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Growth Hormone Treatment Reduces Abdominal Visceral Fat in Postmenopausal Women with Abdominal Obesity: A 12-Month Placebo-Controlled Trial

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Abdominal obesity is associated with blunted GH secretion and a cluster of cardiovascular risk factors that characterize the metabolic syndrome. GH treatment in abdominally obese men reduces visceral adipose tissue and has beneficial effects on the metabolic profile. There are no long-term data on the effects of GH treatment on postmenopausal women with abdominal obesity.

Forty postmenopausal women with abdominal obesity participated in a randomized, double-blind, placebo-controlled, 12-month trial with GH (0.67 mg/d). The primary aim was to study the effect of GH treatment on insulin sensitivity.

Measurements of glucose disposal rate (GDR) using a euglycemic, hyperinsulinemic glucose clamp; abdominal fat, hepatic fat content, and thigh muscle area using computed tomography; and total body fat and fat-free mass derived from ^{40}K measurements were performed at baseline and at 6 and 12 months.

GH treatment reduced visceral fat mass, increased thigh muscle area, and reduced total and low-density lipoprotein cholesterol compared with placebo. Insulin sensitivity was increased at 12 months compared with baseline values in the GH-treated group. In the GH-treated group only, a low baseline GDR was correlated with a more marked improvement in insulin sensitivity ($r = -0.68$; $P < 0.001$). A positive correlation was found between changes in GDR and liver attenuation as a measure of hepatic fat content between baseline and 12 months ($r = 0.7$; $P < 0.001$) in the GH-treated group.

In postmenopausal women with abdominal obesity, 1 yr of GH treatment improved insulin sensitivity and reduced abdominal visceral fat and total and low-density lipoprotein cholesterol concentrations. The improvement in insulin sensitivity was associated with reduced hepatic fat content. (*J Clin Endocrinol Metab* 90: 1466–1474, 2005)

ABDOMINAL OBESITY IS a strong independent risk factor for cardiovascular disease and type 2 diabetes mellitus (DM), a condition often clustered with insulin resistance, hypertension, and dyslipidemia and known as the metabolic syndrome (1). Efforts have been made to reach a consensus on the definition of the metabolic syndrome to enhance new strategies for its prevention and treatment. Although the World Health Organization (WHO) (2) definition proposes insulin resistance as the underlying etiological factor (3), the National Health and Nutrition Examination Survey of 1999–2000 (NHANES III) and the National Cholesterol Education Program's Adult Treatment Panel III (NCEP's ATP III) definition suggests that abdominal obesity is a major risk factor associated with or leading to the clustering of metabolic perturbations such as atherogenic dyslipidemia, insulin resistance, and a proinflammatory and a prothrombotic state (4).

An increase in the prevalence of the metabolic syndrome has been reported in several population studies (3, 4), regardless of which definition is used. In contrast to previous reports suggesting that the syndrome tends to be more common in men than in women (5), recent evidence indicates that the condition may be equally prevalent in both sexes (6) with an equal risk of developing type 2 DM. According to the Framingham Heart Study, the metabolic syndrome is a stronger denominator among women who develop cerebrovascular disease than among men (7), but this finding has not been confirmed by another study (8).

Abdominal obesity is associated with nonalcoholic fatty liver disease, an entity encompassing a broad spectrum ranging from simple steatosis to nonalcoholic steatohepatitis that is strongly associated with insulin resistance, type 2 DM, and hypertriglyceridemia (9). The pathophysiological mechanisms leading to the accumulation of visceral fat are still not known, but multiple endocrine aberrations affecting the hypothalamic-adrenal, gonadal, and somatotropic axes, as well as the sympathetic nervous system, may be of importance (10).

Several similarities exist between patients with the metabolic syndrome and individuals with adult GH deficiency (11). Both conditions include increased abdominal fat depots,

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Abbreviations: Apo, Apolipoprotein; AT, adipose tissue; BF, body fat; BMI, body mass index; BW, body weight; CT, computed tomography; CV, coefficient of variation; DM, diabetes mellitus; FFM, fat-free mass; GDR, glucose disposal rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of the insulin resistance index; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; Lp (a), lipoprotein (a); OGTT, oral glucose tolerance test; TG, triglyceride; VAT, visceral adipose tissue; W/H, waist-to-hip.

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insulin resistance, high serum levels of triglycerides, and low serum levels of high-density lipoprotein (HDL)-cholesterol. GH secretion is markedly blunted in abdominally obese individuals and demonstrates a strong exponential inverse relationship with the amount of visceral adipose tissue (VAT), which is similar in men and women (12–14). GH replacement therapy in GH-deficient patients reduces visceral fat mass and improves the lipid profile and other well-known cardiovascular risk factors (15, 16). Similar data have been produced in men with abdominal obesity where 9 months of GH treatment was able to improve insulin sensitivity (17). Treatment with GH for 5 wk in obese women was followed by a reduction in body fat mass (18), and 12 wk of GH treatment combined with a diet and exercise program in postmenopausal women reduced truncal fat, an effect not different from diet and exercise alone (19). There are no long-term data on the effect of GH treatment in women with abdominal obesity, and previous studies have not been able to show that GH is more efficient than weight reduction alone to reduce total body fat in subjects with simple obesity (20, 21).

The primary aim of this study was to explore the effects of GH treatment on insulin sensitivity in postmenopausal women with abdominal obesity, and the secondary aim was to study effects on visceral fat mass and glucose tolerance.

Patients and Methods

Forty women with a mean age of 57.3 yr (range, 51–63 yr) were studied (Table 1). They were recruited by advertisements in a local newspaper. The criteria for inclusion in the study were age 50–65 yr, a body mass index of 25–35 kg/m^2, a waist-to-hip (W/H) ratio and/or a sagittal diameter larger than 0.85 and 21.0 cm, respectively, and a serum IGF-I concentration of between –1 and –2 SD score. The criteria for exclusion were DM, cardiovascular disease, claudicatio intermittens, stroke, any malignancy, and any other hormone treatment, including estrogen replacement therapy. Of 607 women who responded to the advertisement, 145 were screened and 40 were then found to be eligible for inclusion (Fig. 1).

Study design

This study was designed as a 12-month, randomized, double-blind, parallel group trial with subjects receiving placebo or recombinant human GH. After a 1-month run-in period in which concomitant medications were optimized, 40 women were randomized to receive GH or placebo treatment. A computerized randomization was performed by the Sahlgrenska hospital pharmacy.

Ethics

Informed consent was obtained from each patient before entry into the study. The study was approved by the Ethics Committee at the University of Göteborg and by the Medical Products Agency, Uppsala, Sweden.

TABLE 1. Clinical characteristics of 40 postmenopausal abdominally obese women treated with GH/placebo during 12 months

Characteristics	GH	Placebo
No. of women	20	20
Age [mean (range), yr]	58.2 (51–63)	56.5 (51–63)
BMI (kg/m^2)	30.6 (0.7)	30.0 (0.8)
Smokers	5	5
Alcohol consumption	20	20
Antihypertensive treatment[a]	4	4
ACE inhibitors/AT II antagonists	2	2

[a] β-Blockers, angiotensin I-converting enzyme (ACE) inhibitors, Ca antagonists, and angiotensin II (AT-II) antagonists.

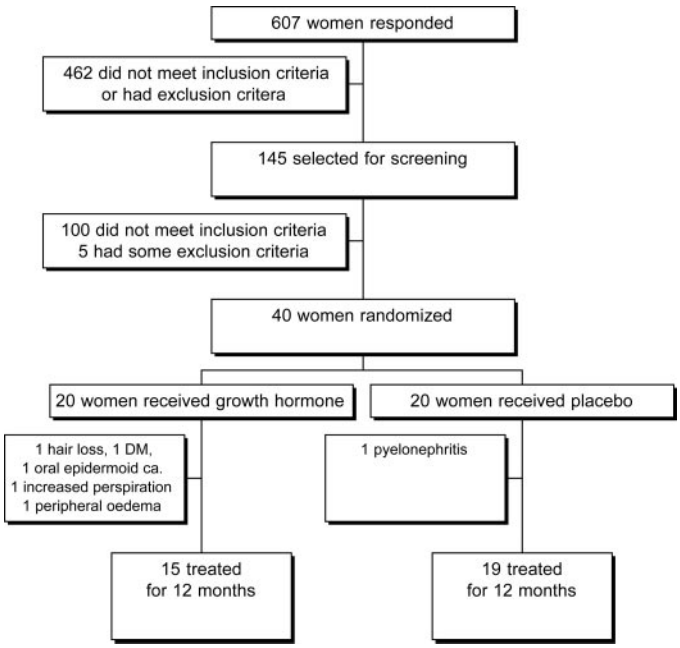

FIG. 1. Trial profile.

Treatment

The subjects were treated with GH (Genotropin, Pfizer, Stockholm, Sweden), administered sc before bedtime. The treatment regimen was initially formulated in international units per day and later converted to milligrams per day. The initial dose of GH was 0.13 mg/d (0.4 IU/d), which was then increased to 0.27 mg/d (0.8 IU/d) after 2 wk, 0.4 mg/d (1.2 IU/d) after 4 wk, 0.53 mg/d (1.6 IU/d) after 5 wk and, after 6 wk, to the target dose of 0.67 mg/d (2.0 IU/d). Symptoms and signs of adverse effects were carefully monitored at each visit. The dose was reduced by half in the event of fluid-related side effects. Oral and written instructions about administration and dose were given. Compliance was assessed by counting the returned empty vials and expressing that number as a percentage of the vials needed for the treatment period.

Study protocol

Body composition assessments of insulin sensitivity and glucose tolerance were made before the start of treatment and after 6 and 12 months of treatment. Computed tomography (CT) of the abdomen and thigh area was performed, and physical activity and quality of life questionnaires were used at baseline and at 12 months. Physical and laboratory examinations including safety assessments were performed at the start; after 1, 2, 3, 6, 9, and 12 months; and 1 month after discontinuing treatment. Body weight (BW) was measured in the morning to the nearest 0.1 kg using a calibrated scale. Body height was measured barefoot to the nearest 0.01 m. The body mass index (BMI) was calculated as BW 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, whereas the hip girth was measured at the widest part of the hip. Systolic and diastolic blood pressures were measured after 5 min supine rest with an automatic sphygmomanometer. The mean of three measurements with a 1-min interval in between was used for evaluation.

Body composition

Total body potassium was measured by counting the emission of 1.46 MeV γ-radiation from the naturally occurring ^{40}K isotope in a highly sensitive 3-π whole-body counter with a coefficient of variation (CV) of 2.2%. Fat-free mass (FFM) was estimated by assuming a potassium

content of 62 mmol/kg FFM (22). Total body fat (BF) was then calculated as BW – FFM. A CT technique was used to measure abdominal adipose tissue and thigh muscle. Tissue areas were determined with the subject in a recumbent position with a General Electric High Speed Advantage CT system (HAS), version RP2, GE Medical Systems, Milwaukee, WI. The tube voltage was 120 kV, and the slice thickness was 5 mm. Four scans were obtained from each participant. Scan 1 was obtained in the mid-thigh region 1 cm below the gluteal fold, scan 2 at the fourth lumbar vertebra level (L4), scan 3 at the mid-liver level, and scan 4 at the fourth cervical vertebra level (C4). From scan 1, the tissue areas of the right leg are reported. Tissue areas were determined as previously described (23) with precision errors calculated from double determinations: sc adipose tissue (AT) (0.5%), the sum of ip and retroperitoneal AT (1.2%), and muscle plus skin (0.3%). To assess hepatic fat content, the attenuation of the liver and spleen was determined within three circular regions of interest placed in the dorsal aspect of each organ. Attempts were made to avoid vessels, artifacts, and areas of homogeneity. Hepatic fat content was studied as the liver attenuation absolute values or as the liver-to-spleen attenuation ratio. This ratio shows a linear correlation to hepatic fat content when determined using either histomorphometric (24) or biochemical methods (25), whereas cutoff values for the diagnosis of fatty liver were considered to be a liver attenuation of 30 or less or a liver/spleen ratio of less than 1 Hounsfield unit. The effective dose equivalent per examination was less than 0.8 mSv.

Insulin sensitivity measures

A euglycemic hyperinsulinemic glucose clamp was performed after an overnight fast, as described previously (26). An iv catheter was placed in an antecubital vein for the infusion of insulin (0.12 IU/kg·min) and 20% dextrose. A second catheter was placed in the contralateral arm for arterialized blood. The plasma insulin level was maintained between 150 and 250 mU/liter to suppress endogenous hepatic glucose production. Blood glucose was monitored every 10 min during the insulin infusion and, during the last 30 min, every 5 min. Euglycemia was maintained (5.5 mmol/liter) by infusing 20% dextrose in variable amounts. The glucose disposal rate (GDR) was measured for 20 min in steady-state conditions, which were reached after 100 min. The mean insulin concentrations during steady state were 208.9 (12.4) *vs.* 219.4 (12.3) mIU/liter at baseline, 210.2 (11.9) *vs.* 210.1 (8.9) mIU/liter at 6 months, and 210.6 (11.0) *vs.* 210.6 (11.1) mIU/liter at 12 months.

All the subjects performed an oral glucose tolerance test (OGTT) before the start, at 6 and 12 months, respectively, and 1 month after treatment. A standard dose of 75 g of glucose was administered, and fasting blood samples were obtained at baseline and every 30 min for 2 h. The definition criteria for normal, impaired glucose tolerance, and DM were based on the American Diabetes Association (ADA) recommendations (27). To eliminate any type of interference, OGTT assessments were performed 1 wk after the glucose clamp. The homeostasis model assessment of the insulin resistance index (HOMA-IR) was estimated as described previously (28).

Biochemical assays

Blood samples were drawn in the morning after an overnight fast. The serum concentration of IGF-I was determined by a hydrochloric acid ethanol extraction RIA using authentic IGF-I for labeling (Nichols Institute Diagnostics, San Juan Capistrano, CA) with a within-assay CV of 2.2 and 4.2% at serum concentrations of 125 and 345 μg/liter, respectively. The SD score for IGF-I was calculated from the predicted IGF-I values, adjusted for age and sex values obtained from the normal population (29).

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 and 3.49 mg/liter, respectively. The IGF-binding protein 1 concentration was determined by ELISA (Immunotech, Marseille, France), with a CV of 12.8%.

Serum total cholesterol and triglyceride (TG) concentrations were determined with enzymatic methods (Thermo Clinical Lab Systems, Espoo, Finland)). The within-assay CV for total cholesterol and TG determinations was 2.2 and 2.3%, respectively. HDL cholesterol was determined after the precipitation of apolipoprotein B (apoB)-containing lipoproteins with magnesium sulfate and dextran sulfate (Thermo Clinical Labsystems), with a CV of 1.9%. The low-density lipoprotein (LDL) cholesterol concentration was calculated as described previously (30). ApoB and apoA-I were determined by immunoprecipitation enhanced by polyethylene glycol at 340 nm (Thermo Clinical Labsystems), with CV of 3.2 and 5.9%, respectively. Lipoprotein (Lp) (a) was measured by an immunoturbidinemic test (DiaSys Diagnostic Systems Gmbh & Co., Holzheim, Germany), with a CV of 6.7%. All analyses were performed on a Konelab 20 autoanalyzer (Thermo Clinical Labsystems).

Serum insulin was determined using RIA (Pharmacia, Uppsala, Sweden), and blood glucose was measured by the Gluco-quant method (Roche/Hitachi, Mannheim, Germany). Hemoglobin A1c was determined by HPLC (Walters, Millipore AB, Sweden), whereas C-peptide was determined by an immunoenzymetric method (Dako Diagnostics Ltd., Dakopatt AB, Glostrup, Denmark). Free fatty acid levels were determined using an enzymatic colorimetric method (NEFAC; Waco, Neuss, Germany).

Physical activity and quality of life questionnaires

Physical activity was studied by assessing indices of habitual physical activity at work, sport, and during leisure time using a questionnaire developed by Baecke *et al.* (31). Quality of life was assessed using the Psychological General Well-Being index, which includes an overall score and six subscores (anxiety, depression, well-being, self-control, health, and vitality), described elsewhere (32).

Statistical methods

All the descriptive statistical results are presented as the mean (SEM). The results have been analyzed on an intention-to-treat basis with the exception of the subgroup analysis of GDR and weight including only subjects who fulfilled 1 yr of treatment. Between-group treatment effects were analyzed using a two-way ANOVA for repeated measurements. Within-group treatment effects were estimated by one-way ANOVA or a paired *t* test. Log transformation before statistical analysis was used for variables that did not have a normal distribution. An unpaired *t* test was used for between-group analyses. Correlation analyses were performed using Pearson's linear regression coefficient. Spearman's rank test was applied for analyses of categorical data. A two-tailed P value $\leq$ 0.05 was considered significant.

Results

The GH and placebo groups were well matched at baseline in terms of age, BMI, W/H ratio, smoking habits, alcohol consumption, and antihypertensive treatment (Tables 1 and 2).

GH dose, serum IGF-I, and IGF-I SD score

At 12 months, the mean dose of GH in the GH group was 0.51 (0.05) mg/d, whereas it was 0.65 (0.01) mg/d in the placebo group; $P < 0.001$. Serum IGF-I increased from a baseline value of 105 (7) μg/liter to 211.2 (16) μg/liter at 6 months in the GH-treated group and was unchanged in the placebo group, 121 (5) μg/liter at baseline and 119 (6) μg/liter at 6 months. There was no significant change in serum IGF-I concentrations between 6 and 12 months in both groups. The IGF-I SD score increased in the GH-treated group (Fig. 2).

Symptoms, side effects, and compliance

Twelve women in the GH-treated group experienced side effects related to fluid retention (arthralgia, joint stiffness, or peripheral edema). They appeared during the first 4 wk of treatment and were all considered to be of mild to moderate severity. In 11 subjects, dose adjustments were required, although in one subject the symptoms subsided spontaneously after 9 months. At the end of the trial, only two of the

TABLE 2. Assessment of anthropometrical variables and body composition by ^{40}K and CT scan of 40 postmenopausal abdominally obese women treated with GH/placebo during 12 months

Variable	Group	Baseline	6 months	12 months	*P* (0–1 yr)
Weight (kg)	GH	86.0 (2.4)	86.1 (2.6)	87.2 (2.5)[a]	0.9
	Placebo	80.9 (2.2)	80.7 (2.3)	81.8 (2.3)[a]	
Waist (cm)	GH	104 (1.4)	103 (1.5)	104 (1.6)	0.7
	Placebo	102 (1.6)	102 (1.8)	102 (2.0)	
Sagittal diameter (cm)	GH	25.8 (0.34)	25.4 (0.43)	25.7 (0.40)	0.8
	Placebo	25.0 (0.45)	24.8 (0.48)	25.1 (0.56)	
W/H ratio	GH	0.93 (0.01)	0.92 (0.01)	0.93 (0.01)	0.3
	Placebo	0.94 (0.012)	0.94 (0.01)	0.93 (0.01)	
Total BF (kg)	GH	37.4 (1.9)	37.1 (2.1)	38.9 (2.0)	0.9
	Placebo	34.0 (1.8)	33.1 (1.8)	35.0 (1.7)	
FFM (kg)	GH	48.7 (1.3)	48.9 (1.2)	48.2 (1.1)	0.9
	Placebo	46.9 (1.1)	47.6 (1.2)	46.8 (1.2)	
Thigh muscle area (cm^2)	GH	110.4 (2.7)		113.0 (2.5)[c]	0.002
	Placebo	110.9 (3.4)		110.7 (3.2)	
Abdominal sc AT area (cm^2)	GH	430.2 (20.2)		432.0 (22.3)	0.8
	Placebo	400.9 (20.8)		400.5 (22.0)	
Visceral AT area (cm^2)	GH	177.2 (8.7)		170.6 (10.0)	0.003
	Placebo	161.0 (7.9)		172.0 (8.9)[b]	
Mean liver attenuation (Hounsfield units)	GH	49.0 (2.3)		51.1 (2.2)	0.6
	Placebo	51.0 (2.9)		51.2 (2.5)	

All values are expressed as the mean (SEM). BF and FFM were estimated by total body potassium. *P* values represent overall treatment effect analyzed using one-way ANOVA.

[a] $P < 0.05$ (at the given time point *vs.* baseline value).

[b] $P < 0.01$ (at the given time point *vs.* baseline value).

[c] $P < 0.001$ (at the given time point *vs.* baseline value).

11 subjects presenting signs of fluid retention had an IGF-I score greater than 2 SD.

Five dropouts occurred in the GH-treated group, four of which could be potentially attributed to the GH treatment (Fig. 1). One subject left the trial after 3 months of persistent swelling and numbness despite dose adjustments. One subject developed DM and was excluded from further treatment at 6 months. In retrospect, the diagnosis of DM was present during OGTT at the first visit, data that were not available until 1 wk after the performed test. One subject complained of profuse perspiration 1 month after the start of treatment and was excluded from the trial after 2 months when estrogen treatment was commenced, although one subject decided to discontinue treatment after 3 months as she experienced increased hair loss. The fifth case was withdrawn after 4 months of treatment because of the diagnosis of an epidermoid tumor in the oral cavity. The lesion was already present several months before the start of the trial, but the diagnosis was first established by biopsy 2 months later.

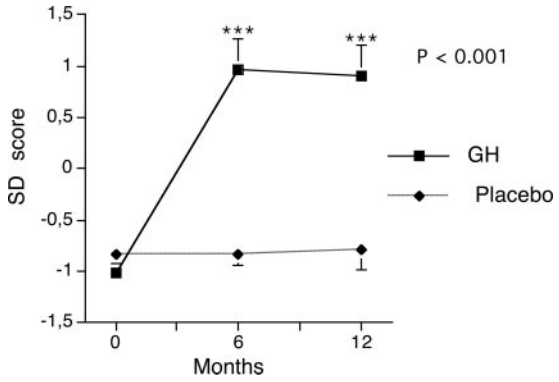

FIG. 2. Effect of GH treatment on IGF-I, expressed as IGF-I score SD, adjusted for age and gender in 40 postmenopausal women receiving GH or placebo for 12 months. $P < 0.001$ represents overall treatment effect analyzed using one-way ANOVA; ***, $P < 0.001$ compared with baseline.

There were dose adjustments made in one of the five subjects, who discontinued treatment. In the placebo group, two women complained of slight peripheral edema, and dose adjustments were made in one of them who decided to discontinue treatment after 6 months because of a recurrent pyelonephritis.

Compliance with treatment was 97.4% in the GH-treated group and 95% in the placebo group.

Glucose metabolism

GDR was similar in both groups at baseline. Between-group analysis did not reveal any difference in GDR after 1 yr of treatment. After a slight decrease, GDR increased significantly after 12 months of GH treatment compared with baseline levels in the GH-treated group with no changes in the placebo group (Fig. 3). In a subgroup analysis, women were divided into groups depending on whether they had GDR above or below the median value for the whole group (8.4 mg/kg·min) (Fig. 4). The increase in GDR between baseline and 12 months was more marked in women receiving GH with baseline values below the median for the group. A similar pattern was not seen in the placebo group.

The baseline HOMA-IR and GDR showed an inverse correlation ($r = -0.34$; $P < 0.033$). HOMA-IR and fasting insulin levels increased within the GH-treated group at 12 months and were unchanged in the placebo group (Table 3). Between-group analysis did not reveal significant changes in fasting plasma glucose, 2-h glucose values after an oral glucose load, or hemoglobin A1c (Table 3). No differences were observed in the estimation of the glucose area under the curve during the OGTT. The baseline 2-h glucose after an

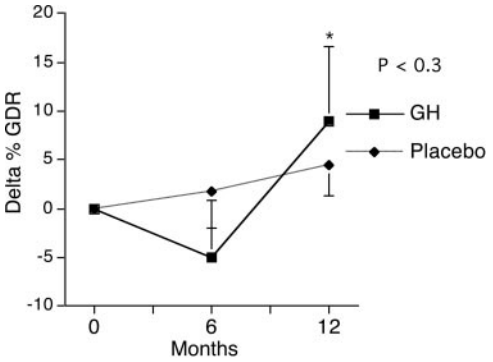

FIG. 3. Insulin sensitivity expressed as percent change in GDR in postmenopausal women receiving GH/placebo treatment for 12 months. $P < 0.3$, overall effect between groups using one-way ANOVA; *, $P < 0.05$ compared with baseline.

OGTT revealed impaired glucose tolerance (IGT) in two individuals in each group. After 6 months, there were four subjects with IGT in both groups, whereas two subjects in the GH group and one subject in the placebo group had diabetic values. After 1 yr, two GH-treated subjects normalized their 2-h glucose, although two new subjects presented IGT. In the placebo group, three subjects remained glucose intolerant.

Lipid metabolism

Total cholesterol and LDL cholesterol decreased after 6 months in the GH-treated group compared with the placebo group. This effect was sustained at 12 months. A transient increase in TG and a decrease in HDL cholesterol concentrations were observed after 6 months of treatment in the GH-treated group. ApoA-I, apoB, Lp (a), and the apoB/apoA-I ratio remained unaffected in the GH-treated subjects compared with the placebo group (Table 4).

Body composition

Mean body weight increased in both groups, with seven of 15 women in the GH-treated group and 11 of 19 women in the placebo group gaining more than 1 kg, whereas the remaining women were regarded as weight stable. Baseline total BF values were 37.4 ± 8.1 kg in the GH group *vs.* 34.0 ± 7.9 kg in the placebo group. No differences in BF or FFM were observed between or within groups at any time during the study (Table 2).

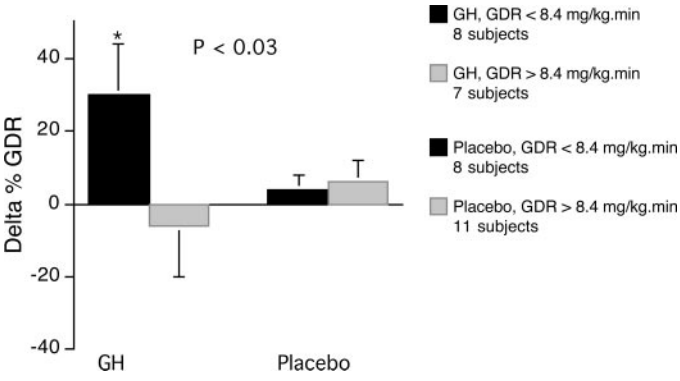

FIG. 4. Subgroup analysis of insulin sensitivity expressed as percent change in GDR from baseline to 1 yr of GH/placebo treatment with GDR value above or below the median for the whole group (8.4 mg/kg·min). $P < 0.03$, overall effect of the subgroups using two-way ANOVA; *, $P < 0.05$ compared with baseline.

After 12 months, GH treatment had reduced VAT (Fig. 5) and increased the muscle area in the mid-thigh region (Table 2). No differences from baseline to the study end were observed in abdominal (Table 2) and thigh sc AT (data not shown). Although VAT decreased after 12 months in the GH group, an increase occurred in the placebo group ($P > 0.01$), resulting in a significant between-treatment difference. Correlation analysis revealed an inverse relationship between changes in IGF-I and VAT in the GH-treated group ($r = -0.53$; $P < 0.02$).

The percentage change between baseline and 12 months in the liver attenuation and liver/spleen attenuation ratio showed a positive linear correlation with the percentage change in GDR ($r = 0.65$, $P < 0.01$ and $r = 0.60$, $P < 0.001$, respectively, in the GH-treated group). At baseline, an inverse correlation was found between VAT and liver attenuation ($r = -0.49$; $P < 0.04$). No significant correlations were seen between the change in VAT and the change in GDR ($r = -0.17$), thigh muscle mass and GDR ($r = 0.01$), or FFM and GDR ($r = -0.2$) in the GH-treated group. Serum aspartate aminotransferase and alanine aminotransferase levels were inversely correlated with increased liver attenuation in the GH-treated group ($r = -0.84$, $P > 0001$; and $r = -0.81$, $P < 0.0001$, respectively). Furthermore, a reduction in visceral fat mass (Fig. 6A) and in hepatic fat content expressed as an increase in liver attenuation (Fig. 6B) and an improvement in GDR occurred particularly among the GH-treated women who had a stable weight or experienced a weight reduction throughout the study period (Fig. 7).

Physical activity and quality of life assessments

Baseline physical activity determined using a questionnaire was similar in both groups and remained unchanged during the study. The Psychological General Well-Being (PGWB) test did not reveal any difference in quality of life between the groups at any time.

Discussion

One year of GH treatment in postmenopausal women with abdominal obesity reduced the amount of visceral fat, increased thigh muscle area, improved the serum lipid pattern compared with placebo treatment, and improved insulin sensitivity within the GH treatment group.

The target dose of GH was selected based on previous reports that suggest that a daily GH dose of approximately 0.6 mg/d would be in agreement with the physiological GH production in middle-aged women (33). An increase of mean IGF-I SD score to 1 SD after 6 months with no additional changes after 12 months indicated that the given dose was within the physiological range. However, dose adjustments were necessary in 11 of the GH-treated subjects, suggesting that a lower dose than the selected target dose might have been suitable for some of the subjects.

Our primary efficacy variable was the change in GDR, an established method for assessing insulin sensitivity. We identified the subjects who had the lowest insulin sensitivity

TABLE 3. Measurements of IGF-I, fasting plasma glucose, 2-h glucose value after OGTT, fasting insulin, HOMA-IR, and GDR during hyperinsulinemic, euglycemic clamp in 40 postmenopausal abdominally obese women treated with GH/placebo during 12 months

Variable	Treatment	Start	6 months	12 months	*P* (0–1 yr)
IGF-I (μg/liter)	GH	101 (7)	211 (16)[c,d]	206 (19)[c,d]	<0.001
	Placebo	121 (5)	119 (6)	120 (7)	
Fasting glucose (mmol/liter)	GH	5.2 (0.1)	5.3 (0.1)	5.5 (0.1)	0.3
	Placebo	5.2 (0.1)	5.4 (0.1)	5.4 (0.1)	
2-h glucose (mmol/liter)	GH	6.3 (0.3)	7.4 (0.5)	7.1 (0.4)	0.9
	Placebo	5.9 (0.3)	7.1 (0.4)	6.6 (0.4)	
Fasting insulin (mU/liter)	GH	10.1 (1.0)	12.8 (1.6)[a]	13.7 (1.3)[b]	0.6
	Placebo	9.7 (1.0)	10.0 (1.0)	10.4 (0.9)	
HOMA-IR	GH	2.4 (0.3)	3.1 (0.4)	3.5 (0.4)[b]	0.4
	Placebo	2.3 (0.3)	2.4 (0.3)	2.5 (0.4)	
GDR (mg/kg·min)	GH	8.27 (0.57)	7.47 (0.45)	8.57 (0.56)[a]	0.3
	Placebo	7.78 (0.48)	7.81 (0.51)	8.09 (0.54)	

All values are expressed as mean (SEM). *P* values represent overall treatment effect analyzed using one-way ANOVA.
[a] $P < 0.05$ (at the given time point *vs.* baseline value).
[b] $P < 0.01$ (at the given time point *vs.* baseline value).
[c] $P < 0.001$ (at the given time point *vs.* baseline value).
[d] $P < 0.001$ (GH *vs.* placebo-treated women at baseline, at 6 months and at the end of the study).

at baseline in both the GH- and placebo-treated group and observed the best improvement in insulin sensitivity in the GH-treated subjects with low baseline GDR. Because this was not seen in the placebo group, the possibility of a regression toward the mean is reduced, indicating that subjects with the most severe insulin resistance responded most to treatment. After an initial deterioration, the glucose metabolism remained unaffected in terms of fasting plasma glucose, plasma insulin, and hemoglobin A1c levels.

In contrast to insulin sensitivity, glucose tolerance did not show any improvement in the GH-treated group as compared with placebo. This apparent discordance may be explained by the fact that insulin sensitivity estimated by the euglycemic insulin clamp represents the whole-body insulin sensitivity (hepatic and peripheral), whereas glucose tolerance estimated by 2-h plasma glucose predominantly reflects the grade of disturbances in the peripheral (primarily muscle) insulin-mediated glucose metabolism (34). Nevertheless, a trial combining 12 wk of GH treatment with caloric restriction in newly diagnosed type 2 DM subjects demonstrated an improvement in both insulin sensitivity and glucose tolerance (35), indicating that GH treatment may have an additional positive effect on insulin resistance, over and above the dietary regimen.

A reduction in serum total cholesterol and LDL cholesterol was observed in the GH-treated women, although the reduction in LDL cholesterol was more marked after the first 6 months (10%) compared with 12 months (5%). In some studies dealing with GH-deficient patients receiving GH replacement therapy, a transient reduction in total cholesterol, LDL cholesterol, and the total cholesterol/HDL ratio and an increase in Lp (a) have been reported (36, 37). In contrast to these data, no significant changes in Lp (a) or total apoB were observed in our study. One plausible explanation is that the target dose of GH in our study was considerably lower than that used in these previous trials and that men may respond more markedly/differently than women in terms of the lipoprotein metabolism (38).

Assessments of body composition by CT scan showed a clear reduction in VAT and an increased amount of thigh

TABLE 4. Measurements of total cholesterol, LDL cholesterol, HDL cholesterol, TG, apoB, apoA1, Lp (a), and Apob/ApoA-1 in 40 postmenopausal abdominally obese women treated with GH/placebo during 12 months

Variable	Treatment	Start	6 months	12 months	*P* (0–1 yr)
Total cholesterol (mmol/liter)	GH	6.31 (0.15)	5.82 (0.18)[b]	6.09 (0.16)	0.05
	Placebo	6.34 (0.26)	6.30 (0.23)	6.21 (0.24)	
LDL cholesterol (mmol/liter)	GH	4.33 (0.16)	3.87 (0.18)[a]	4.13 (0.17)	<0.05
	Placebo	4.39 (0.24)	4.29 (0.20)	4.21 (0.23)	
HDL cholesterol (mmol/liter)	GH	1.31 (0.06)	1.23 (0.06)[a]	1.31 (0.05)	0.6
	Placebo	1.27 (0.08)	1.24 (0.08)	1.27 (0.07)	
TG (mmol/liter)	GH	1.49 (0.12)	1.71 (0.19)	1.55 (0.15)	0.8
	Placebo	1.49 (0.10)	1.74 (0.24)	1.61 (0.14)	
ApoB (g/liter)	GH	1.13 (0.03)	1.07 (0.04)	1.10 (0.04)	0.1
	Placebo	1.16 (0.06)	1.18 (0.06)	1.13 (0.06)	
ApoA-I (g/liter)	GH	1.44 (0.04)	1.35 (0.04)[a]	1.38 (0.03)[a]	0.4
	Placebo	1.41 (0.05)	1.38 (0.04)	1.37 (0.04)	
Lp (a) (g/liter)	GH	0.28 (0.04)	0.30 (0.05)	0.30 (0.05)	0.7
	Placebo	0.42 (0.07)	0.43 (0.07)	0.42 (0.07)	
Apo B/Apo A-I	GH	0.8 (0.03)	0.8 (0.04)	0.8 (0.04)	0.3
	Placebo	0.8 (0.05)	0.9 (0.06)	0.8 (0.05)	

All values are expressed as mean (SEM). *P* values represent overall treatment effect analyzed using one-way ANOVA.
[a] $P < 0.05$ (at the given time point *vs.* baseline value).
[b] $P < 0.01$ (at the given time point *vs.* baseline value).

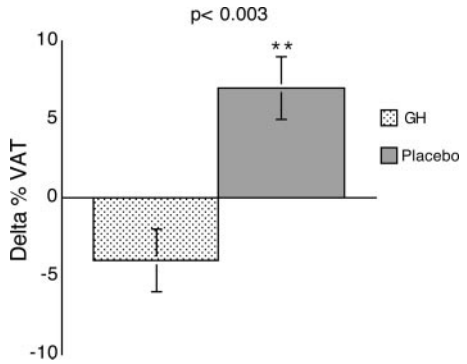

FIG. 5. Change in VAT expressed as Δ percent in VAT after 12 months of GH/placebo treatment. $P < 0.003$ represents overall treatment effect analyzed using one-way ANOVA; **, $P < 0.01$ compared with baseline.

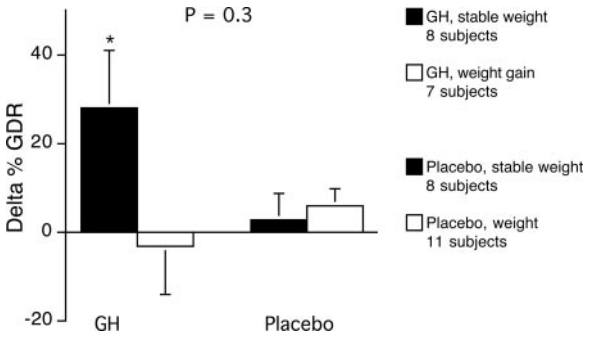

FIG. 7. Percent change in GDR in GH/placebo-treated subjects related to stable weight/weight gain after 1 yr of treatment. $P = 0.3$ represents overall effect of the subgroups using two-way ANOVA; *, $P < 0.05$ compared with baseline.

muscle mass in the GH-treated women. In contrast to a similar study involving middle-aged men with abdominal obesity who received GH treatment for 9 months (17), we did not find any changes in abdominal or thigh sc AT, suggesting that postmenopausal women are less responsive to the lipolytic effect of GH in the sc fat depots. It is known that young women with GH deficiency caused by a pituitary disease require higher doses of GH than men at a similar age to achieve comparable serum IGF-I response, which is associated with the level of estradiol (39, 40). In addition, data comparing *in vitro* abdominal and gluteal sc adipose tissue metabolism suggest that the menopausal status is associated with changes in AT metabolism that predispose to lower lipolysis and higher activity by lipoprotein lipase, in abdominal and gluteal sc AT (41). There are conflicting results relating to whether GH reduces fat mass through direct effects on the adipocyte, making the adipocyte more responsive to catecholamine, or by inhibitory effect on lipoprotein lipase (42, 43). We did not examine cellular fat metabolism, but our results suggest major responsiveness by VAT compared with sc AT, which is in agreement with previous data in GH-deficient subjects (44, 45), promoting a more favorable peripheral fat distribution (46).

Classical unenhanced CT in terms of absolute attenuation values (Hounsfield units) of the liver is an accurate and reproducible, noninvasive, quantitative assessment of hepatic fat content (24). In our study, a reduction in VAT as well as in total and LDL cholesterol and the linear correlation found between changes in GDR and liver attenuation in the GH group suggest that the improvement in some of the features of the metabolic syndrome was associated with reduced hepatic fat content. This is consistent with previous observations showing that the degree of insulin sensitivity is strongly linked to liver attenuation and hepatic fat content (47, 48). In contrast to other AT depots, VAT has a direct connection to the liver through the portal vein. Visceral obesity probably increases the delivery of fatty acids to the liver, contributing to hepatic fat accumulation. GH treatment, with its strong lipolytic action on VAT, might therefore induce or aggravate nonalcoholic fatty liver disease. Our data, however, suggest that 12 months of treatment reduces the hepatic fat content as a result of reduced VAT and/or an increase in the output of fat from the liver by enhanced VLDL production and secretion (49) or increased biliary lipid output (50). These data therefore support the hypothesis that the improvement in insulin sensitivity exhibited in our GH-treated subjects might be mediated at least in part by the reduction in hepatic fat content. A more effective peripheral glucose use by the increase in muscle mass might also have contributed to the improvement in insulin sensitivity. However, the positive correlation between liver attenuation and GDR, but not between muscle mass and GDR, suggests that the reduction in hepatic fat content was of more importance. The increase in BW observed during the trial was not unexpected, as the participants were not given any dietary restrictions and had a sedentary lifestyle, as shown by the questionnaire used. The correlation analysis and subgroup analyses performed suggest that women who had a stable weight or lost weight during the study were more responsive to the metabolic effects of GH than women who gained weight during the trial. Our findings therefore suggest that GH treatment

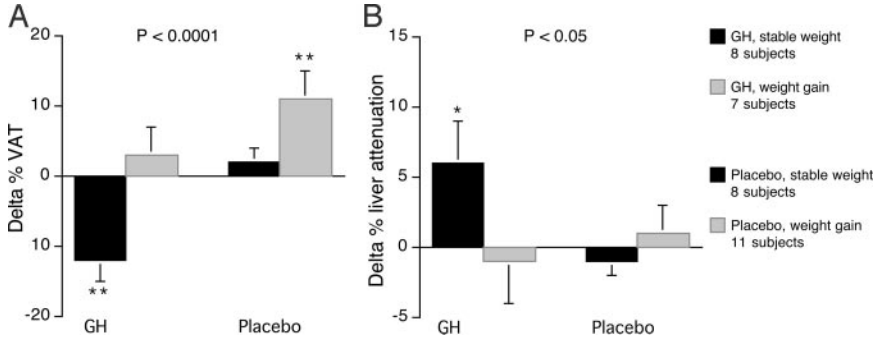

FIG. 6. A, Reduction in VAT expressed as Δ percent VAT from baseline to 1 yr of GH/placebo treatment with stable weight/weight gain. B, Reduction in hepatic fat content expressed as Δ percent in liver attenuation in GH/placebo-treated subjects related to stable weight/weight gain after 1 yr of treatment. $P < 0.0001$ and $P < 0.05$, respectively, represent overall effect of the subgroups using two-way ANOVA; *, $P < 0.05$ and **, $P < 0.01$ compared with baseline.

may have a beneficial effect over and above the weight loss obtained by modifications in caloric intake or any other form of lifestyle interventions.

In subjects of both genders with the metabolic syndrome, with predominantly abdominal obesity, low-calorie regimens have not proved to be successful in long-term interventions (51). Physical activity of moderate intensity is not sufficient for effective weight control (52), although higher levels of exercise, particularly in combination with other lifestyle modifications, have been shown to reduce the risk of developing DM in individuals with glucose intolerance (53). In our study, the improvement in insulin sensitivity and muscle mass, as well as the reduction in VAT, is less likely to be explained by caloric restriction or increased exercise, as the participants did not receive any dietary intervention and did not show any change in physical activity as determined by a questionnaire.

This placebo-controlled trial demonstrated beneficial metabolic effects by GH in women with abdominal obesity. In women with the strongest features of the metabolic syndrome, insulin sensitivity improved, an improvement that was associated with reduced hepatic fat content. GH treatment therefore improves some of the symptoms associated with the metabolic syndrome, which may in turn have a beneficial impact on the risk of vascular disease.

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