Growth Hormone Decreases Visceral Fat and Improves Cardiovascular Risk Markers in Women with Hypopituitarism: A Randomized, Placebo-Controlled Study

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Context: Data regarding gender-specific efficacy of GH on critical endpoints are lacking. There are no randomized, placebo-controlled studies of physiological GH therapy solely in women.

Objective: Our objective was to determine the effects of physiological GH replacement on cardiovascular risk markers and body composition in women with GH deficiency (GHD).

Design: This was a 6-month, randomized, placebo-controlled, double-blind study.

Setting: The study was conducted at the General Clinical Research Center.

Study Participants: 43 women with GHD due to hypopituitarism were included in the study.

Intervention: Study participants were randomized to receive GH (goal mid-normal serum IGF-1) or placebo.

Main Outcome Measures: Cardiovascular risk markers, including high-sensitivity C-reactive protein, tissue plasminogen activator, and body composition, including visceral adipose tissue by cross-sectional computed tomography, were measured.

Results: Mean daily GH dose was 0.67 mg. The mean IGF-1 SD score increased from -2.5 ± 0.3 to -1.4 ± 0.9 (GH) ($P < 0.0001$ *vs.* placebo). High-sensitivity C-reactive protein decreased by $38.2 \pm 9.6\%$ (GH) *vs.*$18.2 \pm 6.0\%$ (placebo) ($P = 0.03$). Tissue plasminogen activator and total cholesterol decreased, and high-density lipoprotein increased. Homeostasis model assessment-insulin resistance and other markers were unchanged. Body fat decreased [-5.1 ± 2.0 (GH) *vs.* $1.9 \pm 1.0\%$ (placebo); $P = 0.002$] as did visceral adipose tissue [-9.0 ± 5.9 (GH) *vs.* $4.3 \pm 2.7\%$ (placebo); $P = 0.03$]. Change in IGF-1 level was inversely associated with percent change in visceral adipose tissue ($r = -0.61$; $P = 0.002$), total body fat ($r = -0.69$; $P < 0.0001$), and high-sensitivity C-reactive protein ($r = -0.51$; $P = 0.003$).

Conclusions: Low-dose GH replacement in women with GHD decreased total and visceral adipose tissue and improved cardiovascular markers, with a relatively modest increase in IGF-1 levels and without worsening insulin resistance. **(*J Clin Endocrinol Metab* 93: 2063–2071, 2008)**

Despite the established use of GH therapy in men and women with GH deficiency (GHD), data regarding gender-specific efficacy on critical endpoints are lacking. There are no randomized, placebo-controlled trials of physiological GH therapy solely in women. GH appears to have a greater effect on body composition in men than women (1), but whether this is attrib-

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Abbreviations: GHD, GH deficiency; HbA_{1c}, glycosylated hemoglobin; PAI, plasminogen activator inhibitor; SDS, SD score.

utable to inadequate dosing in women or differential gender effects is unknown. Studies demonstrating a positive effect of GH on cardiovascular risk markers have been performed predominantly in men. Cardiovascular disease is the leading cause of mortality in women (2), and, therefore, data regarding the cardiovascular effects of GH therapy in women may have important implications.

Cardiovascular mortality is increased in adults with hypopituitarism, and women are affected disproportionately more than men (3–7). A number of putative etiologies for the excess mortality associated with hypopituitarism have been proposed, including GHD (8, 9) and untreated gonadotropin deficiency (6). The GHD syndrome is associated with a cluster of cardiovascular risk factors, including central adiposity (10–12), increased visceral fat (13), insulin resistance (14), dyslipoproteinemia (5, 15), and decreased plasma fibrinolytic activity (16). Moreover, increased arterial intima-media thickness, and an increased prevalence of atherosclerotic plaques and endothelial dysfunction have been reported in hypopituitary patients with both childhood and adult onset GHD (17–22). We have reported higher levels of IL-6 and high-sensitivity C-reactive protein in women with hypopituitarism compared with controls, independent of age and body mass index, suggesting that chronic inflammation may be involved in the pathogenesis of atherosclerosis in this population (23). However, isolating the effects of GHD from confounding factors, including obesity and other hormone deficiencies, in cross-sectional studies is difficult.

We reported decreases in high-sensitivity C-reactive protein and IL-6 levels after GH administration to GH-treated hypopituitary men with GHD (24). Although beneficial changes in lipids and lipoproteins have been reported in some studies of men with GHD (25), we did not observe such effects in our randomized, placebo-controlled study (24). Other groups have reported favorable changes in cardiovascular risk markers in other pathways, including the fibrinolytic system (26), in response to GH administration in patients with hypopituitarism. Most published studies of the effects of GH therapy on cardiovascular risk markers in hypopituitary adults have been open label (18, 27, 28), have studied only men (18), or have included a small number of women, and in all but one of these (1), data on the effects of GH therapy in women have not been reported separately (26–33). The aim of this study was to determine whether physiological GH replacement has beneficial effects on cardiovascular risk markers and body composition in women with GHD secondary to pituitary disease. Therefore, we investigated the effect of long-term physiological GH administration on high-sensitivity C-reactive protein, serum lipids, tissue plasminogen activator, soluble E-selectin, insulin resistance, and visceral fat mass in women with GHD in a randomized, placebo-controlled study.

Subjects and Methods

Study participants

The study was an investigator-initiated, single-center, randomized, placebo-controlled, double-blind, 6-month study of GH or placebo treatment. A total of 43 women with histories of pituitary and/or hypothalamic disease and GHD were recruited for the study. Clinical characteristics at baseline are shown in Table 1. Potential study participants were considered GH deficient based on GH response to a GHRH-arginine stimulation test (n = 24) or insulin tolerance test (n = 9), or an IGF-1 level more than two SD below the age-specific normal range in a patient with at least two documented anterior pituitary hormone deficiencies (34) (n = 10). Complete GHD was defined as a GH peak of less than 5 ng/ml on stimulation (n = 25), and partial GHD was defined as a GH peak of 5–9 ng/ml (n = 8) (35). The degree of GHD in the 10 patients diagnosed on the basis of low IGF-1 levels was unknown. Insulin tolerance and GHRH-arginine tests were performed as previously described (36). Subjects on thyroid hormone, gonadal steroid, and/or cortisol replacement therapy were required to have been receiving stable replace-

TABLE 1. Baseline clinical characteristics

	GH group	Placebo group	*P* value
No. of patients	20	23	
Type of pituitary disease			
Prolactinoma	6	4	0.33
Cushing's disease	5	5	0.81
Nonfunctioning adenoma	4	4	0.83
Craniopharyngioma	3	4	0.83
Empty sella	0	3	0.06
Rathke's cleft cyst	1	0	0.21
Congenital GHD	0	1	0.28
Pituitary stalk lesion	0	1	0.30
TSH-secreting adenoma	0	1	0.26
Sheehan's syndrome	1	0	0.21
Hypogonadal	13	14	0.78
Hypoadrenal	14	7	0.009
Hypothyroid	16	14	0.17
Tobacco use	4	1	0.14
Estrogen use	9	9	0.13
Age (yr)	45 (26–66)	47 (24–62)	0.41
BMI (kg/m^2)	30.2 (22.0–51.3)	28.9 (18.7–40.9)	0.22
IGF-1 ng/ml)	52 (25–127)	58 (25–117)	0.47
IGF-1 SDS	−2.5 (−3.0 to −1.9)	−2.5 (−3.0 to −1.7)	0.22

Data are presented as number or median (range). BMI, Body mass index; SDS, Standard deviation score.

ment doses for at least 3 months before entry into the study. Exclusion criteria included history of acromegaly, growth of pituitary or hypothalamic mass during the 12 months before enrollment, active Cushing's disease within 1 yr of enrollment, history of malignancy (except for nonmelanoma skin cancer), hemoglobin less than 10.0 gm/dl, alanine aminotransferase/aspartate aminotransferase more than three times the upper limit of normal, creatinine level more than 2.5 mg/dl, congestive heart failure (New York Heart Association's Class II-IV), unstable coronary artery or cerebrovascular disease within 1 yr of entry into the study, diabetes mellitus (fasting glucose $\geq$ 126 mg/dl or 2-h oral glucose tolerance test glucose $\geq$ 200 mg/dl), active carpal tunnel syndrome, GH therapy within 1 yr of entry into the study, pregnancy, or breast-feeding. Subjects age 40 and older were required to have screening mammograms within 1 yr of their baseline visits. The study was conducted in the General Clinical Research Centers of the Massachusetts General Hospital and Massachusetts Institute of Technology. The study was approved by the Partners Healthcare and Massachusetts Institute of Technology Institutional Review Boards, and all subjects gave written informed consent.

Protocol

After baseline evaluation, subjects were randomized to receive daily sc placebo or recombinant human GH (Genotropin; Pfizer, Inc., New York, NY) for 6 months. Randomization was stratified for age (age $\geq$ 50 *vs.* $<$ 50 yr), use of oral estrogen, and degree of GHD (complete *vs.* partial GHD). Starting GH dose was determined *a priori* as follows. For study participants 50 yr or older who were not receiving oral estrogen, the starting dose was 3 μg/kg·d. For women younger than 50 yr and not receiving oral estrogen, the starting dose was 5 μg/kg·d. Women younger than 50 yr, who were receiving oral estrogen or had childhood-onset GHD, regardless of estrogen status, were started at 6 μg/kg·d. GH or placebo was self-administered sc daily at bedtime. Six individuals were randomized but did not complete the 6-month study. Of the six, two study participants dropped out of the study before starting study medication, two discontinued within 1 wk of starting (one because of an elevated baseline blood glucose, which had not been elevated at screening, and the other due to an elevated incidentally discovered carcinoembryonic antigen level), and two dropped out after the 3-month visit (carpal tunnel syndrome, medication noncompliance).

Follow-up visits were performed at 1, 3, 4.5, and 6 months after study entry. IGF-1 levels were measured at each follow-up visit. A health care professional that did not interact with study participants was unblinded to randomization assignments to monitor IGF-1 levels and determine dose adjustments. IGF-1 levels were targeted to be in the mid- to upper-normal age-appropriate range. To maintain blinding of all study staff and participants, one subject receiving placebo was sham "dose-adjusted" when a dose adjustment was made for a participant receiving GH. Individualized downward dose titration was performed for individuals experiencing side effects.

Fasting oral glucose tolerance testing was performed by administering 75 g oral glucose, and measuring glucose and insulin at baseline and every 30 min for 2 h. Fat-free mass and fat mass were measured by dual-energy x-ray absorptiometry using a Hologic QDR-4500 densitometer (Hologic Inc., Waltham, MA), with an accuracy error for body fat mass of 1.7%, and for fat-free mass of 2.4% (37). Abdominal adipose distribution, including cross-sectional total abdominal fat, sc fat, and intra-abdominal fat compartments, was determined in duplicate using single-slice quantitative computed tomography scans at the level of L4 using 10-mm thick axial images (General Electric RP High Speed Helical Computed Tomography Scanner; General Electric, Milwaukee, WI) and graphical analysis software (General Electric Advantage Windows Work Station Version 2.0; General Electric). Technical factors for the scanning were as follows: 80 kVp, 70 mA, and 2-sec scan time. Caloric intake was assessed by 4-d self-documented food records that each included three weekdays and 1 weekend day. Each food record was reviewed by a registered dietician and then analyzed using a computerized database (Nutrition Data System for Research, version 5.0–35, 2006; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). Indirect calorimeter assessments (V_{max} 29N Sensor Medics; Vyasis Healthcare, Loma Linda, CA) were obtained in subjects after a 12-h fast and at least 24-h abstention from physical activity of moderate or greater intensity. Resting energy expenditure and respiratory quotient were calculated from the substrate oxidation rates (38).

Biochemical analysis

Serum and plasma samples were collected and stored at −80 C. Serum IGF-1 levels were measured by Immulite 2000 automated immunoanalyzer (Diagnostic Products Corp., Los Angeles CA), a solid-phase, enzyme-labeled chemiluminescent immunometric assay, with an interassay coefficient of variation of 3.7% (at an IGF-1 level of 75 ng/ml) to 4.2% (at an IGF-1 level of 169 ng/ml). High-sensitivity C-reactive protein was measured using a latex particle enhanced immunoturbidimetric assay on the Hitachi 917 (Equal Diagnostics, Exton, PA), with an interassay coefficient of variation for high-sensitivity C-reactive protein less than 5.08%. Tissue plasminogen activator was measured by an ELISA assay (American Diagnostica, Greenwich, CT). The assay has a sensitivity of 1 ng/ml, and interassay coefficients of variation at concentrations of 6.5 and 14.9 ng/ml of 4.9 and 4.2%, respectively. Soluble E-selectin was measured by ELISA (R&D Systems, Inc., Minneapolis, MN), with an interassay coefficient of variation of 5.0% at a concentration of 21.9 ng/ml and a sensitivity of 0.1 ng/ml. Homocysteine was measured by an enzymatic assay on the Hitachi 917, with an interassay percent coefficient of variation of less than 4.0%. Insulin was measured by solid-phase RIA (Diagnostic Products), with an intraassay percent coefficient of variation of insulin at a concentration of 17 μIU/ml of 9.3%. Homeostasis model assessment-insulin resistance has been validated as an accurate measurement of insulin resistance and was calculated as: insulin (μIU/ml) $\times$ glucose (mmol/liter)/22.5 (39–41). Homeostasis model of assessment-β cell index is a measure of β cell function and was calculated as insulin [(μIu/ml) $\times$ 20]/[glucose (mmol/L) − 3.5)] (39). Total cholesterol, high-density lipoprotein, triglycerides, and low-density lipoprotein were measured using previously described methods (42).

Statistical analysis

JMP statistical discoveries software (version 4.0.2; SAS Institute Inc., Cary, NC) was used for statistical analysis. All variables were tested for normality using the Shapiro-Wilk test. Results are expressed as mean and SEM, except for Table 1, in which results are median (range). Means were compared with ANOVA for normally distributed variables. For non-normally distributed variables, nonparametric comparisons were performed using the Wilcoxon test. Univariate regression models were constructed to determine whether change in IGF-1 levels predicted changes in the endpoints studied. Statistical significance was defined as a two-tailed P value less than 0.05.

Results

Endocrine data

The mean daily starting dose of GH was 0.41 mg, and the mean daily dose at 6 months was 0.67 mg (range 0.23–1.10). Mean IGF-1 increased by 82.7 $\pm$ 72.0 (SD) ng/ml to 142.0 $\pm$ 64.8 ng/ml in the GH group and decreased slightly (by 0.7 $\pm$ 12.7 ng/ml) in the placebo group ($P < 0.0001$) (Fig. 1). The IGF-1 SD score (SDS) increased from −2.5 $\pm$ 0.3 to −1.4 $\pm$ 0.9 over 6 months in the GH group compared with −2.3 $\pm$ 0.5 to −2.3 $\pm$ 0.4 in the placebo group ($P = 0.0001$). No patient had a 6-month IGF-1 level above the normal range.

Cardiovascular risk markers

Cardiovascular risk marker data are presented in Table 2. Mean baseline high-sensitivity C-reactive protein was 10.4 $\pm$ 2.0

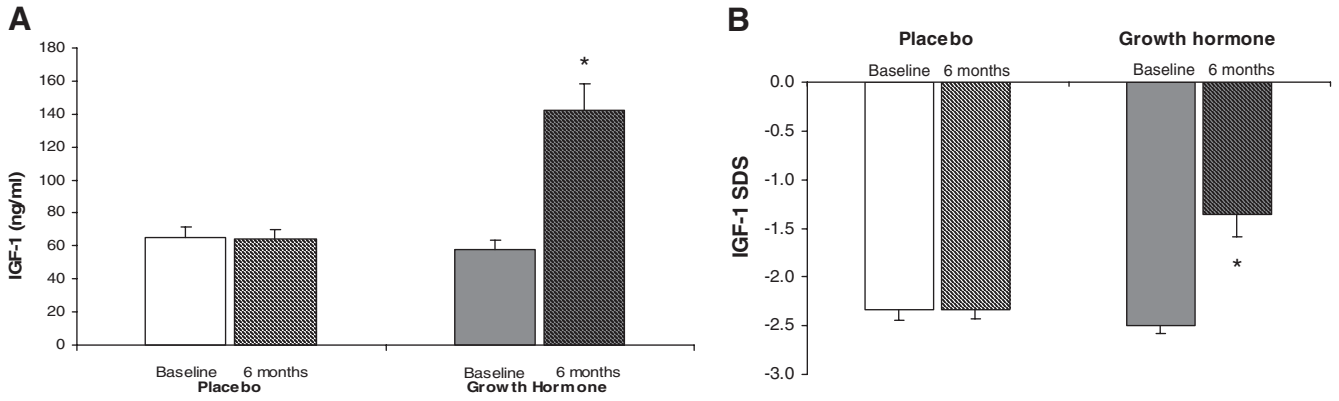

FIG. 1. Mean IGF-1 (*Panel A*) and IGF-1 SDS (*Panel B*) increased in the GH group compared with placebo. *, $P \leq 0.0001$.

mg/liter in the GH group and 6.9 ± 1.4 mg/liter in the placebo group ($P = 0.3$), with 68% of subjects in the "high-risk" category (high-sensitivity C-reactive protein level > 3.0 mg/liter) for future cardiovascular risk (43). Mean high-sensitivity C-reactive protein decreased by 38.2 ± 9.6% in subjects receiving GH compared with 18.2 ± 6.0% in the placebo group ($P = 0.03$) (Fig. 2A). Tissue plasminogen activator decreased by a mean 13.0 ± 4.6% in the GH group and increased a mean 1.1 ± 5.2% in the placebo group ($P = 0.02$) (Fig. 2B). There was no change in homocysteine or soluble E-selectin.

Body composition

Mean body weight decreased in the group that received GH compared with placebo (−1.1 ± 0.7 *vs.* 1.3 ± 0.5 kg; $P = 0.01$) over 6 months. Body composition data are presented in Table 2. Mean body fat, as measured by dual energy x-ray absorptiometry, decreased 5.1 ± 2.0% in the group that received GH and increased 1.9 ± 1.0% in the placebo group ($P = 0.002$) (Fig. 3A), with a decrease in visceral fat mass, as measured by cross-sectional computed tomography, of 9.0 ± 5.9% in the GH group compared with a gain of 4.3 ± 2.7% ($P = 0.03$) in the placebo group (Fig. 3B). These differences remained significant after controlling for the presence or absence of adrenal insufficiency at baseline ($P = 0.005$ for percent change in body fat and $P = 0.04$ for percent change in visceral fat mass). Waist to hip ratio also decreased in the GH compared with placebo group (−1.0 ± 0.8 *vs.* 2.4 ± 1.2%; $P = 0.04$) (Fig. 3C). Mean resting energy expenditure increased in the group receiving GH compared with placebo (13.1 ± 3.8 *vs.* 0.8 ± 3.1%; $P = 0.02$) (Fig. 3D). There was no significant change in sc fat (measured by cross-sectional computed tomography) and no change in fat-free mass (measured by dual-energy x-ray absorptiometry). Change in mean caloric intake was similar in the two groups [115 ± 107 (GH) *vs.* −116 ± 96 (placebo) kcal/d; $P = 0.1$].

TABLE 2. Percent change in body composition and cardiovascular risk marker variables

	Placebo		GH		*P* value comparing % change
	Baseline	% Change	Baseline	% Change	
Total body fat (kg)	32.9 ± 2.5	1.9 ± 1.0	36.0 ± 3.0	−5.1 ± 2.0	**0.002**
Subcutaneous fat (mm^2)	36,264 ± 3,000	−1.8 ± 2.7	40,602 ± 4,399	−5.6 ± 2.6	0.41
Visceral fat (mm^2)	15,424 ± 1,745	4.3 ± 2.7	46.1 ± 16.9	−9.0 ± 5.9	**0.03**
Total fat-free mass (kg)	46.1 ± 1.7	1.7 ± 0.8	47.4 ± 1.9	1.7 ± 0.8	1.00
Waist to hip ratio	0.87 ± 0.01	2.4 ± 1.2	0.89 ± 0.02	−1.0 ± 0.8	**0.04**
Total cholesterol (mg/dl)	203.3 ± 9.4	3.8 ± 2.5	203.4 ± 10.4	−3.1 ± 1.7	**0.04**
HDL (mg/dl)	55.8 ± 4.3	−10.1 ± 2.1	52.6 ± 3.7	0.4 ± 2.7	**0.004**
LDL (mg/dl)	119.5 ± 8.3	6.1 ± 3.2	122.8 ± 9.1	−0.4 ± 3.5	0.18
Triglycerides (mg/dl)	153.6 ± 17.7	15.2 ± 7.9	137.7 ± 15.8	−3.0 ± 9.1	0.14
hsCRP (mg/liter)	6.9 ± 1.4	−18.2 ± 6.0	10.4 ± 2.0	−38.2 ± 9.6	**0.03**
Homocysteine (μMol/liter)	6.3 ± 0.3	−2.6 ± 3.6	7.2 ± 0.5	−8.6 ± 4.9	0.32
sE-selectin (ng/ml)	51.9 ± 8.4	3.7 ± 11.0	37.3 ± 5.0	34.9 ± 14.9	0.10
tPA (ng/ml)	12.5 ± 1.5	1.1 ± 5.2	12.0 ± 3.0	−13.0 ± 4.6	**0.02**
Fibrinogen (mg/dl)	301.7 ± 14.0	0.7 ± 4.5	303.3 ± 14.3	9.6 ± 5.2	0.21
Fasting glucose (mg/dl)	85.5 ± 2.1	1.3 ± 1.5	81.7 ± 2.5	3.9 ± 1.6	0.59
Insulin (μIU/ml)	12.2 ± 1.6	10.3 ± 8.6	13.0 ± 3.4	26.5 ± 13.8	0.31
HOMA-IR	2.7 ± 0.4	12.9 ± 10.1	2.8 ± 0.7	32.3 ± 15.8	0.30
HOMA-β	202.3 ± 32.0	25.4 ± 18.7	213.2 ± 43.8	2.6 ± 9.0	0.68
Resting energy expenditure (kcal/d)	1,401.7 ± 68.3	0.8 ± 3.1	1,382.0 ± 70.6	13.1 ± 3.8	**0.02**
Respiratory quotient	0.89 ± 0.02	−0.70 ± 1.89	0.88 ± 0.01	−1.95 ± 1.59	0.63
Total caloric intake (kcal)	1,637.3 ± 96.5	−4.0 ± 5.2	1,687.8 ± 134.3	7.5 ± 7.2	0.20

Data are presented as mean ± SEM. HDL, High-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment-insulin resistance; LDL, low-density lipoprotein; sE-selectin, soluble E-selectin; tPA, tissue plasminogen activator. Significant *P* values are bolded.

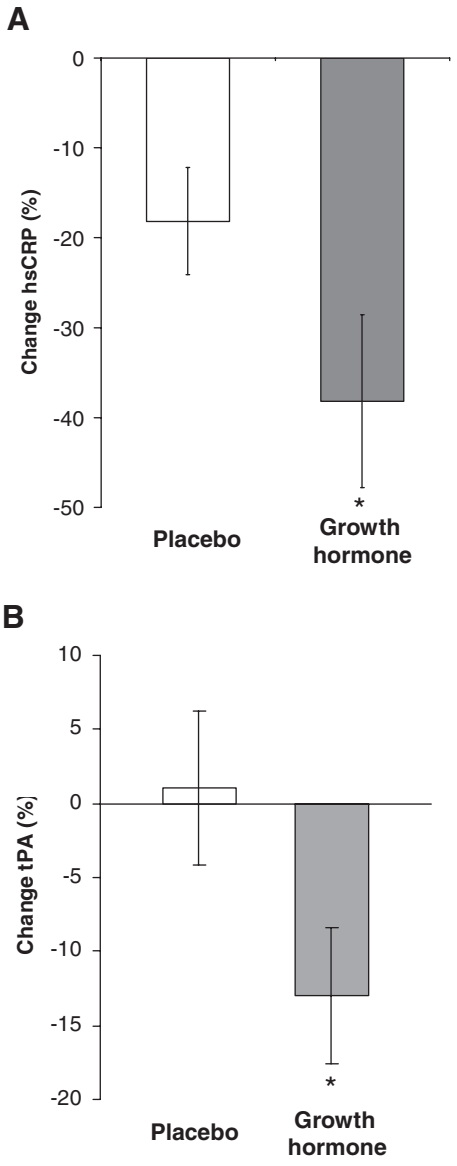

FIG. 2. *Panel A*, Mean high-sensitivity C-reactive protein (hsCRP) decreased more in the GH then in the placebo group (−38.2 ± 9.6% *vs.* −18.2 ± 6.0%, $P = 0.03$). *Panel B*, Mean tissue plasminogen activator (tPA) decreased in the GH compared with placebo group (−13.0 ± 4.6% *vs.* +1.1 ± 5.2%; $P = 0.02$). *, $P < 0.05$.

Lipids and lipoproteins

Mean total cholesterol decreased and high-density lipoprotein increased in the GH group [total cholesterol: −3.1 ± 1.7 (GH) *vs.* 3.8 ± 2.5% (placebo), $P = 0.04$; high-density lipoprotein: 0.4 ± 2.7 (GH) *vs.* −10.1 ± 2.1% (placebo), $P = 0.004$], with nonsignificant decreases in low-density lipoprotein and triglycerides.

Glucose metabolism

There was no difference in fasting glucose, fasting insulin, homeostasis model assessment-insulin resistance, homeostasis model assessment-β, or glycosylated hemoglobin (HbA_{1c}) between groups at baseline, nor was there any change in these variables over 6-month GH administration compared with placebo. No patient randomized to receive GH had a 2-h glucose level more than 200 mg/dl at the 6-month visit (*vs.* one patient in the placebo group). One patient in the GH group had an elevated HbA_{1c} at the 6-month visit (*vs.* two in the placebo group).

Association of changes in study endpoints with increase in IGF-1 levels

Change in IGF-1 level was strongly inversely associated with change in high-sensitivity C-reactive protein ($r = -0.51$; $P = 0.003$) (Fig. 4A), but not tissue plasminogen activator. Change in IGF-1 level was strongly inversely associated with percent change in visceral fat mass ($r = -0.61$; $P = 0.002$) (Fig. 4B) and total body fat mass ($r = -0.69$; $P < 0.0001$). There was a trend toward an inverse association between change in IGF-1 level and percent change in body weight ($r = -0.33$; $P = 0.06$) and waist to hip ratio ($r = -0.30$; $P = 0.1$). Change in IGF-1 level was not associated with percent change in high-density lipoprotein or total cholesterol.

Adverse effects

The dose of GH was reduced when significant side effects occurred. There were six dose reductions for edema and/or arthralgias, and two for symptoms suggestive of carpal tunnel syndrome in the group receiving GH. One woman in the GH group was dose-reduced because of an IGF-1 level above the third quartile (but still in the normal range). Two women in the GH group temporarily discontinued GH, one due to headaches and one during follow-up for an abnormal mammogram. One woman in the GH group discontinued the study after 3 months due to the development of carpal tunnel syndrome signs and symptoms. One woman in the placebo group was "dose-reduced" due to edema.

Discussion

We undertook this placebo-controlled, randomized study to examine the effects of 6-month GH replacement on cardiovascular effects in women with hypopituitarism and report that a modest mean increase in IGF-1 decreases visceral fat, high-sensitivity C-reactive protein, total cholesterol, and tissue plasminogen activator but does not increase fat-free mass. This was achieved at the low mean GH dose of 0.67 mg daily, resulting in no deterioration of fasting insulin, glucose, or measures of insulin resistance. Epidemiological studies have demonstrated that hypopituitarism confers an increased risk of cardiovascular events as well as death, and GHD has been hypothesized to be a contributory factor (8, 9). The mechanisms underlying the effects of GHD and GH on the cardiovascular system may include effects on inflammatory pathways. GH is a cytokine (44–46), and we have shown that when GH replacement is administered to GH-deficient men, high-sensitivity C-reactive protein and IL-6 decrease compared with controls (24). In a study of men and women combined, a 41% decrease in high-sensitivity C-reactive protein was subsequently demonstrated (29). However, there have been no studies examining inflammatory effects solely in women. A metaanalysis has suggested possible beneficial effects on lipids and lipoproteins (25), and studies have shown effects on

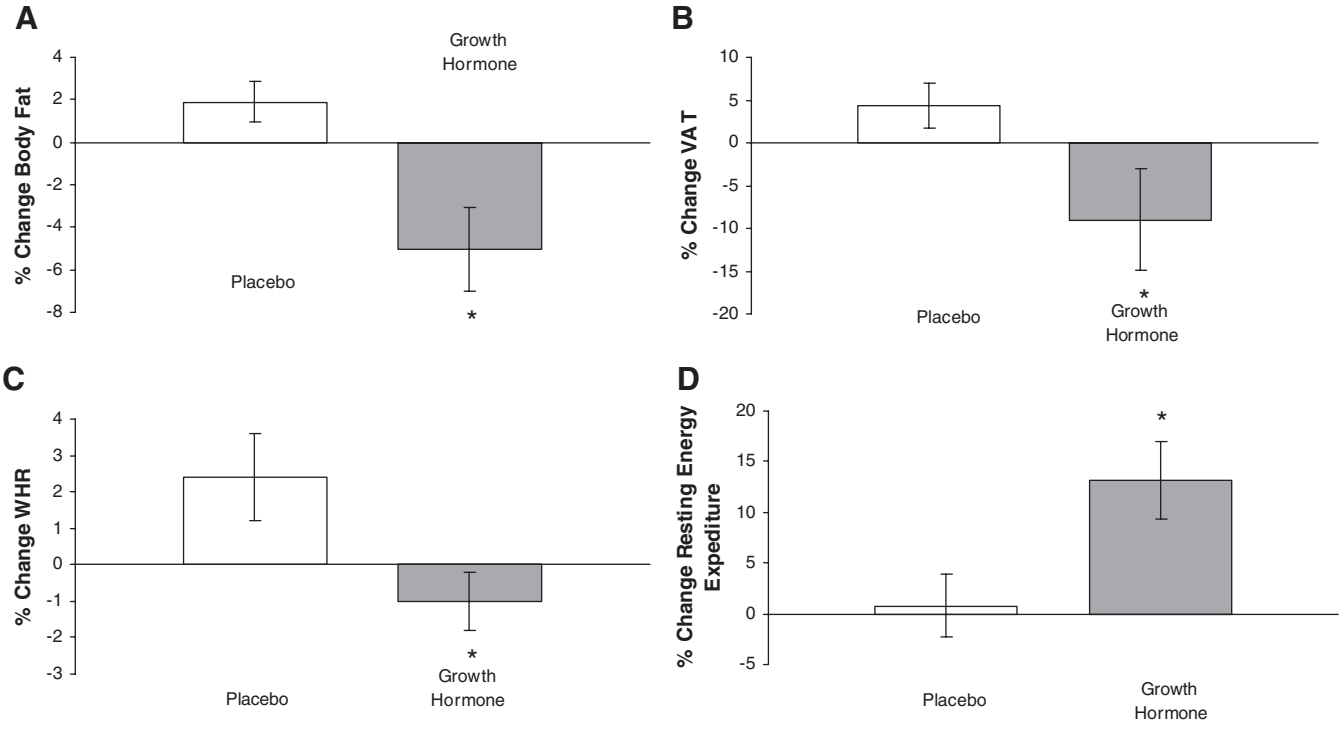

FIG. 3. *Panel A*, Mean body fat, as measured by dual-energy x-ray absorptiometry, decreased in the GH compared with placebo groups ($-5.1 \pm 2.0\%$ *vs.* $1.9 \pm 1.0\%$). *Panel B*, Mean visceral adipose tissue (VAT), as measured by cross-sectional computed tomography, decreased in the GH compared with placebo groups ($-9.0 \pm 5.9\%$ *vs.* $+4.3 \pm 2.7\%$). *Panel C*, Mean waist to hip ratio (WHR) decreased in the GH compared with placebo groups (-1.0 ± 0.8 *vs.* $+2.4 \pm 1.2\%$). *Panel D*, Mean resting energy expenditure increased in the GH compared with placebo groups (13.1 ± 3.8 *vs.* $0.8 \pm 3.1\%$). *, $P < 0.05$.

other pathways, including clotting factors (26), but these studies have focused primarily on men. When women have been included, they have composed the minority of study subjects, results from both sexes have been pooled for analyses, and/or data for the subset of women studied have not been presented (26–33). An exception is a study by Burman *et al.* (1), who performed a randomized, placebo-controlled study of GH administration in 21 men and 15 women. Although randomization was not stratified for sex, results were analyzed separately for each sex and compared. Women did not lose as much body fat as men and, in contrast to men, demonstrated no beneficial effects on serum lipids, lipoproteins, or clotting factors; lipoprotein(a) increased in both men and women. However, inflammatory markers were not studied; therefore, gender-specific effects on these endpoints are not established. Moreover, in both healthy (47) and hypopituitary (48) women, IGF-1 levels are lower for a given level of GH secretion than in their male counterparts. Therefore, women with hypopituitarism may have a relatively more severe IGF-1 deficiency than men despite a similar degree of hypopituitarism and GHD, and GHD, therefore, may have a more significant impact on cardiovascular health in hypopituitary women than men. Because hypopituitarism carries a greater risk of mortality in women than in men (4, 6, 7), investigation into the pathophysiology of atherosclerosis in women with hypopituitarism may have important clinical implications.

We report that low-dose GH administration results in a decline in high-sensitivity C-reactive protein compared with placebo in hypopituitary women with GHD. Inflammation plays a central role in the pathophysiology of atherosclerosis (49). Each atherosclerotic lesion represents a different stage of a chronic inflammatory process in the arterial wall, and markers along the inflammatory cascade have predicted the risk of cardiovascular events (50). Among these, high-sensitivity C-reactive protein, which is produced by the liver and is a downstream, late-stage marker of inflammation at all levels of the inflammatory atherosclerotic pathway, is one of the best validated (51). Prospective studies have demonstrated that increased levels of high-sensitivity C-reactive protein are more strongly predictive of the future risk of coronary events than low-density lipoprotein cholesterol (52), and measurement of high-sensitivity C-reactive protein adds considerable value to total and high-density lipoprotein cholesterol in the prediction of cardiovascular risk (53). GH has important immunomodulatory effects (44–46), and the current findings in hypopituitary women are in concert with those from one randomized, placebo-controlled study in men (24) and one in men and women combined (29). Our finding of a mean 20% reduction in high-sensitivity C-reactive protein levels in hypopituitary women with GHD, 68% of whom had high-sensitivity C-reactive protein levels in the highest risk category, may imply that multiple steps in the inflammatory pathway are affected by GH treatment and may have significant clinical implications. Large prospective studies would be needed to determine whether the reduction in high-sensitivity C-reactive protein levels results in decreased cardiovascular event rates in hypopituitary women with GHD.

An improvement in tissue plasminogen activator levels was also shown in the current study, suggesting a beneficial effect on the fibrinolytic system. Pro-thrombotic markers, including fibrinogen and PAI-1, are elevated in hypopituitary patients with GHD (16), and Johansson *et al.* (26) demonstrated decreases in

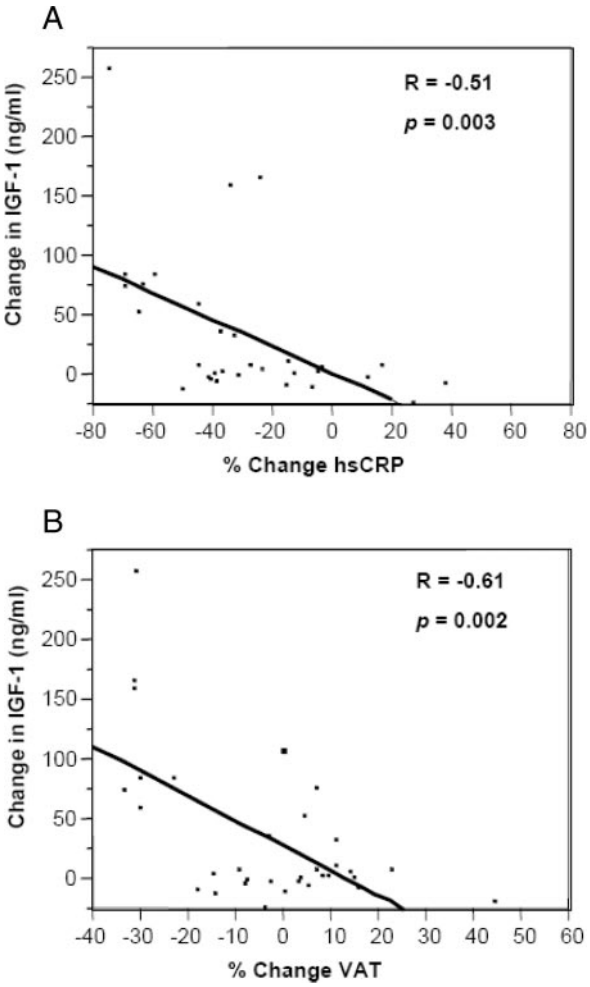

FIG. 4. Change in IGF-1 level inversely predicted percent change in high-sensitivity C-reactive protein (hsCRP) (*Panel A*) and percent change in visceral adipose tissue (VAT) (*Panel B*).

PAI-1, tissue plasminogen activator, α-2-antiplasmin, and protein C, but not antithrombin, or factors VII or VIII in 17 hypopituitary adults, eight of whom were women. We demonstrated a decrease in tissue plasminogen activator levels in hypopituitary women receiving GH compared with placebo. This supports a positive effect of GH replacement on clotting factors in women with GHD due to hypopituitarism.

Similar to many other studies of GH replacement, we demonstrated a decrease in total cholesterol. However, there was no significant improvement in low-density lipoprotein levels to which to attribute this reduction. The mean high-density lipoprotein level declined in the placebo group by a mean 10% but remained stable in the GH-treated group, suggesting a possible small beneficial effect on high-density lipoprotein. Therefore, the effects on lipids and lipoproteins of 6-month GH replacement in women with hypopituitarism were modest. We did not show an effect of GH on soluble E-selectin, suggesting that GH does not act on adhesion, or homocysteine at the IGF-1 levels achieved. The latter finding is in contrast to our findings in men (54).

We demonstrate a decline in body fat, primarily due to a significant decrease in visceral fat mass, in women with hypopituitarism treated with GH compared with placebo, as has been shown in men (55, 56). We also report a decrease in weight in women receiving GH compared with placebo, which we did not find in a randomized, placebo-controlled study of GH replacement in men with hypopituitarism (56). A decrease in weight would be expected to be associated with a decline in resting metabolic rate. However, in the GH-treated subjects, a decline in weight was accompanied by an increase in resting metabolic rate. Moreover, the decrease in weight does not appear to be a function of decreased energy intake because the total caloric intake was similar in the GH- and the placebo-treated subjects. In contrast to published effects in GH-deficient males, GH administration did not result in increases in fat-free mass, and a net decrease in weight in the GH group was observed. Whether these differences reflect gender-specific effects of GH or a dose effect is unclear. Further studies to determine whether higher doses of GH resulting in a larger change in serum IGF-1 levels, commensurate with those achieved in most studies in men, would result in an increase in fat-free mass in women with GHD should be performed.

Insulin resistance is a well-established risk factor for the development of cardiovascular disease and can be exacerbated acutely by GH administration, whereas chronic effects appear to be neutral or positive (24, 57, 58). A metaanalysis suggested that women may experience less of a deleterious effect on glucose than men (25). In our study there was no effect of GH administration on fasting glucose, homeostasis model assessment-insulin resistance, or HbA_{1c} in women treated for 6 months. Thus, the beneficial effects of GH on decreasing visceral fat and high-sensitivity C-reactive protein do not appear to be negated by a worsening of insulin resistance.

Our data indicate that GH replacement decreases visceral fat mass, high-sensitivity C-reactive protein, and tissue plasminogen activator in hypopituitary women with GHD, and suggest that GH may modulate inflammatory pathways involved in the pathogenesis of atherosclerosis. This may be particularly important for women with hypopituitarism, who are at increased risk for cardiovascular events. These favorable changes occurred despite administration of low doses of GH, resulting in relatively modest increases in IGF-1 levels, and was associated with few side effects, and no worsening of insulin resistance.

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