

## ARTICLE

# Effects of Physiologic Growth Hormone Therapy on Bone Density and Body Composition in Patients with Adult-Onset Growth Hormone Deficiency

## A Randomized, Placebo-Controlled Trial

▶ Howard B.A. Baum, MD; Beverly M.K. Biller, MD; Joel S. Finkelstein, MD; Kristin Baker Cannistraro, BS, RN; Daniel S. Oppenheim, MD, PhD; David A. Schoenfeld, PhD; Theresa Hoskins Michel, PT, MS; Harriet Wittink, PT, MS; and Anne Klibanski, MD

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**Background:** Patients with adult-onset growth hormone deficiency have reduced bone density and increased fat mass. Growth hormone at high doses may decrease body fat in these patients, but the effects of growth hormone at more physiologic doses on bone density and body composition have not been convincingly shown.

**Objective:** To determine whether long-term growth hormone therapy at a dose adjusted to maintain normal insulin-like growth factor 1 (IGF-1) levels has clinical effects in patients with adult-onset growth hormone deficiency.

**Design:** Randomized, placebo-controlled study.

**Setting:** Tertiary referral center.

**Patients:** 32 men with adult-onset growth hormone deficiency.

**Intervention:** Growth hormone (initial daily dose, 10  $\mu$ g/kg of body weight) or placebo for 18 months. The growth hormone dose was reduced by 25% if IGF-1 levels were elevated.

**Measurements:** Body composition and bone mineral density of the lumbar spine, femoral neck, and proximal radius were measured by dual energy x-ray absorptiometry at 6-month intervals. Markers of bone turnover were also measured during the first 12 months of the study.

**Results:** Growth hormone therapy increased bone mineral density in the lumbar spine by a mean ( $\pm$ SD) of 5.1%  $\pm$  4.1% and bone mineral density in the femoral neck by 2.4%  $\pm$  3.5%. In the growth hormone group, significant increases were seen in the following markers of bone turnover: osteocalcin (4.4  $\pm$  3.6 mg/L to 7.2  $\pm$  4.6 mg/L) and urinary pyridinoline (39.0  $\pm$  19.8 nmol/mmol of creatinine to 55.7  $\pm$  25.5 nmol/mmol of creatinine) and deoxypyridinoline (8.4  $\pm$  7.1 nmol/mmol of creatinine to 14.9  $\pm$  9.4 nmol/mmol of creatinine). Percentage of body fat in the growth hormone group decreased (from 31.9%  $\pm$  6.5% to 28.3%  $\pm$  7.0%), and lean body mass increased (from 59.0  $\pm$  8.5 kg to 61.5  $\pm$  6.9 kg). These changes were significant compared with corresponding changes in the placebo group ( $P < 0.01$  for all comparisons).

**Conclusions:** Growth hormone administered to men with adult-onset growth hormone deficiency at a dose adjusted according to serum IGF-1 levels increases bone density and stimulates bone turnover, decreases body fat and increases lean mass, and is associated with a low incidence of side effects.

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Adults with hypopituitarism receive therapy that replaces cortisol, thyroid hormone, and gonadal steroids, but growth hormone replacement has typically been reserved for children with growth hormone deficiency. However, several observations suggest that growth hormone may have an important role in maintaining bone density and body composition in adults. Bone density is reduced in patients with growth hormone deficiency that develops during childhood or adulthood [1-3]. In vitro, growth hormone binds to growth hormone receptors on rat osteoblast-like cells and produces a mitogenic response mediated by local synthesis and action of insulin-like growth factor 1 (IGF-1) [4, 5]. Administration of growth hormone to adults with growth hormone deficiency increases serum and urine markers of bone turnover [6-10]. In adults with childhood-onset growth hormone deficiency (in whom osteopenia probably results from a failure to reach peak bone mass), growth hormone therapy increases bone density [3, 8, 10, 11]. However, the effects of growth hormone replacement on bone density in adult-onset growth hormone deficiency are largely unknown.

In addition to having an increased risk for fracture, adults with growth hormone deficiency have an excess risk for cardiovascular-related death that may be attributed to increased central fat mass [12-17]. Growth hormone therapy reduces body fat and increases lean mass in adults with growth hormone deficiency, primarily those in whom the deficiency developed during childhood [6-9, 18-20]. However, previous studies of growth hormone replacement in adults have several important limitations. First, most of these studies used pharmacologic rather than physiologic doses of growth hormone. Second, most have focused on childhood-onset growth hormone deficiency. Third, effects of growth hormone on bone density in patients with adult-onset growth hormone deficiency have not been examined in a controlled study. Because of these limitations, the critical question of whether long-term growth hormone therapy is beneficial in patients with adult-onset growth hormone deficiency has not been definitively answered.

We sought to determine whether long-term growth hormone replacement therapy, given at a dose adjusted according to IGF-1 levels, improves bone density, bone turnover, body composition, and several variables associated with quality of life in patients with adult-onset growth hormone deficiency.

## Methods

### Patients

Thirty-two men (median age, 51 years; range, 24 to 62 years) with a history of pituitary disease were recruited from the Massachusetts General Hospital Neuroendocrine Clinical Center and from surrounding communities. Growth hormone secretion profiles in 23 of these patients have been reported elsewhere [21]. All patients met the following inclusion criteria: 1) normal growth and development, 2) benign sellar neoplasm, pituitary apoplexy, or idiopathic hypopituitarism diagnosed after age 18 years, and 3) peak serum growth hormone levels less than 5 mg/L after receipt of two pharmacologic stimuli on separate mornings. The 13 patients younger than 50 years of age received intravenous insulin, 0.1 U/kg of body weight, and oral clonidine, 0.15 mg. The 18 patients 50 years of age or older received oral clonidine, 0.15 mg, and intravenous arginine, 30 g; these patients were given arginine rather than insulin to avoid potential cardiovascular complications of hypoglycemia.

Patients were excluded if they had a history of acromegaly or diabetes mellitus; were taking drugs (such as phenytoin or etidronate) known to affect bone density; were not receiving standard thyroid or adrenal hormone replacement therapy if the patient was deficient in those hormones; or had begun receiving adrenal, gonadal, or thyroid hormone replacement therapy within 6 months before study enrollment.

Growth hormone deficiency was caused by a clinically nonfunctioning pituitary adenoma in 12 patients, prolactinoma in 9 patients, craniopharyngioma in 9 patients, pituitary apoplexy in 4 patients, Cushing disease in 1 patient, and adult-onset idiopathic hypopituitarism in 1 patient. Twenty-one patients were deficient in adrenocorticotropin, thyroid-stimulating hormone, and gonadotropins. Five patients had two of these deficiencies, 5 patients had one, and 1 patient had none. Twenty-five patients were treated surgically (16 of the 25 were also treated with radiation or bromocriptine, or both). Five patients received bromocriptine with or without radiation therapy, and 2 were treated with hormonal replacement only.

The Subcommittee on Human Studies of the Massachusetts General Hospital approved the study, and all patients gave written informed consent.

### Protocol

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Patients were randomly assigned to receive recombinant human growth hormone (Nutropin, Genentech, Inc., South San Francisco, California) at a daily dose of 10 µg/kg subcutaneously or a placebo. The computerized randomization, done by statisticians at Genentech, Inc., stratified patients to assure balance between the groups with respect to age. Staff at Genentech, Inc., informed the primary investigator of treatment assignment by telephone; the study physician kept the information in a private computer database. Only the study physician was aware of the treatment assignment. Patients were admitted to the General Clinical Research Center for measurements of bone mineral density of the lumbar spine, femoral neck, and proximal radius. Body mass index, lean body mass, and percentage of body fat were also measured. Patients had echocardiography and were tested for strength and exercise capacity. Urine was collected for 24 hours for measurement of pyridinoline, deoxypyridinoline, calcium, and creatinine excretion. Fasting blood samples were drawn at 0900 hours for measurement of IGF-1, glucose, insulin, lipids, and hemoglobin A<sub>1c</sub> values. Patients returned at 1 week, 1 month, and 3 months for outpatient measurement of serum IGF-1, glucose, insulin, lipid (at 1 and 3 months), and hemoglobin A<sub>1c</sub> (at 3 months only) values.

Patients were readmitted at 6, 12, and 18 months so that the baseline evaluation could be repeated. Echocardiography and tests of strength and exercise capacity were repeated only at the 18-month visit. The growth hormone dose was reduced by 25% if the patient's serum IGF-1 level was found to be elevated at the 6- or 12-month visit; serum IGF-1 levels were remeasured approximately 1 month after the dose was decreased. The dose was further adjusted if necessary. To maintain patient blinding, each placebo recipient was asked to reduce his dose by 25% during the first 6 months of the study.

## Bone Density

Bone mineral density of the lumbar spine, femoral neck, radius, and total body was determined by dual-energy x-ray absorptiometry (Hologic QDR-2000, Waltham, Massachusetts). Density of the nondominant radius was measured at the junction of the proximal two thirds and the distal one third of the radial shaft; the coefficient of variation for this measurement is 1.5% [22]. The bone mineral density of the lumbar spine was assessed in the anteroposterior projection in all patients and in the lateral projection in the 22 patients whose body thickness did not exceed the manufacturer's specified limit for the lateral measurement. Because lateral measurements of bone density in the spine eliminate the contribution of the posterior vertebral elements, they estimate trabecular bone mass better than do measurements made in the anteroposterior projection [23]. In 50 persons with paired measurements, the SDs for the anteroposterior and lateral measurements were 0.010 g/cm<sup>2</sup> and 0.013 g/cm<sup>2</sup>, respectively; these values did not vary with bone density. The coefficient of variation for bone density at the femoral neck was 2.1% in 51 persons with paired measurements [24]. All scans were reviewed by one physician who did not know the patients' treatment assignment. Follow-up scans were matched to baseline scans to ensure that identical bone regions were measured.

## Body Composition

A research dietitian determined body mass index. Lean body mass and percentage of body fat were measured by dual-energy x-ray absorptiometry (Hologic QDR-2000). According to the manufacturer, the coefficient of variation is 1.0% for lean mass and 1.5% for percentage of body fat. This compares favorably with the coefficients of variation of other techniques for determining body composition, such as bioelectrical impedance (5%), <sup>40</sup>K counting (3%), and deuterium oxide dilution (3%) [25].

## Biochemical Assays

Serum IGF-1 levels were measured by radioimmunoassay after acid-alcohol extraction (Nichols Institute, San Juan Capistrano, California). The age-adjusted normal ranges for this assay were 83.3 to 378.0 mg/L for men 20 to 40 years of age and 54.0 to 328.5 mg/L for men older than 40 years of age. Interassay coefficients of variation were 5.2% at 121.5 mg/L and 15.2% at 84.5 mg/L. Serum osteocalcin levels were measured by immunoradiometric assay (SmithKline Beecham, Van Nuys, California). The intra-assay coefficients of variation were 11.5% for low control serum pools (3 to 6 mg/L), 11.6% for medium pools (6 to 10 mg/L), and 10.6% for high pools (25 to 35 mg/L). Urinary excretion of total pyridinoline and deoxypyridinoline was measured using high-performance liquid chromatography (SmithKline Beecham). The intra-assay coefficients of variation for measurement of pyridinoline levels were 9.5% at 13.8 nmol/mmol of creatinine, 9.6% at 37.0 nmol/mmol of creatinine, and 10.7% at 47.5 nmol/mmol of creatinine. The intra-assay coefficients of variation for measurement of deoxypyridinoline excretion were 15.8% at 3.2 nmol/mmol of creatinine, 13.5% at 6.7 nmol/mmol of creatinine, and 9.8% at 10.7 nmol/mmol of creatinine. Other assays were done at the Massachusetts General Hospital as described elsewhere [26].

## Echocardiography

Transthoracic two-dimensional echocardiography was done while patients were in the left lateral decubitus position; views included those of the parasternal long and short axis and apical four- and two-chamber views. All studies were done by one

echocardiographer, who was unaware of the patients' treatment assignment and other information on clinical outcome. A phased-array sector scanner (Hewlett-Packard 77020A, Camas, Washington) with a 2.5-MHz transducer was used for all scans. Left ventricular mass and volume were calculated on the basis of American Society of Echocardiography standards [27].

## Strength and Exercise Capacity

Patients completed the Seven-Day Physical Activity Recall questionnaire [28]; energy expenditure for the previous week was calculated on the basis of responses to this questionnaire. Patients had a submaximal treadmill test that used a modified Bruce protocol; expired gas was concurrently analyzed by a metabolic cart (Beckman, Fullerton, California). The metabolic cart calculated peak oxygen consumption by using a 10-second sample from the mixing chamber at the end of each 3-minute stage. The predicted maximal peak oxygen consumption was then calculated by extrapolation. Predicted maximal peak oxygen consumption per kg of body weight was also calculated.

Isokinetics of the thigh muscles was tested by using a dynamometer (Cybex II, Cybex, Ronkonkoma, New York). Peak torque for flexion and extension and total work were recorded. Maximal inspiratory and expiratory pressures were measured by using a respiratory muscle trainer (Ambu, Inc., Hanover, Maryland). The best of three trials was recorded. Patients also participated in a wall squat test. During this test, the patient sat with his back flush against a wall and his hips and knees at right angles. Timing began when the patient assumed this position and stopped when the patient stood up or sat on the floor because of fatigue.

## Statistical Analysis

We used two primary methods of analysis. For variables that were expected to change linearly with time (bone mineral density variables), we compared change per unit of time between treatment groups. The change per unit of time was estimated by using a mixed-model regression with a fixed group times time effect and a random patient and patient times time effect. For all other variables, which were expected to change by the first follow-up visit and then stabilize, the average change from baseline over all the follow-up visits was compared between treatment groups. This method used a mixed-model analysis of variance with a fixed group effect and a random patient effect (Proc Mixed, SAS version 6.09, SAS Institute, Cary, North Carolina). We used the Student two-tailed *t*-test to compare baseline values. All *P* values are for comparisons between treatment groups, and all are two sided. Unless otherwise noted, results are reported as the mean  $\pm$ SD. *P* values less than 0.05 were considered significant.

## Results

Clinical characteristics, including age, body mass index, weight, and physical activity, did not significantly differ between the growth hormone group and the placebo group (Table 1).

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**View this table:** [\[in this window\]](#) [\[in a new window\]](#) **Table 1. Baseline Clinical and Laboratory Characteristics of Patients with Growth Hormone Deficiency Who Received Growth Hormone or Placebo\***

## Growth Hormone Dosing

The mean daily dose of growth hormone at 18 months was  $4 \pm 2$   $\mu$ g/kg. Serum levels of IGF-1 increased significantly in the growth hormone group (*P* < 0.001; Table 2). At 18 months, the mean IGF-1 level in the growth hormone group was  $320.2 \pm 73.0$  mg/L. Most patients in the growth hormone group who completed the study (10 of 14 patients) had normal serum IGF-1 levels at 18 months.

**View this table:** [\[in this window\]](#) [\[in a new window\]](#) **Table 2. Biochemical Values in Patients with Growth Hormone Deficiency Who Received Growth Hormone or Placebo\***

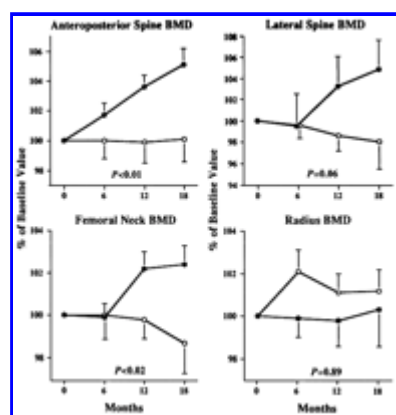
## Side Effects and Adverse Events

In the growth hormone group, two patients developed peripheral edema, one developed edema and arthralgias, and one developed myalgias. All side effects occurred when serum IGF-1 levels were elevated and resolved after the dose was reduced. Patients with elevated IGF-1 levels, however, were not always symptomatic.

Three adverse events that were not thought to be due to growth hormone therapy occurred in the growth hormone group. Systolic function decreased in a patient with a remote history of myocardial infarction. Subsequent evaluation showed ischemia caused by an obstruction in a small coronary artery that had not been seen on a catheterization 20 years earlier. One patient was excluded from the study before the 6-month visit because of a seizure that occurred when he discontinued therapy with anti-convulsant medication. Because our analysis is based on change from baseline values, the data from this patient are not included. We excluded a 62-year-old patient with a history of hypercholesterolemia who had a parietal stroke before the 18-month visit. One other patient in each group dropped out of the study after the 12-month visit for nonmedical reasons.

## Bone Density and Bone Turnover

Data on bone mineral density are shown in [Figure 1](#). In the growth hormone group, mean ( $\pm$  SE) bone mineral density of the lumbar spine increased by  $5.1\% \pm 1.1\%$  when measured in the anteroposterior projection ( $P = 0.0056$ ), but the change was not significant when bone mineral density was measured in the lateral projection ( $4.8\% \pm 2.8\%$ ;  $P = 0.06$ ). Bone mineral density of the femoral neck increased by  $2.4\% \pm 0.9\%$  in the growth hormone group ( $P = 0.011$ ). Bone mineral density of the proximal radius was not significantly affected by treatment. When the four patients with elevated IGF-1 levels at the 18-month visit were excluded from the analysis, changes in bone density of the lumbar spine in the anteroposterior projection and femoral neck remained significant ( $P = 0.022$  and  $0.028$ , respectively).



**Figure 1. Bone mineral density (BMD) of the lumbar spine in the anteroposterior projection, lateral projection, and femoral neck and of the one third distal radius in patients with growth hormone deficiency receiving growth hormone (#9679;) or placebo ○. Values are percentages of the baseline values, and error bars represent  $\pm 1$  SE. *P* values are for comparisons of rates of change between the two groups.**

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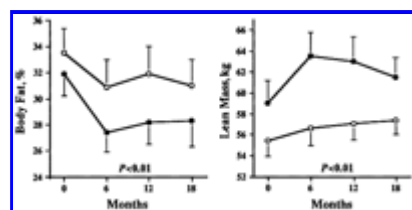
Biochemical values are shown in [Table 2](#). Serum levels of osteocalcin, a marker of bone formation, increased significantly in the growth hormone group ( $P < 0.001$ ). Urinary excretion of deoxypyridinoline and pyridinoline, markers of bone resorption, also increased significantly in the growth hormone group ( $P < 0.001$  for both comparisons). When the four patients with elevated IGF-1 levels at the 18-month visit were excluded from the analysis, these changes remained significant ( $P < 0.001$  for all three markers).

Serum calcium and serum phosphate levels increased significantly in the growth hormone group compared with the placebo group ( $P = 0.036$  and  $0.0014$ , respectively). In no patient did the serum calcium or phosphorus level exceed values in the normal range. Twenty-four-hour urinary calcium excretion was unaffected by treatment.

## Body Composition

Changes in body composition are shown in ([Figure 2](#)). In the growth hormone group, the percentage of body fat decreased significantly ( $P < 0.001$ ) and lean body mass increased significantly ( $P < 0.001$ ). When the four patients who had elevated IGF-1

levels at the 18-month visit were excluded from the analysis, changes in percentage of body fat and lean body mass remained significant ( $P = 0.0098$  and  $0.0054$ , respectively). Neither body mass index nor weight changed significantly in either group.



**Figure 2. Percentage of body fat and lean mass as determined by dual-energy x-ray absorptiometry in patients with growth hormone deficiency receiving growth hormone (#9679;) or placebo ○. Error bars represent  $\pm 1$  SE.  $P$  values are for comparisons of average change from baseline between the two groups.**

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## Glucose Levels and Lipid Metabolism

Baseline fasting serum glucose levels were slightly lower in the growth hormone group ( $P = 0.038$ ). Fasting glucose levels increased slightly in the growth hormone group ( $P = 0.0026$ ; [Table 2](#)), but mean hemoglobin A<sub>1c</sub> and fasting serum insulin values did not change. No patient developed fasting hyperglycemia. In one patient in the growth hormone group, the hemoglobin A<sub>1c</sub> value had increased slightly to 6.8% (normal value < 6.4%) at the 18-month visit; his fasting serum glucose level, however, was normal (5.5 mmol/L). Serum levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides did not change.

## Echocardiographic Findings, Strength, and Exercise Capacity

Left ventricular mass, volumes, ejection fraction, and stroke volume were unaffected by growth hormone treatment. As measured during submaximal treadmill testing, predicted maximal oxygen consumption and predicted maximal oxygen consumption per kg of body weight did not change. Isokinetic test results, respiratory pressure, and wall squat time also remained the same.

## Discussion

We examined the long-term effects of growth hormone on bone density in adult-onset growth hormone deficiency by using IGF-1 levels as a guide to dose adjustment. Our data show that long-term growth hormone therapy increases bone density and improves body composition in patients with adult-onset growth hormone deficiency. These effects are maintained even when growth hormone is used in relatively low doses, which reduce the likelihood of long-term adverse consequences of sustained growth hormone excess.

In our study, growth hormone therapy increased bone mineral density of the lumbar spine in the anteroposterior projection and the femoral neck. These results are important because increases in bone density that result from growth hormone replacement may alleviate osteopenia in patients with growth hormone deficiency, thereby reducing the risk for future fractures. Earlier studies showing measurable effects of growth hormone replacement on bone density in adults have included few patients with adult-onset growth hormone deficiency [[3](#), [8](#), [10](#), [29](#)]. For purposes of comparison, a previous study [[30](#)] showed that etidronate, a bisphosphonate, increased spinal bone density in a group of postmenopausal women by 5% over a 2-year period (an increase similar to that seen in our study) and decreased the rate of fractures by 50%. Bone mineral density of the lumbar spine in the lateral projection also increased in our study, but the difference between the growth hormone and placebo groups did not reach statistical significance, probably because relatively few patients had lateral scans that could be interpreted. Bone mineral density increased at sites composed mostly (lumbar spine) or partially (femoral neck) of trabecular bone but not at a site composed of cortical bone (proximal radius). This finding suggests that the beneficial effects of growth hormone occurred primarily in trabecular bone.

In our study, growth hormone therapy increased indices of bone turnover during a 12-month period; the peak occurred at 6 months. A similar pattern was noted in a 30-month study of growth hormone replacement in adults with childhood-onset growth hormone deficiency [[10](#)] in which markers of bone turnover peaked at 6 to 10 months and then decreased; bone density,

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however, continued to increase, possibly because of a lag time between deposition of osteoid and mineralization. In our study, serum calcium and phosphate levels also increased in response to growth hormone; this result may reflect increased gastrointestinal absorption of calcium and increased tubular reabsorption of phosphate [31].

Our data also show that growth hormone administered at doses adjusted to maintain normal IGF-1 levels decreased body fat and increased lean mass in patients with adult-onset growth hormone deficiency. These changes in body composition were maintained by using doses of growth hormone one third to one sixth of those used in previous studies [7, 20]. Because body fat decreased and lean mass increased slightly in the placebo group, the differences between the two groups were small. These differences were statistically significant, but their clinical significance is unclear.

Previous studies [19, 20, 32] have shown that growth hormone therapy may increase maximum power output and maximum oxygen consumption during exercise testing in younger adults with growth hormone deficiency. In those studies, patients exercised to exhaustion so that power and oxygen uptake could be measured directly. In our study, patients had submaximal testing, after which the amount of oxygen consumption was extrapolated to a predicted maximum. We used this approach in order to limit cardiovascular risk to our middle-aged study population, but it may have introduced variability sufficient to obscure any positive result.

A critical issue in the treatment of adults with growth hormone deficiency is whether growth hormone is administered as physiologic replacement or pharmacologic therapy. No previous study has addressed this question in adult-onset growth hormone deficiency, and how best to titrate the growth hormone dose in this population is unknown. We chose to adjust growth hormone doses to maintain normal levels of IGF-1 so that the drug could be administered in a more physiologic manner. Although four patients had elevated IGF-1 levels at the 18-month visit, the final mean growth hormone dose was lower than that used in previous studies of adults with growth hormone deficiency. Daily growth hormone doses of 12.5 to 26  $\mu\text{g}/\text{kg}$  given to patients with adult-onset growth hormone deficiency have resulted in side effect rates of 40% to 70%; side effects include edema, arthralgias, and the carpal tunnel syndrome [7, 20]. In our study, only 4 of 17 patients receiving growth hormone developed side effects that resolved with dose reduction. This suggests that IGF-1 levels may help guide growth hormone replacement in adult-onset growth hormone deficiency and that maintenance of normal levels of IGF-1 may eliminate side effects.

Our relatively small patient sample limits definitive conclusions about growth hormone dosing in adults, but these data suggest that IGF-1 levels in patients receiving growth hormone should be kept below the upper limit of the age-appropriate normal range and that a daily dose of 6  $\mu\text{g}/\text{kg}$  (with subsequent adjustment as necessary) may be a reasonable starting point. Despite the limited side effects seen during our 18-month study, we do not know whether such an approach might produce side effects over several years.

Two patients had adverse vascular events during the study. It is unlikely that either of these events was related to growth hormone therapy. Both patients had preexisting risk factors for vascular disease, and previous data suggest that patients with growth hormone deficiency may be at increased risk for death from vascular events [12]. Furthermore, although acromegaly (an extreme example of growth hormone excess) can be associated with left ventricular hypertrophy and cardiomegaly, the prevalence of macrovascular disease is not increased [33, 34]. This suggests that the modest doses of growth hormone used in our study were not responsible for worsening atherosclerosis.

Certain limitations of the design and scope of our study prevent firm conclusions about the benefits of growth hormone therapy in patients with adult-onset growth hormone deficiency. A study of this size and duration could not determine whether changes in bone density and body composition will translate into improvements in such functional end points as fracture rates and cardiovascular illness. Furthermore, changes in body composition, although statistically significant, were modest and of unclear clinical significance. Because we do not have data on changes in bone density and body composition after discontinuation of growth hormone therapy, the extent to which these changes depended on continued administration of growth hormone is uncertain. Finally, because of differences in bone density and body composition between men and women, our study was limited to men. It is unknown whether our results can be applied to women.

In summary, we showed that long-term growth hormone therapy in patients with adult-onset growth hormone deficiency increases bone density at two skeletal sites, decreases body fat, and increases lean mass. Doses were much lower than those typically used in studies of adults with growth hormone deficiency and were adjusted according to serum levels of IGF-1. As a result, measurable effects were achieved with a low incidence of side effects. The long-term clinical significance of these metabolic changes is unknown, but these data suggest that larger studies using true clinical end points, such as fracture rates, are warranted. Studies should also be done in women to determine whether these positive metabolic changes are seen in both sexes. A recommendation for routine therapy with growth hormone replacement in patients with adult-onset growth hormone deficiency must await the outcome of such investigation.

Drs. Biller and Klibanski and Ms. Baker Cannistraro: Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit Street, BUL457B, Boston, MA 02114.

Dr. Finkelstein: Endocrine Division, Massachusetts General Hospital, 55 Fruit Street, BUL327, Boston, MA 02114.

Dr. Oppenheim: Division of Endocrinology, Maine Medical Center, 22 Bramhall Street, Portland, ME 04102.

Dr. Schoenfeld: General Clinical Research Center, Massachusetts General Hospital, 55 Fruit Street, White 13, Boston, MA 02114.

Ms. Hoskins Michel: MGH Institute of Health Professions, 101 Merrimac Street, Boston, MA 02114.

Ms. Wittink: New England Medical Center, Box 298, 750 Washington Street, Boston, MA 02111.

## Author and Article Information

From the Massachusetts General Hospital, Boston, Massachusetts; and the Maine Medical Center, Portland, Maine.

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**Requests for Reprints:** Anne Klibanski, MD, Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit Street, BUL457B, Boston, MA 02114.

**Current Author Addresses:** Dr. Baum: 7777 Forest Lane, Suite C-218, Dallas, TX 75230.

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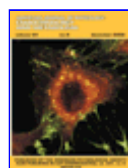
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