

Effects of Growth Hormone Administration on Inflammatory and Other Cardiovascular Risk Markers in Men with Growth Hormone Deficiency

A Randomized, Controlled Clinical Trial

Gemma Sesimalo, MD; Beverly M.K. Biller, MD; Joan Llevadot, MD, PhD; Douglas Hayden, MA; Greta Hanson, BS; Nader Rifai, PhD; and Anne Klibanski, MD

Background: Growth hormone–deficient adults have increased cardiovascular mortality. Growth hormone replacement may affect cardiovascular risk. Inflammation plays an important role in atherosclerosis, and inflammatory markers are predictive of cardiovascular events.

Objective: To investigate the effect of growth hormone replacement on inflammatory and other cardiovascular risk factors.

Design: Randomized, single-blind, placebo-controlled trial.

Patients: 40 men with adult-onset growth hormone deficiency.

Intervention: Growth hormone or placebo given for 18 months at a dose adjusted for normal serum insulin-like growth factor I level.

Measurements: Anthropometric, hemoglobin A_{1c}, and central fat values were assessed every 6 months. Levels of glucose, insulin, insulin-like growth factor I, and lipids were measured at 1, 3, 6, 12, and 18 months. C-reactive protein, serum amyloid polypeptide A, interleukin-6, and lipoprotein(a) levels were determined at baseline and 6 and 18 months.

Results: C-reactive protein and interleukin-6 levels decreased in growth hormone recipients compared with placebo recipients (differences between groups, -1.9 ± 0.6 mg/L [$P = 0.0027$] and -1.3 ± 0.5 ng/L [$P = 0.013$], respectively). Changes in serum amyloid polypeptide A levels between groups did not reach statistical significance (difference between groups, -2.4 ± 1.2 mg/L;

$P = 0.056$). Serum cholesterol levels, low-density lipoprotein cholesterol levels, and ratios of total cholesterol to high-density lipoprotein cholesterol decreased in growth hormone recipients in the first 3 months compared with placebo recipients (differences between groups, -0.86 ± 0.17 mmol/L [-33.2 ± 6.6 mg/dL] [$P < 0.001$], -0.63 ± 0.20 mmol/L [-24.5 ± 5.9 mg/dL] [$P < 0.001$], and -0.56 ± 0.26 [$P = 0.040$], respectively), but the decrease was not maintained from month 6 to month 18. Lipoprotein(a) levels increased (difference between groups, 22.0 ± 8.0 mg/L; $P = 0.0096$). Short-term increases occurred in glucose levels, insulin levels, and insulin-to-glucose ratios (differences between groups, 0.54 ± 0.16 mmol/L [9.6 ± 2.8 mg/dL] [$P = 0.0018$], 37.9 ± 9.6 pmol/L [$P < 0.001$], and 6.0 ± 1.8 [$P = 0.0025$], respectively), but only the increase in glucose level was maintained over the long term (difference between groups, 0.56 ± 0.17 mmol/L [10.0 ± 3.1 mg/dL]; $P = 0.0026$). Hemoglobin A_{1c} values did not change. Truncal fat-to-total fat ratios decreased (difference between groups, -0.018 ± 0.007 ; $P = 0.0087$).

Conclusions: Long-term growth hormone replacement in men reduces levels of inflammatory cardiovascular risk markers, decreases central fat, and increases lipoprotein(a) and glucose levels without affecting lipid levels.

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For author affiliations, current addresses, and contributions, see end of text.

Several studies have shown that cardiovascular mortality is increased among growth hormone–deficient adults (1–3). Increased arterial intima–media thickness and a higher prevalence of atherosclerotic plaques and endothelial dysfunction have been reported in adults with child- or adult-onset growth hormone deficiency (4–7).

The growth hormone deficiency syndrome is associated with a cluster of cardiovascular risk factors (8), including central adiposity (9–11), increased visceral fat (12), insulin resistance (13), and dyslipoproteinemia (3, 14). Growth hormone replacement affects many of these variables, but mechanisms implicated in growth hormone action on the process of atherosclerosis are unknown. In addition, it is not clear whether growth hormone replacement affects the incidence of cardiovascular events.

Long-term growth hormone replacement therapy decreases total body fat (12, 15–19), including visceral fat (17). Decreases in central fat assessed by waist-to-hip ratio have been reported in some studies (12, 15, 17, 19) but not in others (16, 20, 21). Administration of growth hormone causes short-term insulin resistance (12), but long-term therapy may restore insulin sensitivity (22). Growth hormone treatment increases lipoprotein(a) levels, but its effects on other lipoproteins remain controversial. Some studies have reported decreases in low-density lipoprotein (LDL) cholesterol levels, with or without increases in high-density lipoprotein (HDL) cholesterol levels (15, 23, 24), whereas others have not (5, 25, 26). Key factors probably involved in these discrepant findings include heterogeneity of age at onset of growth hormone deficiency (childhood

versus adulthood), sex, and methodologic issues, such as dose and duration of treatment. In addition, most studies were short-term or uncontrolled.

Inflammation plays a central role in the pathophysiology of atherosclerosis (27). Each atherosclerotic lesion represents a different stage of a chronic inflammatory process in the arterial wall, and markers along the inflammatory cascade have been reported to predict cardiovascular risk (28). High-sensitivity testing for C-reactive protein is one of the best validated markers (29–33). Other distal indicators of inflammation, such as serum amyloid polypeptide A and interleukin-6, likewise predict coronary risk (34). Growth hormone is known to have important immunomodulatory effects (35–37). We therefore hypothesized that the effects of growth hormone on the process of atherosclerosis might be mediated through the cytokine inflammatory pathway.

In a randomized, 18-month, placebo-controlled study, we investigated the effect of long-term growth hormone replacement therapy on interleukin-6, C-reactive protein, serum amyloid polypeptide A, and other classic cardiovascular risk factors in men with adult-onset growth hormone deficiency.

Methods

Patients

Forty men (mean age, 49 years [range, 24 to 64 years]) were recruited from the Massachusetts General Hospital, Boston, Massachusetts, and surrounding communities. Methods and other results from this study have been reported elsewhere (16, 38). Patients were identified through hospital records and referrals. All patients met the following criteria: 1) normal growth and development; 2) benign sellar neoplasm, pituitary apoplexy, or idiopathic hypopituitarism diagnosed after age 18 years, and 3) peak growth hormone level less than 5 $\mu\text{g/L}$ after two pharmacologic stimuli. Patients were excluded if they had a history of cancer, acromegaly, or diabetes or if they had not been stable and receiving appropriate replacement for other hormonal deficiencies for at least 6 months. All patients who met the criteria and were willing to participate entered the study. The study was approved by the subcommittee on human studies at Massachusetts General Hospital, and all patients gave written informed consent.

Protocol

After baseline evaluation, patients were randomly assigned to receive either daily injections with recombinant human growth hormone (Nutropin, Genentech, Inc., South San Francisco, California) or placebo for 18 months. The computerized randomization, performed by Genentech, stratified patients by age.

Patients were hospitalized at baseline and every 6 months for anthropometric, nutritional, and fat distribution evaluations. Fasting blood samples were drawn for measurement of insulin-like growth factor I (IGF-I), glucose, insulin, lipids, and hemoglobin A_{1c} values. Levels of IGF-I, glucose, insulin, and lipids were also determined at 1 and 3 months; hemoglobin A_{1c} values were measured at 3 months. Serum and plasma aliquots were collected and frozen at -20°C . Levels of C-reactive protein, serum amyloid polypeptide A, interleukin-6, and lipoprotein(a) were measured in serum that was obtained at the baseline, 6-month, and 18-month visits and had been stored without previous thawing.

The initial growth hormone dosage was 10 $\mu\text{g/kg}$ of body weight per day, and patients self-administered the growth hormone subcutaneously at night. The dose was subsequently titrated to maintain IGF-I levels within the sex- and age-adjusted normal range.

Anthropometry, Nutritional Assessment, and Fat Distribution

Height, weight, and waist and hip circumferences were measured, and percentage of ideal body weight, waist-to-hip ratio, and body mass index were calculated for each patient. Nutritional intake was evaluated every 6 months by using food records. Nutrient calculations were performed by using Nutrition Data System software, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota.

Dual-energy x-ray absorptiometry (Hologic QDR-2000, Waltham, Massachusetts) was performed to determine fat distribution. According to the manufacturer, the coefficient of variation for body fat is 1.5%. The body fat percentage was calculated by dividing the weight of fat by total body weight. Percentage of truncal fat and extremity fat were determined similarly. The ratio of truncal fat to total fat and the ratio of truncal fat to extremity fat were calculated as described elsewhere (39).

Biochemical Analysis

Serum IGF-I levels were measured by radioimmunoassay after acid-alcohol extraction (Nichols Institute, San Juan Capistrano, California). Lipoprotein(a), serum amyloid polypeptide A, and C-reactive protein levels were simultaneously measured on the Behring BNII analyzer (Dade Behring, Newark, Delaware) by using ultrasensitive and latex-enhanced immunotechniques. The interassay coefficients of variation were less than 6%, 7%, and 5.6% respectively, over a wide range of concentrations. Interleukin-6 levels were measured by using ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota) with an interassay coefficient of variation of 5.8%. Other assays were performed at Massachusetts General Hospital, as described elsewhere (40).

Statistical Analysis

We prospectively chose to divide the analysis into two phases: short-term (months 1 and 3) and long-term (months 6, 12, and 18). The short-term effect represents the mean of the month 1 and month 3 changes from baseline, and the long-term effect represents the mean of the month 6, month 12 (when available), and month 18 changes from baseline. The primary analysis used repeated-measures analysis of covariance (SAS PROC MIXED, SAS Institute, Inc., Cary, North Carolina), controlling for baseline value and month, to estimate the mean change from baseline within and between groups. The analysis we used is equivalent to a random-effects model with a fixed group effect and a random patient effect; this analysis correctly accounts for “ignorable” missing data. Results from the primary analysis are reported, unless otherwise noted, as the least-squares mean change from baseline (\pm SE) within the growth hormone group compared with that within the placebo group, as estimated from the model. The *P* value for the comparison between groups is also given. All *P* values are two sided, and values less than 0.05 were considered statistically significant.

In a secondary analysis, we used a random-slopes model with a fixed baseline effect, fixed treatment effect, fixed treatment-by-month interaction, and a random-intercept and a random-month effect for each patient to test for a time-by-treatment interaction over months 6 through 18. The time-by-treatment interaction, which represents the difference in slopes between the two groups, was considered statistically significant if the *P* value was less than 0.1. Pearson product moment correlation coefficients were

Table 1. Characteristics of Pituitary Disorders*

| Characteristic | Growth Hormone Group (n = 20) | Placebo Group (n = 20) |
|------------------------------------|-------------------------------|------------------------|
| | n (%) | |
| Type of pituitary disease | | |
| Nonfunctioning adenoma | 10 (50) | 8 (40) |
| Prolactin-secreting adenoma | 4 (20) | 7 (35) |
| Craniopharyngioma | 3 (15) | 2 (10) |
| Cushing syndrome | 1 (5) | 1 (5) |
| Apoplexy | 1 (5) | 1 (5) |
| Idiopathic | 1 (5) | 1 (5) |
| Treatment for pituitary disease | | |
| Surgery | 17 (85) | 16 (80) |
| Radiation therapy | 9 (45) | 7 (35) |
| Surgery plus radiation therapy | 9 (45) | 5 (25) |
| Medical therapy alone | 3 (15) | 2 (10) |
| Pituitary deficiencies | | |
| Isolated growth hormone deficiency | 1 (5) | 1 (5) |
| One axis | 1 (5) | 5 (25) |
| Two axes | 6 (30) | 4 (20) |
| Three axes | 11 (55) | 9 (45) |
| Three axes plus diabetes insipidus | 1 (5) | 1 (5) |

* Mean (\pm SD) time from diagnosis of pituitary disease: 7.65 \pm 5.29 years in growth hormone group and 7.15 \pm 4.86 years in placebo group.

computed to estimate 1) the correlation between mean IGF-I levels at months 1 and 3 and long-term changes in the outcome variables and 2) changes in IGF-I levels and changes in outcome variables; *P* values less than 0.05 were considered statistically significant. We used SAS software, version 8 (SAS Institute, Inc.), for all data analyses.

Role of Study Sponsor

Genentech provided growth hormone, statistical support for the random assignment of patients, and partial grant support. The company had no involvement in the design of the study, collection and analysis of the data, writing of the paper, or the decision to submit the manuscript for publication.

Results

Table 1 shows clinical characteristics of the pituitary disorder in the study patients. Clinical and biochemical characteristics of the patients at baseline are shown in Tables 2 and 3, respectively. Patients assigned to receive growth hormone or placebo did not differ with regard to any variable studied except central fat (estimated as ratios of truncal fat to total fat and truncal fat to extremity fat), which was slightly higher in the growth hormone group. One patient assigned to the growth hormone group had a history of coronary artery disease. Medications used, in-

Table 2. Baseline Clinical Characteristics*

| Characteristic | Growth Hormone Group (n = 20) | Placebo Group (n = 20) |
|---------------------------------------|-------------------------------|------------------------|
| Age, y | 48.9 ± 9.0 | 49.5 ± 10.4 |
| Systolic blood pressure, mm Hg | 123 ± 11 | 120 ± 17 |
| Diastolic blood pressure, mm Hg | 82 ± 10 | 79 ± 10 |
| Weight, kg | 93.5 ± 17.1 | 90.1 ± 15.3 |
| Body mass index, kg/m ² | 30 ± 4 | 29 ± 5 |
| Ideal body weight, % | 133 ± 19 | 126 ± 22 |
| Body fat, % | 32.6 ± 7.1 | 32.3 ± 6.8 |
| Waist-to-hip ratio | 0.97 ± 0.05 | 0.96 ± 0.05 |
| Truncal fat-to-extremity fat ratio | 1.5 ± 0.4† | 1.2 ± 0.3 |
| Truncal fat-to-total fat ratio | 0.57 ± 0.06† | 0.52 ± 0.06 |
| Smoking status, n | | |
| Current | 4 | 5 |
| Past | 9 | 8 |
| Never | 7 | 7 |
| History of hypercholesterolemia, n | 1 | 1 |
| History of coronary artery disease, n | 1 | 0 |
| History of hypertension, n | 4 | 4 |

* Values with plus/minus sign are the mean ± SD.

† $P < 0.05$ for differences between groups.

cluding statins, nonsteroidal anti-inflammatory drugs, and steroids, did not differ between the two groups.

Thirty-three patients finished the study. Four patients in the growth hormone group and three in the placebo group withdrew from the study. One dropout in the growth hormone group was potentially attributed to treatment. Our analysis was done according to the intention-to-treat principle, and all data available were used. Because one patient in the growth hormone group dropped out before the 1-month visit and our analysis is based on changes from baseline, his data are not included in the analysis. Four other patients (two in each group) dropped

out before the 6-month visit and are not included in the analysis of the long-term effects of growth hormone.

The initial growth hormone dose was reduced in all patients at subsequent visits because of elevated IGF-I levels or adverse events. All placebo recipients had dose reductions to maintain patient blinding. At 18 months, the mean growth hormone dosage was 4 $\mu\text{g}/\text{kg}$ per day (range, 2 to 6 $\mu\text{g}/\text{kg}$ per day) and the mean IGF-I level was 42.2 nmol/L (range, 29.7 to 61.3 nmol/L [normal range, 11.8 to 47.2 nmol/L]).

Anthropometry and Fat Distribution

Changes in weight, body mass index, percentage of ideal body weight, waist-to-hip ratio, and nutrient intake did not differ between groups throughout the study. The truncal fat-to-total fat ratio decreased significantly with long-term growth hormone treatment (months 6 to 18) compared with placebo (within-group changes, -0.014 ± 0.004 compared with 0.004 ± 0.005 , respectively; $P = 0.0087$ for difference between groups), whereas the changes in truncal fat-to-extremity fat ratio did not differ between groups (within-group changes, -0.071 ± 0.026 compared with 0.009 ± 0.027 ; $P = 0.052$ for difference between groups) (Figure 1).

C-Reactive Protein, Serum Amyloid Polypeptide A, and Interleukin-6

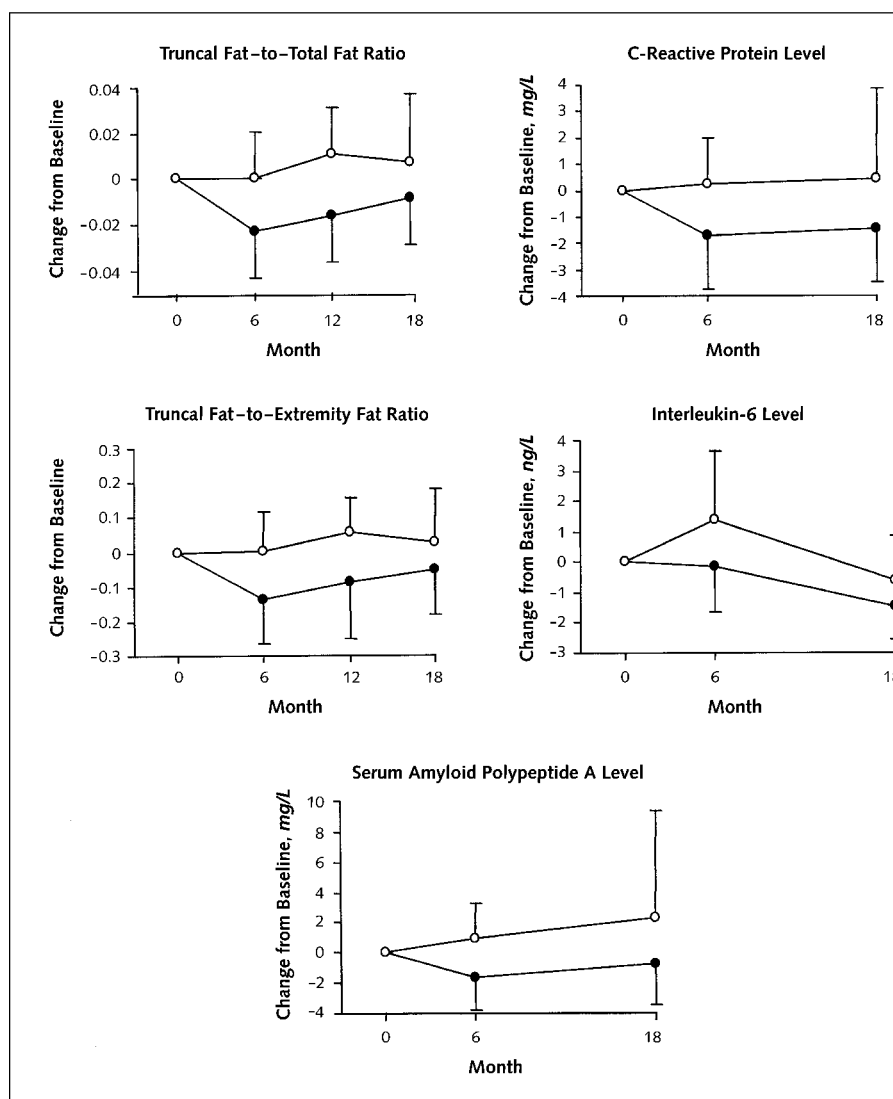
C-reactive protein levels decreased with long-term growth hormone administration compared with placebo (within-group changes, -1.6 ± 0.4 mg/L compared with

Table 3. Baseline Biochemical Characteristics*

| Characteristic | Growth Hormone Group | Placebo Group |
|--|----------------------------|----------------------------|
| Total cholesterol level, mmol/L (mg/dL) | 5.59 ± 0.82 (216.1 ± 31.9) | 5.69 ± 1.21 (220.0 ± 46.6) |
| LDL cholesterol level, mmol/L (mg/dL) | 3.71 ± 0.83 (143.4 ± 32.1) | 3.74 ± 0.89 (144.7 ± 34.6) |
| HDL cholesterol level, mmol/L (mg/dL) | 0.81 ± 0.18 (31.4 ± 7.1) | 0.91 ± 0.20 (35.2 ± 7.7) |
| Total cholesterol-to-HDL cholesterol ratio | 7.13 ± 1.6 | 6.5 ± 1.9 |
| Triglyceride level, mmol/L (mg/dL) | 2.32 ± 0.96 (206.0 ± 84.4) | 2.10 ± 0.25 (185.7 ± 21.9) |
| Lipoprotein(a) level, mg/L | 65 ± 73 | 46 ± 43 |
| IGF-I level, nmol/L | 14.7 ± 1.5 | 16.5 ± 1.5 |
| Glucose level, mmol/L (mg/dL) | 4.7 ± 0.5 (85.1 ± 9.1) | 4.9 ± 0.3 (88.2 ± 6.3) |
| Insulin level, pmol/L | 91.8 ± 63.1 | 63.1 ± 32.3 |
| Insulin-to-glucose ratio | 0.05 ± 0.007 | 0.08 ± 0.009 |
| Hemoglobin A _{1c} value | 6.5 ± 7.3 | 6.5 ± 7.3 |
| C-reactive protein level, mg/L | 4.4 ± 4.3 | 3.6 ± 3.3 |
| Serum amyloid A level, mg/L | 4.1 ± 2.8 | 4.3 ± 6.2 |
| Interleukin-6 level, ng/L | 3.33 ± 1.2 | 3.3 ± 2.6 |

* Values are expressed as the mean ± SD. $P > 0.05$ for all comparisons between groups. HDL = high-density lipoprotein; IGF-I = insulin-like growth factor I; LDL = low-density lipoprotein.

Figure 1. Central fat ratios and inflammatory markers in growth hormone (black circles) and placebo (white circles) recipients.



Error bars represent 1 SD. *P* values for the mean difference between groups over months 6, 12, and 18 were 0.0087 for truncal fat-to-total fat ratio and 0.052 for truncal fat-to-extremity fat ratio. *P* values for the mean difference between groups over months 6 and 18 were 0.0027 for C-reactive protein levels, 0.013 for interleukin-6 levels, and 0.056 for serum amyloid polypeptide A levels.

0.3 ± 0.4 mg/L, respectively; *P* = 0.0027 for difference between groups), as did interleukin-6 levels (within-group change, -0.83 ± 0.35 ng/L compared with 0.49 ± 0.35 ng/L; *P* = 0.013 for difference between groups). Long-term changes in serum amyloid polypeptide A levels did not reach statistical significance (within-group changes, -0.9 ± 0.8 mg/L compared with 1.4 ± 0.8 mg/L; *P* = 0.056 for difference between groups) (Figure 1 and Table 4).

Lipid Metabolism

Compared with placebo, growth hormone had a significant short-term effect (months 1 and 3) on lipids. Decreases occurred in total cholesterol levels (within-group changes, -0.59 ± 0.12 mmol/L in the growth hormone group compared with 0.27 ± 0.12 mmol/L in the placebo group [-22.9 ± 4.7 mg/dL compared with 10.3 ± 4.7 mg/dL]; *P* < 0.001 for difference between groups), LDL cholesterol levels (within-group changes, -0.43 ± 0.11

Table 4. Estimated Changes from Baseline within and between Groups*

| Variable | Phase | Change in Growth Hormone Group | Change in Placebo Group | Net Difference between Groups [95% CI] | P Value |
|--|------------|--------------------------------|-------------------------|---|---------|
| Cholesterol level, mmol/L (mg/dL) | Short-term | -0.59 (-22.9)† | 0.27 (10.3)† | -0.86 [-1.2 to -0.5] (-33.2 [-46.7 to -19.8]) | <0.001 |
| | Long-term | 0.01 (0.5) | 0.21 (8.0) | -0.2 [-0.53 to 0.14] (-7.6 [-20.6 to 5.5]) | >0.2 |
| LDL cholesterol level, mmol/L (mg/dL) | Short-term | -0.43 (-16.6)† | 0.20 (7.9) | -0.63 [-0.94 to -0.33] (-24.5 [-36.4 to 12.6]) | <0.001 |
| | Long-term | 0.05 (2.1) | 0.27 (10.6)† | -0.22 [-0.52 to 0.08] (-8.5 [-20.2 to 3.3]) | 0.15 |
| HDL cholesterol level, mmol/L (mg/dL) | Short-term | 0.05 (1.9) | 0.12 (4.6)† | -0.07 [-0.15 to 0.01] (-2.6 [-5.8 to 0.5]) | 0.1 |
| | Long-term | 0.07 (2.6)† | 0.06 (2.3) | 0.01 [-0.08 to 0.10] (0.4 [-3.1 to 3.8]) | >0.2 |
| Total cholesterol-to-HDL cholesterol ratio | Short-term | -1.12 | -0.55 | -0.56 [-1.1 to -0.03] | 0.04 |
| | Long-term | -0.4 | -0.18 | -0.26 [-0.79 to 0.33] | >0.2 |
| Triglyceride level, mmol/L (mg/dL) | Short-term | -0.42 (-37.0)† | -0.13 (-11.2) | -0.29 [-0.70 to 0.12] (-25.8 [-61.9 to 10.3]) | 0.15 |
| | Long-term | -0.21 (-18.4)† | -0.31 (-27.6)† | 0.10 [-0.18 to 0.38] (9.1 [-15.7 to 34.0]) | >0.2 |
| Lipoprotein(a) level, mg/L | Long-term | 29.9 | 8.0 | 22.0 [5.7 to 38.2] | 0.0096 |
| Glucose level, mmol/L (mg/dL) | Short-term | 0.79 (14.2)† | 0.25 (4.5) | 0.54 [0.21 to 0.86] (9.6 [3.9 to 15.4]) | 0.0018 |
| | Long-term | 0.45 (8.1)† | -0.11 (-1.9) | 0.56 [0.21 to 0.90] (10.0 [3.8 to 16.3]) | 0.0026 |
| Insulin level, pmol/L | Short-term | 41.9† | 4.1 | 37.9 [18.5 to 57.3] | <0.001 |
| | Long-term | 11.7 | -8.9 | 20.6 [-1.2 to 42.5] | 0.064 |
| Insulin-to-glucose ratio | Short-term | 6.01 | 0.002 | 6.01 [2.28 to 9.74] | 0.0025 |
| | Long-term | 0.2 | -1.7 | 1.8 [-2.2 to 5.8] | >0.2 |
| Hemoglobin A _{1c} value | Short-term | -0.08 | 0.04 | -0.12 [-0.5 to 0.3] | >0.2 |
| | Long-term | 0.09 | -0.2 | 0.3 [-0.01 to 0.55] | 0.061 |
| C-reactive protein level, mg/L | Long-term | -1.6† | 0.3 | -1.9 [-3.1 to -0.7] | 0.0027 |
| Serum amyloid A level, mg/L | Long-term | -0.9 | 1.4 | -2.4 [-4.8 to 0.06] | 0.056 |
| Interleukin-6 level, ng/L | Long-term | -0.83† | 0.49 | -1.32 [-2.33 to -0.30] | 0.013 |

* Estimated changes from baseline in each group and net differences between groups with 95% CIs, as obtained from the mixed linear model. Short-term changes represent estimated mean changes at 1 and 3 months. Long-term changes represent estimated mean changes at 6, 12 (when available), and 18 months. The *P* value refers to the difference between groups. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† *P* < 0.05 for changes from baseline within groups.

mmol/L compared with 0.20 ± 0.11 mmol/L [-16.6 ± 4.1 mg/dL compared with 7.9 ± 4.2 mg/dL]; $P < 0.001$ for difference between groups), and total cholesterol-to-HDL cholesterol ratio (within-group changes, -1.1 ± 0.2 compared with -0.6 ± 0.2 ; $P = 0.040$ for difference between groups). No between-group differences were observed for HDL cholesterol or triglyceride levels. However, HDL cholesterol levels increased over the short term in the placebo group (within-group change, 0.12 ± 0.03 mmol/L [4.6 ± 1.07 mg/dL]; $P < 0.001$) but not in the growth hormone group (within-group change, 0.05 ± 0.03 mmol/L [1.9 ± 1.1 mg/dL]; $P = 0.078$).

Compared with placebo, growth hormone had no significant long-term effect (months 6 to 18) on lipids. Levels of HDL cholesterol increased in the growth hormone group (0.07 ± 0.03 mmol/L [2.6 ± 1.2 mg/dL]; $P = 0.033$) but not in the placebo group (0.06 ± 0.03 mmol/L

[2.3 ± 1.2 mg/dL]; $P = 0.064$). Triglyceride levels decreased in both groups (-0.21 ± 0.10 mmol/L [-18.4 ± 8.6 mg/dL] in the growth hormone group [$P = 0.040$] and -0.31 ± 0.10 mmol/L [-27.6 ± 8.6 mg/dL] in the placebo group [$P = 0.0031$]) (Figure 2 and Table 4).

Lipoprotein(a)

The median lipoprotein(a) level at baseline was 25 mg/L (range, 13 to 210 mg/L). Lipoprotein(a) levels increased significantly with long-term growth hormone therapy compared with placebo (within-group changes, 29.9 ± 5.7 compared with 8.0 ± 5.6 mg/L; $P < 0.001$ for difference between groups) (Figure 2 and Table 4).

Glucose Metabolism

Growth hormone was associated with a short-term increase in glucose levels compared with placebo (within-

group changes, 0.79 ± 0.11 mmol/L compared with 0.25 ± 0.11 mmol/L [14.2 ± 2.0 mg/dL compared with 4.5 ± 1.9 mg/dL], respectively; $P < 0.001$ for difference between groups). Short-term increases among growth hormone recipients were also seen in insulin levels (within-group changes, 41.9 ± 6.5 pmol/L compared with 4.1 ± 6.8 pmol/L; $P = 0.0018$ for difference between groups) and the insulin-to-glucose ratio (within-group changes, 6.0 ± 1.3 compared with 0.002 ± 1.2 ; $P = 0.0025$ for difference between groups). The increase in glucose levels was maintained in the long-term phase (0.45 ± 0.12 mmol/L in the growth hormone group compared with -0.11 ± 0.11 mmol/L in the placebo group [8.1 ± 2.2 mg/dL compared with -1.9 ± 2.0 mg/dL]; $P = 0.0026$ for difference between groups), but the changes in insulin levels and insulin-to-glucose ratio were not maintained (Figure 3 and Table 4). Two patients in the growth hormone group had glucose values greater than 7 mmol/L (126 mg/dL) once and twice, respectively. Two other growth hormone recipients had fasting glucose levels

between 6.1 and 7 mmol/L (110 and 126 mg/dL) within the first 6 months but normal values thereafter. Hemoglobin A_{1c} values did not change significantly.

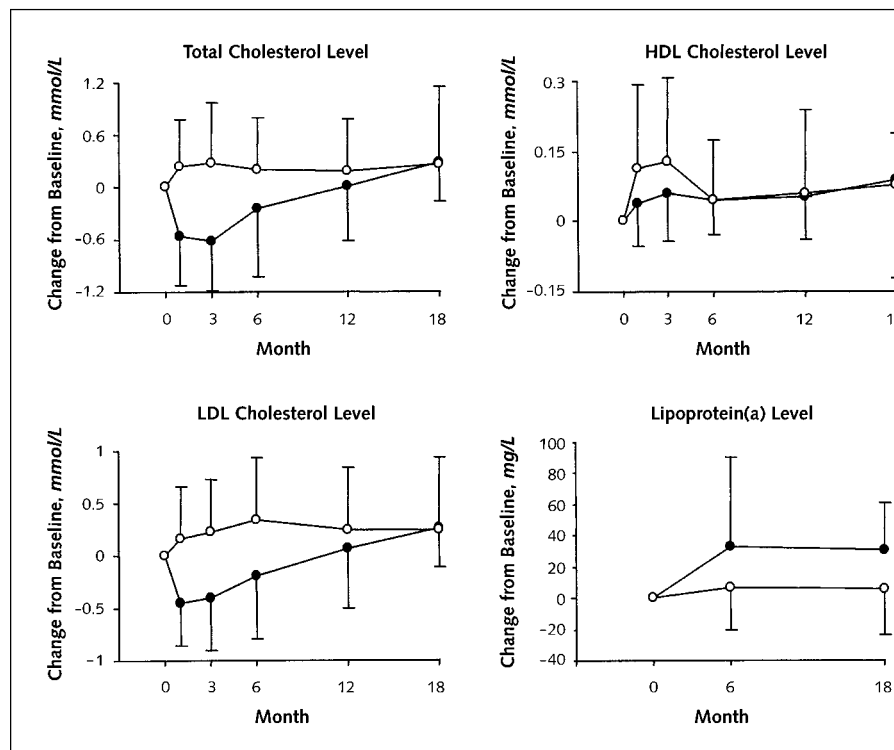
Correlation between Insulin-Like Growth Factor I and Outcome Variables

Within each phase, changes in IGF-I did not correlate with any other outcome variable. Mean IGF-I levels at 1 and 3 months did not correlate with long-term changes in any variable.

Time-by-Treatment Interaction

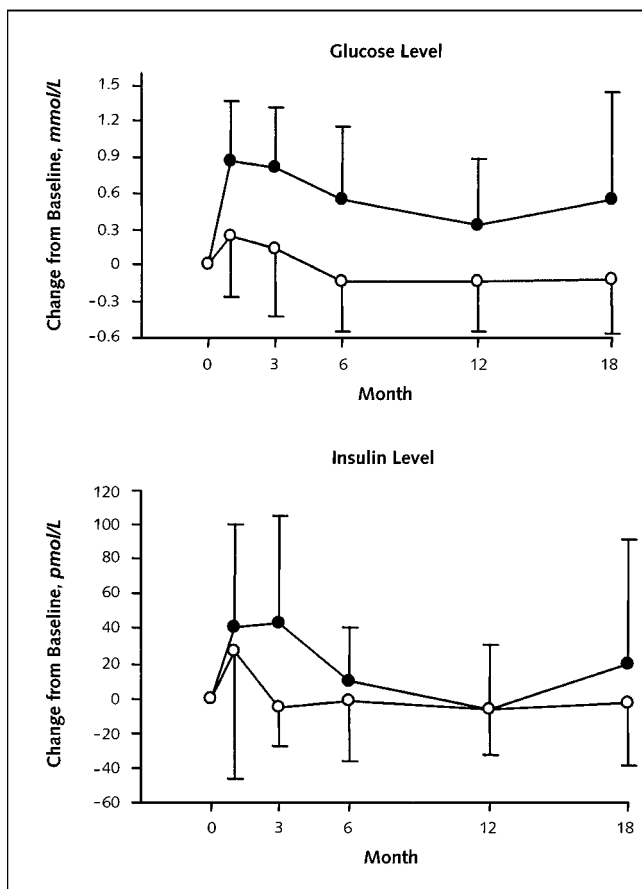
No significant time-by-treatment interaction was seen between months 6 and 18 for any variable for which the primary analysis showed a significant treatment effect in the long-term phase. This finding is consistent with a sustained effect of growth hormone in those variables. Total cholesterol and LDL cholesterol levels, for which the primary analysis showed a short-term effect of treatment but

Figure 2. Lipid values and lipoprotein(a) levels in growth hormone (black circles) and placebo (white circles) recipients.



Error bars represent 1 SD. P values for the mean difference between groups over months 1 and 3 were <0.001 for total cholesterol levels, 0.10 for high-density lipoprotein (HDL) cholesterol levels, and <0.001 for low-density lipoprotein (LDL) cholesterol levels. P values for the mean difference between groups over months 6 to 18 were >0.2 for total cholesterol levels, >0.2 for HDL cholesterol levels, 0.15 for LDL cholesterol levels, and <0.001 for lipoprotein(a) levels. To convert total, HDL, and LDL cholesterol values to mg/dL, divide by 0.0286.

Figure 3. Glucose and insulin levels in growth hormone (black circles) and placebo (white circles) recipients.



Error bars represent 1 SD. *P* values for the mean difference between groups over months 1 and 3 were 0.0018 for glucose levels and <0.001 for insulin levels. *P* values for the mean differences between groups over months 6 to 18 were 0.0026 for glucose levels and 0.064 for insulin levels. To convert glucose values to mg/dL, divide by 0.0555.

no long-term effect, did have a significant time-by-treatment interaction between months 6 and 18. This result is consistent with a return to baseline in the long-term phase for the growth hormone group (Figure 2).

Discussion

Our study shows that long-term growth hormone replacement therapy decreases serum interleukin-6 and C-reactive protein levels, which are recognized markers of cardiovascular risk (29, 41, 42). These results suggest a pathophysiologic mechanism whereby growth hormone mediates the process of atherosclerosis by way of the inflammatory pathway.

Atheromatous lesions represent inflammatory foci in

the arterial wall, with macrophages and lymphocytes releasing cytokines and growth factors (27). Interleukin-6, a proinflammatory cytokine present in the atherosclerotic vessel wall, promotes lymphocyte adhesion to the endothelium, increases endothelial permeability, stimulates monocyte transformation into macrophages, and induces vascular smooth-muscle proliferation (43, 44). Interleukin-6 stimulates the synthesis of acute-phase reactants in the liver, such as C-reactive protein and serum amyloid polypeptide A. It is hypothesized that cytokines arising either from atheroma or from nonvascular sources, such as inflammatory states, may accelerate atherogenesis and its manifestations (28). The reduction in interleukin-6 and C-reactive protein levels seen in our study may indicate that growth hormone replacement modulates the inflammatory activity. Whether this is a direct consequence of growth hormone or IGF-I action on the arterial wall or at a distal site remains to be established. Regardless of its source, the reduction in inflammatory markers shown here may be associated with growth hormone-induced reduction in cardiovascular risk.

Two prospective, open-label studies have reported reduction in carotid intima-media thickness, a morphologic indicator of atherosclerosis, with growth hormone replacement (5, 26). Changes in the lipid pattern in response to treatment could not explain the reduction in intima-media thickness in either study, suggesting another mechanism for the effects of growth hormone on the vascular wall. Growth hormone acts through a receptor that is a member of the cytokine-hematopoietin superfamily, sharing molecular pathways with interleukin-6 and other cytokines (45). Both growth hormone and IGF-I have important immunomodulatory properties (35, 36, 46–48). Growth hormone decreases excess production of cytokines and acute-phase reactants in experimental and clinical models of acute injury (35, 37). Although no clinically significant immunodeficiency has been found in growth hormone-deficient patients, elevation in serum interleukin-6 and tumor necrosis factor- α levels, along with monocyte dysfunction, was recently reported in these patients compared with controls (44). This finding suggests a state of chronic inflammatory dysfunction. In agreement with our results, short-term treatment with growth hormone decreased monocyte production of interleukin-6 and tumor necrosis factor- α (44).

C-reactive protein is a useful prognostic tool in the evaluation of cardiovascular risk. Prospective studies have

consistently shown a relation between C-reactive protein levels and risk for cardiovascular events (30–32, 49, 50). The mean C-reactive protein level in our study sample at baseline was in the highest quartile when compared to values in the Physicians' Health Study. That study involved a cohort of apparently healthy U.S. men 40 to 84 years of age and used the same assay for C-reactive protein as our study did (51). Although our sample was younger (median age, 50 years [range, 24 to 64 years]), C-reactive protein levels increase with age, supporting the assessment that values in our patients were high. In the Physicians' Health Study, baseline C-reactive protein levels in the highest quartile conferred a threefold increased risk for future myocardial infarction and twofold increased risk for stroke, independent of other cardiovascular risk factors (30). Although there are limitations in study comparisons, C-reactive protein levels declined in half of our growth hormone recipients by one (37.5%) or two (12.5%) quartiles, as defined by the Physicians' Health Study. Approximately one third of patients (31%) experienced reductions without changes in quartiles, and slight increases occurred in three patients (19%).

To date, few therapies have been shown to influence serum C-reactive protein levels (52, 53). Of interest, the absolute mean reduction compared with placebo in our study (-1.91 mg/L) is similar to the reduction reported for pravastatin (-1.37 mg/L) in patients from the Cholesterol and Recurrent Events study, who were followed for 5 years (53). Pravastatin may affect inflammation in addition to reducing lipid levels. Use of this drug was associated with a 24% reduction in risk for death from coronary heart disease or nonfatal myocardial infarction (54) and with a 54% risk reduction in patients whose initial serum C-reactive protein level exceeded the 90% percentile (55).

Although growth hormone treatment decreased total and LDL cholesterol levels and the total cholesterol-to-HDL cholesterol ratio in the first 3 months of therapy, this effect was not maintained. The initial dose of growth hormone was supraphysiologic in 70% of the patients and was gradually reduced to maintain IGF-I levels at normal or close to normal levels. Whether the short-term lipid changes were due to a dose- or time-dependent effect cannot be ascertained from our study. Growth hormone has dose-dependent effects in both healthy persons (56, 57) and growth hormone-deficient persons (58). This may explain the discrepant findings among studies. Initial unsustained decreases in LDL cholesterol levels with growth hor-

mone replacement have been previously reported (26, 59). In our patients, the baseline HDL cholesterol level was low in both groups according to National Cholesterol Education Program guidelines (60). Long-term increases in HDL cholesterol levels did not differ between groups. Several studies have reported that growth hormone increases HDL cholesterol levels (61, 62), but most controlled trials have not found such an effect (15, 19, 23, 24, 63). Our lipid results may differ from those reported elsewhere because of the randomization, the long placebo period, and the single-sex study sample.

Growth hormone treatment increased lipoprotein(a) levels in our study, a finding also reported by other authors (56, 61, 64). Of interest, median lipoprotein(a) values at baseline were low. There is discordance among large-scale studies with regard to the association of lipoprotein(a) levels with cardiovascular risk (65–68). Further studies are needed to determine the consequences of the increase in lipoprotein(a) level associated with growth hormone replacement.

We observed a short-term increase in glucose and insulin levels and the insulin-to-glucose ratio, but only elevations in glucose level were sustained. Although short-term growth hormone administration impairs insulin sensitivity (12, 22), it is not clear whether the effect can be reversed with long-term treatment. A study using high doses of growth hormone reported recovery of insulin sensitivity, as assessed by euglycemic clamp after 26 weeks of treatment (22). Another study involving more physiologic doses did not show recovery after 12 months of treatment (12). More accurate studies of glucose metabolism in growth hormone-deficient patients are needed to assess the long-term effect of physiologic growth hormone replacement on insulin sensitivity.

Finally, although waist-to-hip ratio did not change, the truncal fat-to-total fat ratio assessed by dual-energy x-ray absorptiometry decreased significantly. This may indicate an effect of growth hormone replacement on central fat distribution that may not be easily demonstrated by using the waist-to-hip ratio, a measurement with more intertest variability. Changes in central fat distribution after growth hormone administration have been reported by others (12, 15, 17, 19).

Potential limitations of our data must be considered. First, we evaluated interleukin-6 and acute-phase reactants, which theoretically could be influenced by exogenous inflammatory stimuli other than growth hormone. We be-

lieve, however, that the randomization makes such a possibility unlikely. Second, our dose strategy resulted in initially high levels of IGF-I that were adjusted with dose reductions. Although we found no correlation between short-term IGF-I levels and long-term changes in any variables reported, we cannot exclude the possibility that initially high levels affected the final outcome. Third, our study was limited to men. Further studies should include women and should use a more consistently physiologic approach to confirm our results.

In conclusion, our study shows that 18 months of growth hormone replacement therapy in men with growth hormone deficiency reduces serum levels of inflammatory cytokines and acute-phase reactants, improving the cardiovascular risk profile. The effect on inflammatory markers may reflect one of the mechanisms by which growth hormone modulates the atherosclerotic process, with potential beneficial effects. Lipoprotein(a) and glucose levels increased, and central fat decreased. Further studies are needed to confirm the functional significance of these results by using long-term cardiovascular clinical end points and to explore cardiovascular risk factors in growth hormone-deficient women.

From Massachusetts General Hospital, Harvard Medical School, Brigham and Women's Hospital, and Children's Hospital, Boston, Massachusetts.

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Requests for Single Reprints: Anne Klibanski, MD, Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit Street, Bulfinch 457B, Boston, MA 02114.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Drs. Sesmilo, Biller, and Klibanski: Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit Street, Bulfinch 457 B, Boston, MA 02114.

Dr. Llevadot: TIMI Office, Brigham and Women's Hospital, 333 Longwood Avenue, Suite 402, Boston, MA 02115.

Dr. Rifai and Ms. Hanson: Department of Laboratory Medicine and

Pathology, Children's Hospital, 300 Longwood Avenue, Farley 7, Boston, MA 02115.

Mr. Hayden: Biostatistics Center, Massachusetts General Hospital, 50 Staniford Street, 5th Floor, Boston, MA 02114.

Author Contributions: Conception and design: G. Sesmilo, B.M.K. Biller, J. Llevadot, N. Rifai, A. Klibanski.

Analysis and interpretation of the data: G. Sesmilo, J. Llevadot, N. Rifai, G. Hanson, D. Hayden, A. Klibanski.

Drafting of the article: G. Sesmilo, A. Klibanski.

Critical revision of the article for important intellectual content: G. Sesmilo, B.M.K. Biller, J. Llevadot, N. Rifai, D. Hayden, A. Klibanski.

Final approval of the article: G. Sesmilo, B.M.K. Biller, J. Llevadot, N. Rifai, G. Hanson, D. Hayden, A. Klibanski.

Provision of study materials or patients: G. Sesmilo, B.M.K. Biller, A. Klibanski.

Statistical expertise: D. Hayden.

Obtaining of funding: B.M.K. Biller.

Administrative, technical, or logistic support: B.M.K. Biller, G. Hanson.

Collection and assembly of data: G. Sesmilo, B.M.K. Biller, G. Hanson, D. Hayden, A. Klibanski.

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