± 0.42	2.31 ± 0.23	1.78 ± 0.23	0.02
Placebo	1.65 ± 0.13	1.80 ± 0.20	1.85 ± 0.22	2.05 ± 0.26	
LPL activity; mU/g AT					
GH	287 ± 26	205 ± 15	ND	371 ± 65	0.2
Placebo	224 ± 31	228 ± 29	ND	263 ± 25	
Fibrinogen; g/L					
GH	3.13 ± 0.13	3.44 ± 0.10	3.49 ± 0.13	3.24 ± 0.19	0.04
Placebo	3.03 ± 0.11	2.73 ± 0.09	3.39 ± 0.28	2.84 ± 0.10	
PAI-1 activity; U/mL					
GH	31.3 ± 6.4	23.2 ± 2.6	18.3 ± 3.1	22.9 ± 3.5	0.4
Placebo	17.0 ± 3.8	22.9 ± 4.2	19.9 ± 4.5	27.1 ± 6.3	

All values are expressed as the mean (SEM).

^a P-values denote the differences between the two groups by two-way ANOVA for repeated measurements.

initial rhGH doses administered were seemingly too high, as judged by the frequency of side effects and the initial high average serum IGF-I concentrations. After a dose reduction, the average serum IGF-I concentration was within the normal range, indicating that the doses of rhGH during the latter part of the study were more physiologic. This might, in turn, explain the less marked anabolic action of the rhGH treatment demonstrated in this study in comparison with previous trials in healthy adults (25, 27).

The marked effect of GH replacement on body composition in GH-deficient adults has been a consistent observation in many studies (17). The profound lipolytic effect of GH also was demonstrated in the present study, with a preferential reduction in visceral adipose tissue depots (28). These changes have been associated with a GH-induced reduction in the antilipolytic effects of insulin, which is markedly different in different adipose tissue regions (29).

GH exerts direct insulin-antagonistic effects, even after the administration of physiologic doses of rhGH. GH has been considered to be the principal factor in the decrease in insulin sensitivity observed in the early morning, the so-called dawn phenomenon (30), and the insulin resistance after hypoglycemia (31). Thus, our observation of increased insulin sensitivity during prolonged rhGH treatment is unexpected, although not inexplicable. We have shown previously that 6 weeks of rhGH treatment in GH-deficient adults only induced a temporary decrease in insulin sensitivity that after 6 months of treatment, was restored to baseline values (32). The response of GDR to rhGH treatment in this trial showed a similar initial tendency to induce insulin resistance, but after 9 months, an improvement was found. This improvement could be explained by the decrease in visceral adipose tissue mass induced by GH, followed by a decrease in FFA exposure to the liver, counteracting the insulin-antagonistic



FIG. 3. Mean fasting blood glucose, serum insulin, and GDR assessed with a euglycemic hyperinsulinemic glucose clamp during 9 months of treatment with rhGH or placebo in 30 men with abdominal/visceral obesity. The *horizontal bars* indicate the SE for the mean values shown and P values denote the differences between the two groups by two-way ANOVA for repeated measurements.

effects of GH. Alternatively, because the major site of glucose disposal is in the skeletal muscle (33), the possibility has to be considered that the improvement in GDR in response to the more prolonged rhGH treatment also might be an effect of increased glucose transport in the skeletal muscle, possibly mediated through the IGF-I receptor (34), an increased proportion of insulin-sensitive type I muscle fibers (35), or increased capillarization in the skeletal muscle.

GH has been found to be an important regulator of the hepatic LDL receptor (36) and the overall lipoprotein metabolism (37). The reduction in total cholesterol conceivably is an effect of enhanced hepatic LDL-receptor activity in response to GH (36). In healthy adults, short-term rhGH administration has been reported to increase serum TG concentrations (25). In this study, the serum TG concentration also displayed an initial increase in response to rhGH treatment. This could be an effect of both an increased flux of FFA to the liver and a direct stimulatory effect on the esterification of oleic acid into TG and phospholipids in hepatocytes (38) in response to GH, which in turn, enhances the very-low density lipoprotein production from the liver. However, after 9 months of rhGH treatment, the serum TG concentration had decreased again, probably as an effect of the increased insulin-stimulated glucose uptake, which is known to be inversely related to the very-low density lipoprotein secretion rate from the liver and serum TG levels (4).

The initial tendency towards a decline in LPL activity observed in the present study is in accordance with a previous 5-week treatment trial with rhGH (39). During the more prolonged rhGH treatment, however, LPL activity tended to increase, which may, at least in part, explain the decrease in serum TG concentration at 9 months. The changes in GDR and LPL activity showed a similar biphasic pattern in response to GH. It may thus be speculated that the suggested influence of GH on LPL activity is mediated through insulin sensitivity because insulin is known to be a potent stimulator of LPL.

Nine months of rhGH treatment reduced diastolic blood pressure without affecting systolic blood pressure. This is in line with results from GH-deficient adults, in whom rhGH administration reduced diastolic blood pressure, possibly as an effect of reduced peripheral vascular resistance (40). The mechanisms behind the reduction in peripheral vascular resistance might be indirect, through the reduced abdominal obesity and increased insulin sensitivity (41), or more direct, through the action of IGF-I on the vascular wall (42).

Abdominal/visceral obesity is associated with increased plasma fibrinogen concentration and PAI-1 activity (43, 44), both of which are established risk factors for myocardial infarction and stroke (45, 46). Plasma fibrinogen levels in healthy elderly women did not change significantly in response to high doses of rhGH for 6 months (26). The slightly increased plasma fibrinogen concentration, in response to GH observed in this study, may be mediated through increased serum IGF-I concentration (18). In GH-deficient adults, 2 yr of rhGH treatment tended to decrease plasma fibrinogen levels and diminish PAI-1 activity (47). This further illustrates the importance of the duration of rhGH treatment on the metabolic effects of GH.

Previous studies have shown that testosterone treatment in middle-aged men with abdominal/visceral obesity induced improved insulin sensitivity, plasma lipid levels, and diastolic blood pressure, as well as a specific decrease in the visceral adipose tissue mass (14, 48). Because testosterone treatment in men with hypogonadotrophic hypogonadism increases GH secretion (49), the similarities between testosterone and rhGH treatment might be explained by increased GH levels or by additional or synergistic effects by GH and testosterone on adipose tissue metabolism (50).

The multiple endocrine alterations associated with abdominal/visceral obesity can either be primarily responsible

Variable	Baseline	6 weeks	6 months	9 months	P^a
IGF-I; μg/L					
GH	134 ± 8	338 ± 16	320 ± 23	268 ± 23	< 0.001
Placebo	120 ± 11	121 ± 11	129 ± 12	119 ± 12	
IGF-I SD score ^{b}					
GH	-0.82 ± 0.17	3.30 ± 0.35	2.91 ± 0.49	1.89 ± 0.48	< 0.001
Placebo	-1.07 ± 0.23	-1.04 ± 0.23	-0.87 ± 0.24	-1.08 ± 0.25	
IGFBP-3; mg/L					
GH	2.36 ± 0.13	3.20 ± 0.10	3.19 ± 0.13	2.71 ± 0.14	0.001
Placebo	2.10 ± 0.16	2.21 ± 0.17	2.45 ± 0.21	2.18 ± 0.19	
FFA; µmol/L					
GH	0.77 ± 0.07	0.99 ± 0.11	0.78 ± 0.11	0.75 ± 0.07	0.5
Placebo	0.73 ± 0.05	0.73 ± 0.05	0.59 ± 0.06	0.67 ± 0.05	
Testosterone; nmol/L					
GH	14.6 ± 1.2	12.9 ± 1.0	13.9 ± 1.3	12.4 ± 1.1	0.12
Placebo	14.6 ± 1.0	15.4 ± 1.2	17.6 ± 2.1	14.6 ± 1.3	
SHBG; nmol/L					
GH	26.4 ± 3.4	25.5 ± 3.5	25.9 ± 3.1	23.4 ± 2.8	0.8
Placebo	28.1 ± 2.9	29.1 ± 3.1	29.2 ± 3.2	25.5 ± 2.7	

TABLE 4. Measurements of serum IGF-I, IGFBP-3, FFA, testosterone, and SHBG in 30 men during 9 months of GH/placebo treatment

All values are expressed as the mean (SEM).

^a P-values denotes the differences between the two groups by two-way ANOVA for repeated measurements.

^b The SD score for serum IGF-I is calculated from predicted IGF-I values, adjusted for age and sex, obtained from the normal population (18).

or be the consequence of the obese condition. This is the first trial to demonstrate clearly favorable effects by GH on the multiple perturbations associated with abdominal/visceral obesity. We suggest, therefore, that a blunted GH secretion could be an important factor in the development of the metabolic and circulatory consequences of abdominal/visceral obesity. The metabolic effects demonstrated in this study are probably of importance for the risk of cardiovascular morbidity and mortality in men with abdominal and central adiposity.

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