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Treatment of Adults with Growth Hormone (GH) Deficiency with Recombinant Human GH*

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ABSTRACT

In a double blind, cross-over placebo-controlled trial, we studied the effects of 26 weeks of replacement therapy with recombinant human GH on body composition, metabolic parameters, and well-being in 10 patients with adult-onset GH deficiency (GHD). All patients received appropriate thyroid, adrenal, and gonadal replacement therapy. The dose of recombinant human GH was 0.25–0.5 U/kg·week (0.013–0.026 mg/kg·day) and was administered sc daily at bedtime. One patient was withdrawn from the study because of edema and atrial fibrillation. Body composition was estimated with three independant methods: computed tomography, bioelectric impedance, and total body potassium combined with total body water assessments. The Comprehensive Psychological Rating Scale and the Symptom Check List-90 were used to assess any change in psychopathology.

After 26 weeks of treatment, adipose tissue (AT) mass decreased 4.7 kg ($P < 0.001$). Subcutaneous AT decreased by an average of 13%, whereas visceral AT was reduced by 30%. Muscle volume increased by 2.5 kg (5%; $P < 0.05$). According to the four-compartment model derived from assessments of total body potassium and total body water, body cell mass and extracellular fluid volume increased significantly by 1.6 and 3.0 kg, whereas body fat decreased by 6.1 kg. Results obtained by the bioelectric impedance technique were similar.

The mean (±SD) concentrations of insulin-like growth factor-I increased from 0.26 (0.06) at baseline to 2.56 (1.55) and 2.09 (1.03) kU/L after 6 and 26 weeks of treatment. Calcium and serum phosphate, osteocalcin, and procollagen-III concentrations were significantly higher, and intact PTH concentrations were reduced after 6 and 26 weeks of treatment, respectively. Total and free T_3 concentrations were significantly increased after 6 and 26 weeks of treatment, whereas free T_4 concentrations were reduced at 6 weeks, but after 26 weeks, free T_4 concentrations had returned to pretreatment values. Finally, after 26 weeks of treatment, there was a decrease in the Comprehensive Psychological Rating Scale score ($P < 0.05$).

The results show that GH replacement in GHD adults results in marked alterations in body composition, fat distribution, and bone and mineral metabolism and reduces psychiatric symptoms. Finally, we conclude that the observed beneficial effects of replacement therapy with GH are of sufficient magnitude to consider treatment of GHD adults. (*J Clin Endocrinol Metab* **76:** 309–317, 1993)

ADULTS with hypopituitarism have so far received replacement therapy with thyroid hormones and adrenal and sex steroids, but not GH, although it is well documented that GH is secreted in adult life. Falkheden (1) showed 30 yr ago that hypophysectomy in adults decreased the basal metabolic rate, cardiac output, the glomerular filtration rate, and blood volume. These changes were not reversed with conventional replacement therapy, suggesting that GH deficiency (GHD) caused some of the alterations observed. Over the last few years, several studies have also indicated an important role of GH in adults. GHD adults are overweight due to an increase in body fat (BF) (2), and they have reduced bone mineral content (3).

Replacement therapy with GH in adults had not been previously considered due to the limited supply of GH from human pituitaries. However, when GH treatment of humans was initiated in the 1950s, GH treatment of adults with GHD in a few cases was found to increase vigor, ambition, and sense of well-being (4).

With the advent of recombinant human GH (rhGH), it has been possible in controlled clinical studies to explore the effects of GH replacement in adults with GH deficiency. Studies from England (5) and Denmark (6) have documented the effects of GH treatment in GHD adults on body composition, metabolism, and quality of life. In the present study, we used a double blind, cross-over design to evaluate the effects of GH replacement in adults.

Subjects and Methods

Study design

This was a double blind, cross-over, placebo-controlled study using rhGH (Humatrope, Eli Lilly Co., Indianapolis, IN) in patients with established GHD. The patients were studied for a total period of 12 months and were randomized to one of two treatment groups: 1) 6-month treatment with rhGH, followed by 6-month treatment with placebo; or 2) 6-month treatment with placebo, followed by 6-month treatment with rhGH. Eli Lilly Co. provided the randomization codes, which were broken only after the last patient had completed the study. Informed consent was obtained from the patients. The study was approved by the ethical committee of the medical faculty of the University of Goteborg and the Swedish Board of Health, Stockholm.

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Treatment

The dosage of rhGH was 0.5 U/kg·week (0.026 mg/kg·day), administered sc by the patient before bedtime. In patients who experienced side-effects (see below), the dosage was reduced by 50%. The vials of rhGH contained 16 U (5.92 mg). The placebo vials contained the same vehicle as the rhGH vials and were visually indistinguishable. Between the injections, opened vials were stored at 5–12 C and protected from light for a maximum of 7 days.

Study protocol

Patients were studied as in-patients in the metabolic ward for 1 week before treatment with placebo or active therapy, and thereafter at 6 and 26 weeks of treatment with both placebo as well as rhGH. The patients were also seen at the out-patient clinic at monthly intervals. Thirty days before starting the study, the patients were interviewed by a dietician, and a 24-h diet recall was performed. The patients received dietary instructions in order to obtain metabolic balance and stable weight. On the metabolic ward, food intake was standardized. Body weight was measured in the morning to the nearest 0.1 kg using a Statmos balance; the patient was weighed in underwear, without shoes and after voiding. Body height was measured to the nearest 0.01 m.

Patients

Ten patients, 34–58 yr, who regularly visited the out-patient clinic at the Division of Endocrinology because of adult-onset pituitary insufficiency were asked to participate in the study (Table 1). All patients had been treated with adequate replacement therapy of glucocorticoids (cortisone acetate, 25–50 mg/day), thyroid hormones (L-T_4, 0.1–0.15 mg/day), and sex hormones. Mean GH concentrations were less than 1 mU/L, measured in 48 samples collected at 30-min intervals over a 24-h period, and in this GH profile, no significant peaks in plasma GH concentration were detected [determined with the Pulsar program (7), as previously described (8)]. After insulin-induced hypoglycemia, all patients had GH concentrations below 1 mU/L. None of the patients had previously been treated with GH. Four patients received bromocriptine (2.5–10 mg/day). In three patients (no. 6, 8, and 9), the dose of L-T_4 was increased from 0.1 to 0.15 mg/day during treatment due to decreasing concentrations of free T_4 (see below).

Specimen collections and biochemical assays

Blood samples were drawn in the morning after an overnight fast. Twenty-four-hour collections of urine and feces were made for nitrogen and electrolyte measurements. Plasma GH concentrations were determined by an immunoradiometric assay according to the manufacturer's protocol (Pharmacia, Uppsala, Sweden), as previously described (8). All samples from each patient were run in the same assay. Patient samples were assayed in duplicate. The concentration of insulin-like growth factor-I (IGF-I) was determined by two different methods. Using a nonextraction assay of EDTA plasma (Nichols Institute Diagnostics, San Juan Capistrano, CA), low affinity bound analyte was determined. For the sake of brevity, in this paper we refer to this concentrations as free IGF-I, although the actual free concentration may be different (reference limits: men, 0.34–1.9 kU/L; women, 0.45–2.2 kU/L). Total serum IGF-I was determined by an immunoradiometric assay after formic acid-ethanol extraction (Byk-Sangtec Diagnostica GmbH, Dietzenbach, Germany). The reference limits for adults have not been defined, but judging from results in children up to the age of 18 yr, the lower reference limit is around 80 μg/L.

Serum free T_4 and free T_3 were determined by ligand analog RIAs (Amerlex M, Amersham International plc, Aylesbury, Buckinghamshire, United Kingdom), and serum total T_3 by a polyethylene glycol-assisted double antibody RIA (Diagnostic Products Corp., Los Angeles, CA). Intact PTH was determined by immunoradiometric assay (Nichols Institute Diagnostics), osteocalcin by a double antibody RIA (International CIS, Gif-sur-Yvette, France), and the amino-terminal peptide of procollagen-III by immunoradiometric assay (Hoechst-Behringwerke, Marburg, Germany). Methods currently used at the Department of Clinical Chemistry were used for the following determinations: blood erythrocytes, leukocytes, hemoglobin, glycosylated hemoglobin, and glucose; serum electrolytes, phosphate, creatinine, total protein, bilirubin, cholesterol, and triglycerides; and serum activities of asparate aminotransferase (EC 2.6.1.1.), alanine aminotransferase (EC 2.6.1.2.), and alkaline phosphatases (EC 3.1.3.1).

Body composition

Body composition was determined by assessment of total body potassium (TBK), total body water (TBW), total body nitrogen (TBN), bioelectrical impedance (BIA), and computed tomography (CT). Except for CT, body composition assessments were performed before and after 6 and 26 weeks in each treatment period. CT was performed before and after 26 weeks in each period.

TBK was determined in a whole body counter, and TBW was measured by an isotope dilution technique using tritiated water as a tracer, as described previously (10). In this study, we used the assessments of TBK and TBW derived from tritiated dilution to calculate body composition in terms of a four-compartment model, *i.e.* BF, extracellular water,

TABLE 1. Clinical and biochemical characteristics of the 10 patients included in the study

Case no.	Age (yr)	Sex	Cause of pituitary deficiency	Diagnosis[a]	Mean GH conc. (mU/L)[b]	Max GH conc. after ITT (mU/L)[c]	Free IGF-I (kU/L)[d]	Total IGF-I (μg/L)[e]
1	57	M	Chromophobe adenoma (op)	TAG	<0.3	<0.3	0.28	89
2	58	M	Chromophobe adenoma (op)	TAG	<0.3	<0.3	0.25	60
3	54	M	Prolactinoma (op)	TAG	<0.3	<0.3	0.22	112
4	34	M	Prolactinoma (op)	TAG	<0.3	<0.3	0.41	144
5	34	M	Prolactinoma (op)	TAG	<0.3	<0.3	0.26	88
6	36	M	Meningeoma (op)	TAG	<0.3	<0.3	0.25	75
7	46	F	Prolactinoma (irr)	TAG	0.33	0.97	0.20	54
8	52	M	Chromophobe adenoma (op)	TAG	<0.30	<0.3	0.22	58
9	51	M	Chromophobe adenoma (op)	TAG	<0.3	0.44	0.26	77
10	43	M	Prolactinoma (op)	TAG	<0.3	0.53	0.30	107

[a] T, Thyroid deficiency; A, adrenal deficiency; G, gonadal deficiency.
[b] Mean of 24-h GH profile (48 samples).
[c] Maximum GH concentration after iv insulin tolerance test.
[d] For the definition of free and total IGF-I, see *Materials and Methods.*

body cell mass, and fat-free extracellular solids. The details of this four-compartment model have been described previously (10).

TBN was measured by *in vivo* neutron activation. A ^{252}Cf source was used to produce the neutrons. The accuracy was approximately ±4%.

BIA was measured in the supine position after voiding. BIA-101 equipment (RJL System, Inc., Detroit, MI) was used, according to the manufacturer's instructions. TBW, fat-free mass (FFM), and BF were calculated according to equations supplied by the manufacturer.

Adipose tissue (AT) and muscle volumes were determined by CT using a Philips Tomoscan 310 (Mahway, NJ), as described previously (11–15). Scanning was performed at 120 kV, with a slice thickness of 12 mm. The patients were examined in the supine position with arms stretched above the head. Twenty-two transsectional scans (14) were obtained at each investigation. In each scan, the area of all picture elements (pixels) in the attenuation interval −190 to −30 Hounsfield units was defined as AT (11–13). Visceral AT was defined as all AT within the abdominal and thoracic cavities. Below the level of Th8, the visceral AT was approximately divided into intra- and retroperitoneal AT by means of cursor separations (15). In each scan, the total area of all soft tissue except AT was determined by keeping the cursor in the air when encircling the body and by summing up the area of pixels in the attenuation interval −29 to 151 Hounsfield units within the circumscription (15). The area of visceral organs (except visceral AT) was obtained in the same attenuation interval by keeping the cursor just inside the muscle-bone wall of the trunk when encircling viscera. Brain areas were obtained in a similar way. The total soft tissue area minus the area of visceral organs or brain constituted the area of skeletal muscle plus skin plus red bone marrow. The current study was started before the multicompartment technique (15) was fully developed and before we had developed methods to separate muscle, skin, and red bone marrow from each other. For reasons of simplicity, the latter three organs are called muscle in this report. Artefacts due to beam hardening were corrected for, as described previously (12, 15).

The distances between scans were measured from frontal scanograms to the nearest millimeter. Total tissue volumes (V) (AT, visceral organs, or muscle) were calculated as

$$V = \sum_{1}^{23} \frac{a(b + c)}{2}$$

where a is the distance between two adjacent scans, and b and c are the areas of muscle, visceral organs, and sc or visceral AT of these two scans. The AT volumes of the following regions were determined: legs, sc trunk, head and neck, arms, ip, and retroperitoneal. Changes in AT distribution were studied by expressing each AT depot as a percentage of the total AT before and after treatment.

The reproducibility of the CT technique is high. As calculated from complete double determinations, the error of the AT method was 0.6% (14).

Psychiatric evaluation

All patients were examined by a psychiatrist (A.S.). The examinations were performed during in-patient examinations 1 week before and 26 weeks after each treatment period. All examinations were performed in the morning of the third day of the in-patient examinations. The psychiatric examination was comprised of a general psychiatric interview covering anamnesis and status. Two rating scales were included, the Comprehensive Psychological Rating Scale (CPRS) (17) and the Symptom Check List-90 (SCL-90) (18, 19).

Statistical methods

One patient (no. 1) did not complete the study, and results from this patient were excluded from the analyses. Analysis of variance was used. Since the subjects were treated according to two different sequences (placebo/rhGH or rhGH/placebo), the placebo/rhGH group was evaluated separately to study possible changes during the 26-week placebo period preceding GH treatment, and the GH/placebo group was analyzed separately to study the effect of withdrawal of rhGH treatment. To analyze the effect of rhGH treatment, both groups were pooled, using values obtained in the week preceding the initiation of active treatment as pretreatment values. All of these analyses were performed in complete blocks. Analysis of variance was followed by the Student-Newman-Keuls test. $P < 0.05$ was considered significant.

Results

Pretreatment period (placebo/rhGH group; n = 5)

There were no significant changes in any of the variables analyzed during the placebo period in the group starting with placebo (data not shown).

Effects of rhGH treatment (n = 9)

Biochemical findings. Concentrations of erythrocytes, leukocytes, and platelets were unchanged over the treatment period. There were no changes in serum concentrations of sodium or potassium. Serum concentrations of creatinine were lower during than before treatment. There were no changes in liver enzyme or bilirubin concentrations (data not shown). Blood glucose and fasting insulin concentrations did not change significantly, nor did the percentage of glycosylated hemoglobin. In seven subjects with normal serum concentrations at baseline, neither cholesterol nor triglyceride concentrations changed significantly. However, in two subjects with initial hypertriglyceridemia, the triglyceride concentrations decreased markedly during treatment (pretreatment concentrations, 3.6 and 4.9 mmol/L; posttreatment concentrations, 1.9 and 1.7 mmol/L, respectively).

Free and total IGF-I concentrations increased markedly during treatment (Table 2 and Fig. 1). All but one subject had free IGF-I concentrations below the lower reference limit before the start of the study. Four of the five subjects who completed the study with unchanged dose of rhGH had free IGF-I concentrations above the upper reference limit after 26 weeks. Among the four subjects who obtained a reduced rhGH dose, all had concentrations of free IGF-I within reference limits after 26 weeks of treatment (Fig. 1).

After 6 weeks of treatment, there was an increase in total and free T_3 concentrations, whereas free T_4 concentrations were decreased. The ratio of free T_3/free T_4 increased markedly (Table 2). After 26 weeks, however, T_3 concentrations were still elevated compared to pretreatment concentrations, but were significantly lower than those after 6 weeks of treatment. Free T_3 concentrations at 26 weeks were unchanged compared to concentrations after 6 weeks, but free T_4 concentrations had returned to pretreatment values. Correspondingly, the ratio of free T_3/free T_4 was lower after 26 weeks than that after 6 weeks, but it was still higher than before treatment.

Calcium as well as serum phosphate concentrations were significantly higher after 6 and 26 weeks of treatment compared to concentrations before treatment (Table 3). Magnesium concentrations were unchanged. PTH concentrations were reduced after 6 and 26 weeks of treatment. Osteocalcin concentrations increased after 6 weeks of treatment and increased further after 26 weeks (to 3–4 times the normal mean; Fig. 2). The concentrations of the amino-terminal peptide of procollagen-III increased after 6 weeks of treatment (to 4–5 times the normal mean). After 26 weeks of

TABLE 2. Effects of GH treatment on IGF-I and thyroid hormone concentrations

Analyte[a]	Conc.[b]		
	0	6 weeks	26 weeks
Free IGF-I (kU/L; *0.34–1.90*)	0.26 (0.06)	2.56 (1.55)[c]	2.09 (1.03)[c]
Total IGF-I (μg/L; *80–600*)[d]	86 (30)	525 (167)[c]	522 (177)[c]
T_3 (nmol/L; *1.0–3.0*)	1.6 (0.31)	2.2 (0.45)[c]	2.0 (0.46)[c,e]
Free T_3 (pmol/L; *3.3–8.2*)	4.7 (1.37)	6.7 (1.30)[c]	6.2 (1.68)[c]
Free T_4 (pmol/L; *10.8–23.0*)	12.4 (3.40)	8.9 (2.80)[c]	11.1 (3.1)
Free T_3/free T_4 (*0.36–0.40*)	0.39 (0.13)	0.78 (0.17)[c]	0.58 (0.14)[c,e]

Values are means, with the SD in parentheses.
[a] Reference intervals in *italics*.
[b] Concentrations before treatment (0) and after 6 and 26 weeks of treatment in samples obtained after an overnight fast.
[c] Significant difference *vs.* pretreatment concentration.
[d] Provisional data; reference interval study under way.
[e] Significant difference *vs.* values obtained at 6 weeks.

treatment, the peptide concentrations were somewhat lower, but still elevated compared to pretreatment concentrations (Table 3). Thus, the concentration changes of this peptide paralelled those of the free T_3/free T_4 ratio (Tables 2 and 3).

Body composition (Table 4). After an initial increase in average body weight of 2.6 kg (P = NS) after 6 weeks of treatment, it was reduced by 3.7 kg ($P < 0.05$); after another 20 weeks of treatment, body weight was 2.1 kg (P = NS) lower than at entry into the study.

After 26 weeks of treatment, the four-compartment model showed an increase in body cell mass and extracellular water of 1.6 and 3.0 kg, respectively, whereas BF had decreased by 6.1 kg. By definition, fat-free extracellular solids did not change, since this compartment was considered to be a constant fraction of ideal body weight in relation to height in this model. Thus, FFM increased by 4.6 kg, while BF was reduced by 6.1 kg (Table 4).

Results obtained with the BIA technique were similar. Compared to values at the start of the study, FFM increased by 3.9 kg, and BF decreased by 6.0 kg after 26 weeks of GH treatment. Similar TBW values were obtained using the BIA technique and tritium dilution both before and at the end of the rhGH treatment period. The increase in FFM was due to both water and nitrogen retention (Table 4).

With the BIA technique, observations were also available after 6 weeks of treatment. The reduction in BF was almost completed after 6 weeks. The increase in body weight was mainly due to water retention (5.9 L), although nitrogen retention also contributed (Table 4). Interestingly, at 26 weeks, 50% of this initial water retention was eliminated in spite of additional, albeit not significant, nitrogen retention. In relative terms, TBW constituted 52.7% of body weight before treatment and 57.5% after 6 and 26 weeks of treatment (Table 4). BF decreased from 24.5% of body weight at the start of the study to approximately 18% after 6 and 26 weeks of GH treatment.

Compared to pretreatment values, TBN had increased by 13.4% at 26 weeks, while TBK had increased by only 4.8%.

The CT technique disclosed a decrease ($P < 0.001$) in AT mass of 4.7 kg, which was explained by decreases in sc and visceral AT of 3.1 ($P < 0.01$) and 1.6 kg ($P < 0.001$), respectively. Subcutaneous AT decreased by an average of 13%, whereas visceral AT was reduced by 30% (Figs. 3 and 4). AT was significantly redistributed ($F = 17.97$; $P < 0.001$) from visceral to sc locations (Fig. 3).

The CT determinations showed an increase in muscle volume of 2.4 kg (5%; $P < 0.05$) and in visceral organ volume by 0.7 kg (17%; $P < 0.01$). TBN increased by 8% and 13% compared to pretreatment levels after 6 and 26 weeks of treatment, respectively.

Psychiatric evaluation. None of the patients suffered from serious psychiatric disease. Complaints before treatment were mainly tiredness, low energy and lack of initiative, lack of concentration, memory difficulties, and irritability. After 26 weeks of GH treatment, there was a significant change in the CPRS score, *i.e.* seven patients had a decreased score, one had an unchanged score, and one had an increased score ($P < 0.05$). No significant change in the results of the SCL-90 were noted.

Side-effects (Table 5). One patient withdrew from the study due to atrial fibrillation after 6 weeks of treatment. Before this, he had experienced swelling around the ankles after 1 week of treatment, which increased further. Body weight had increased after 6 weeks of treatment from 69.2 to 73.5 kg, and BIA disclosed a 7.9-L increase in TBW. After withdrawal from the study and treatment with digitalis gluconides, heart rhythm normalized after 2 days, and body weight returned to pretreatment values after a further 2 weeks. X-Ray of the heart was normal. His free T_4 concentration decreased from 15.7 to 8.9 pmol/L, and free and total T_3 concentrations increased from 5.9 to 7.7 pmol/L and 1.8 to 2.5 nmol/L, respectively.

In the remaining patients, six observed adverse effects during the first month of treatment, mainly due to fluid retention. One patient reported arthralgia in large joints, and one reported swollen fingers. One patient developed a carpal tunnel syndrome, which persisted in a mild form. In four of these six patients, the dose of rhGH was decreased, and the fluid retention and artrhalgia disappeared. Another patient experienced tinnitus, which started 16 weeks after the initiation of treatment.

Changes during the withdrawal period (n = 4; Figs. 1 and 2). There were four patients in the rhGH/placebo group. Due

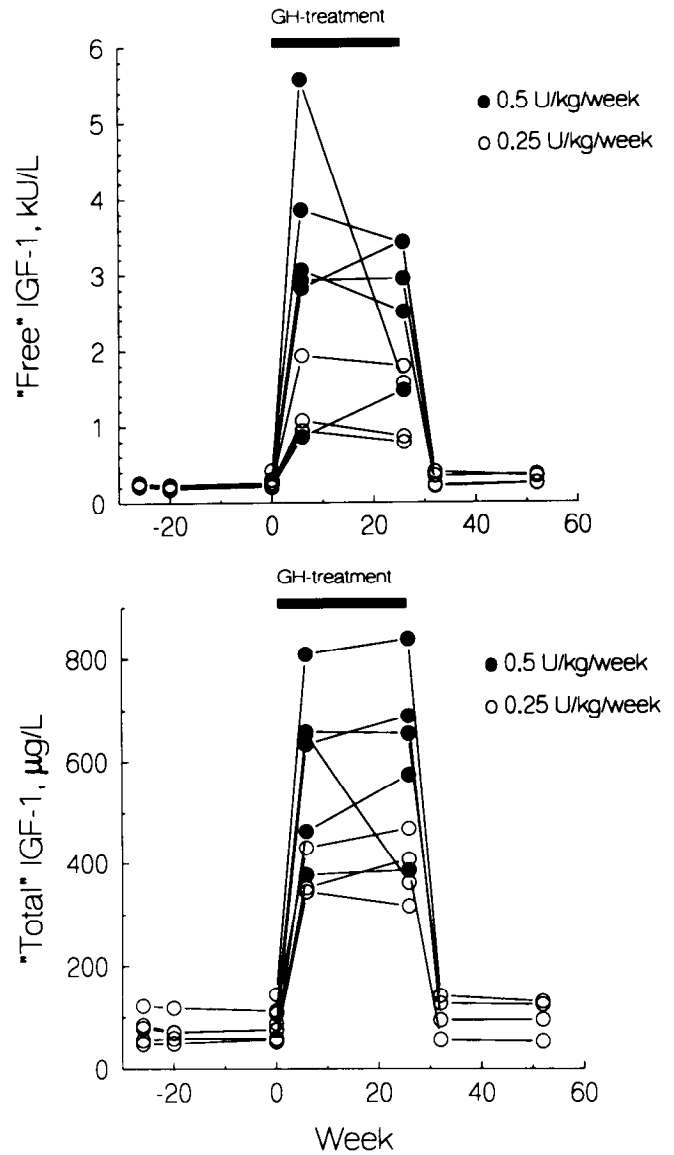

FIG. 1. Free and total IGF-I concentrations during the administration of placebo [weeks −26 to 0 (five patients); weeks 26–52 (four patients)] and rhGH (weeks 0–26; nine patients). In five subjects, the dose of rhGH was 0.5 U/kg·week (0.026 mg/kg·day), and in four, it was 0.25 U/kg·week (0.013 mg/kg·day).

to the small number of patients, none of the variables that were affected by rhGH treatment in the pooled patient sample reached statistical significance in this subgroup of patients. There was no significant difference between values obtained before treatment and those obtained after 26 weeks of withdrawal from treatment for any of the variables analyzed. Significant changes during treatment were observed in creatinine, total T_3, free T_3, and PTH concentrations, all of which had returned to pretreatment values after 26 weeks of withdrawal. IGF-I, osteocalcin, and procollagen-III peptide concentrations were higher during treatment in these four patients and had returned to pretreatment levels by 6 weeks after withdrawal of rhGH.

With respect to the psychiatric evaluation, all four patients had higher scores on the CPRS scale 26 weeks after withdrawal of rhGH treatment. On the SCL-90 scale, two patients had an increased score, and two had unchanged scores. One patient (no. 7) suffered from withdrawal to the extent that she was evaluated for mild depression.

TABLE 3. Effects of GH treatment on components related to bone and connective tissue metabolism

Analyte[a]	Conc.[b]		
	0	6 weeks	26 weeks
Calcium (mmol/L; *2.2–2.6*)	2.28 (0.09)	2.40 (0.06)[c]	2.41 (0.11)[c]
Phosphate (mmol/L; *0.8–1.4*)	1.22 (0.21)	1.82 (0.19)[c]	1.81 (0.23)[c]
Magnesium (mmol/L; *0.7–1.2*)	0.84 (0.14)	0.74 (0.10)	0.79 (0.06)
PTH (ng/L; *10–65*)	23 (10.5)	15 (7.3)[c]	18 (7.0)[c]
Osteocalcin (µg/L; *1.9–11*)	6.5 (2.9)	13.5 (3.6)[c]	19.3 (4.4)[c,d]
P-III-NP (kU/L; *0.3–0.8*)[e]	0.7 (0.39)	2.3 (0.32)[c]	1.7 (0.56)[c,d]

Values are means, with the SD in parentheses.
[a] Reference intervals in *italics*.
[b] Concentrations before treatment (0) and after 6 and 26 weeks of treatment in samples obtained after an overnight fast.
[c] Significant difference *vs.* pretreatment concentrations.
[d] Significant difference *vs.* concentrations at 6 weeks.
[e] P-III-NP, Amino-terminal peptide of procollagen-III; central 0.90 interfractile interval.

Discussion

We have shown that 6 months of treatment with rhGH in GHD adults results in marked alterations in body composition estimated by three independent methods. Fat mass decreased, on the average, by 20%, and AT was redistributed from visceral to sc locations. Extracellular fluid volume and muscle volume increased. Treatment with rhGH also resulted in marked metabolic changes, indicating altered energy metabolism, ground substance, and bone and mineral homeostasis.

There are two recently reported placebo-controlled studies in adults with GHD receiving replacement therapy with rhGH. Salomon *et al.* (5) performed a double blind parallel group trial over 6 months in patients with acquired GHD in adult life, and Jörgensen *et al.* (6) performed a 4-month cross-over study with a wash-out period of 4 months in patients who during childhood had been treated for GHD. In our study, which was initiated at the same time as the other two studies, we designed the trial as a double blind, cross-over study. We did not include a wash-out period, since the duration of such a period could not be predetermined when the study was planned. In fact, the results from this study and previous work (6) indicate that several effects of GH replacement may last for several months. Thus, we did not perform a classical analysis of placebo *vs.* active treatment, since there are substantial carryover effects of GH treatment. In fact, GH is believed to have specific effects not only on cell growth, but also on cell differentiation, for example in AT, skeletal muscle, and cartilage (20). In this context, it is, therefore, not surprising that many effects of GH may be

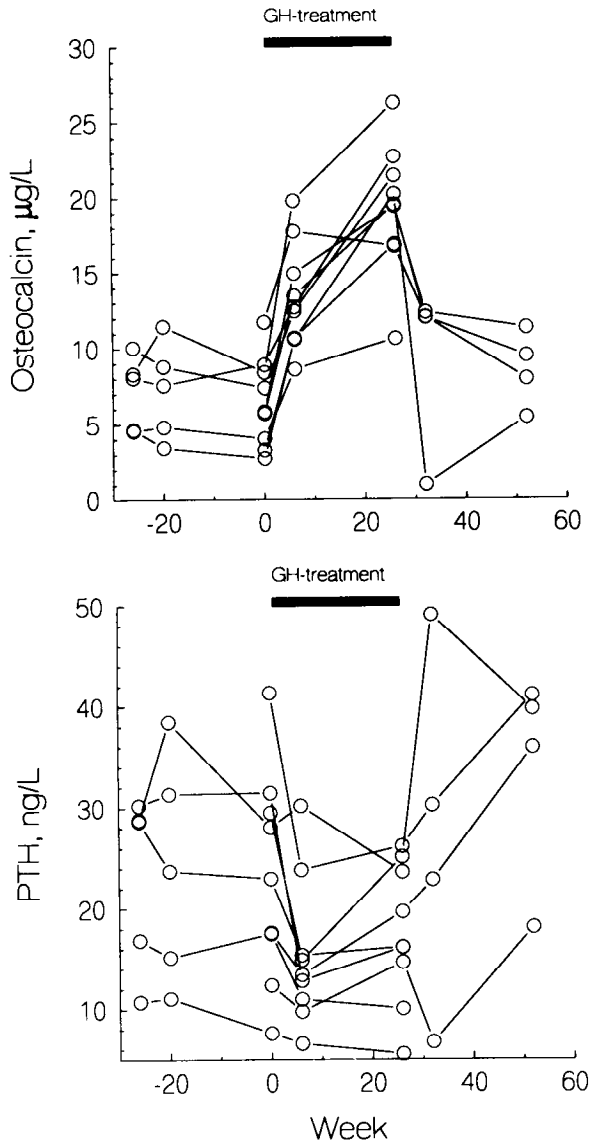

FIG. 2. Osteocalcin and intact PTH concentrations during the administration of placebo [weeks −26 to 0 (five patients); weeks 26–52 (four patients)] and rhGH (weeks 0–26; nine patients).

TABLE 4. Effects of GH treatment on body composition

Variable	Result[a]		
	0	6 weeks	26 weeks
Wt (kg; n = 9)	94.3 (20.9)	96.8 (20.2)	92.2 (21.1)[b]
BIA measurements (n = 9)			
TBW (L)	49.7 (10.5)	55.6 (10.7)[c]	53.0 (10.0)[b,c]
BF (kg)	23.1 (8.3)	17.3 (8.8)[c]	17.1 (5.8)[c]
FFM (kg)	71.2 (16.4)	79.6 (16.7)[c]	75.1 (16.1)[b,c]
Four-compartment model (n = 8)			
TBW (L)[d]	49.3 (12.5)	54.1 (11.2)[c]	53.0 (12.1)[c]
TBK (mmol)	4206 (1026)		4407 (991)[c]
Body cell mass (kg)	35.1 (8.5)		36.7 (8.3)[c]
Extracellular fluid vol (kg)	22.5 (6.9)		25.5 (6.9)[c]
BF (kg)	26.9 (9.5)		20.7 (8.3)[c]
Fat-free extracellular solids (kg)	9.5 (0.98)		9.6 (0.97)
Neutron activation (n = 9)			
TBN (kg)	2.01 (0.59)	2.18 (0.54)[c]	2.28 (0.53)[c]

Values are means, with the SD in parentheses.
[a] Results obtained before treatment (0) and after 6 and 26 weeks of treatment.
[b] Significant difference *vs.* values obtained at 6 weeks.
[c] Significant difference *vs.* pretreatment value.
[d] Obtained from isotope dilution using tritiated water as a tracer.

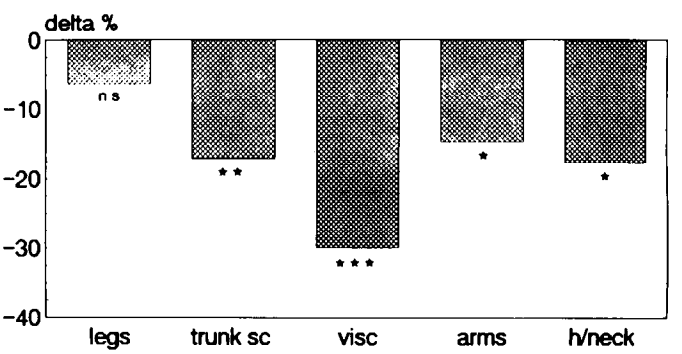

FIG. 3. Changes in different AT depots, estimated from CT, after 26 weeks of treatment with rhGH. The amount of AT in legs, sc trunk, visceral depot, arms, and head/neck areas decreased by 6.3%, 17.1%, 29.9%, 14.7%, and 17.7%, respectively.

long-lasting. Salomon *et al.* (5) included some patients previously treated for Cushing's disease, which could have long-lasting effects on body composition and psychometric testing. Similar to the report of Salomon *et al.* (5), we included only patients with complete GHD. In fact, none of the patients had GH concentrations above 1 mU/L. In the study by Jörgensen *et al.* (6), patients were included with GH levels below 10 mU/L after conventional tests.

The marked effect of GH replacement on body composition in GHD adults has been demonstrated previously (5, 6), although not with multiscan CT techniques. GH has profound lipolytic effects (21), resulting in a decrease in total BF despite elevated levels of insulin (5). In the present study, reduced BF and increased FFM were documented with three different body composition techniques. The redistribution of body carbon from AT lipids to proteins of lean tissues is expected to be energy requiring, and we (unpublished) and others (5) observed increasing energy expenditure in GH-treated subjects.

The CT technique also demonstrated a redistribution of AT from visceral to sc depots. Using anthropometric techniques, several researchers (22–26) have demonstrated a redistribution from sc trunk to more peripheral regions when treating GHD children with GH. These changes have been associated with GH-induced reductions of the antilipolytic effect of insulin, which is markedly different in different AT regions (27). The resulting increase in visceral AT may be one mechanism (28) behind the increased cardiovascular mortality observed in adult GHD patients (29).

The various methods applied in this study to assess the anabolic effects of GH treatment disclosed differences in the magnitude of observed changes. There was a 13% increase

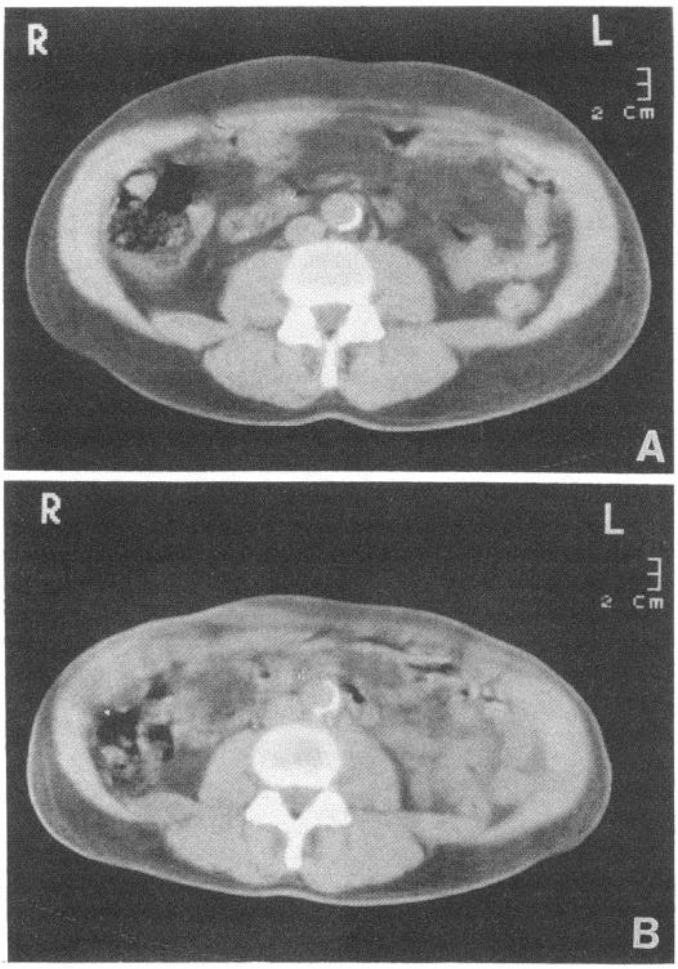

FIG. 4. CT scan at the L3-L4 level (patient 2) before (A) and after 26 weeks of treatment with rhGH (B). The scan clearly demonstrates the reduction of both visceral and sc AT (shown in the pictures as *dark grey*).

TABLE 5. Side-effects during treatment with rhGH

Case no.	Side-effects	rhGH treatment
1	Oedema, atrial fibrillation	Discontinued
2	Swollen fingers	Decreased dose
3	Oedema, tinnitus	Decreased dose
4	None	
5	Carpal tunnel syndrome	
6	Arthralgia	Decreased dose
7	None	
8	Transient oedema	
9	Oedema	Decreased dose
10	None	

in TBN, but only a 5% increase in TBK and muscle mass, determined by CT. Thus, the nitrogen/potassium ratio increased during GH treatment. One possible explanation for this discrepancy could be that GH treatment promotes increased formation of extracellular structural proteins such as collagen, which are not detected by measuring potassium.

GH treatment resulted in an expansion of extracellular fluid volume. The antinatriuretic action of GH was demonstrated in the 1950s (30) and was later shown to be independent of aldosterone (31). Later studies (32) have suggested that the antinatriuretic action of GH is a tubular effect and that GH acts by increasing the sodium pump activity. In GHD adults (2), the volume of extracellular fluid is decreased by approximately 15%, and in acromegaly, it is increased by 25% (33). In our study, TBW, determined by BIA, increased, on the average, by 6 kg after 6 weeks of treatment, but after 26 weeks, TBW was only 4 kg higher than at baseline. In fact, there was a significant fall in TBW between 6–26 weeks. An alleged sodium transport inhibitor could be triggered by the volume expansion and may explain the later decrease in TBW (34).

We found that GH replacement resulted in a decrease in free T_4 concentrations and an increase in total and free T_3 concentrations. These findings agree with those reported by others (35–37). These changes were observed regardless of whether the patients were treated with thyroid hormones (38). In our study, the decrease in free T_4 concentrations was noted and taken as a sign of the possible need for increasing the replacement doses. This consideration was based upon reports on GH treatment of GHD children, in whom treatment has been shown to reduce T_4 concentrations. In some patients, this reduction was accompanied by a decreased growth response, which was improved after T_4 substitution (39), indicating an increased need for thyroid hormones after GH therapy. However, GH treatment in adults increases resting heart rate (6) as well as basal metabolic rate, and these effects may be partly due to an increased conversion of T_4 to T_3. Such a mechanism may be involved in our first patient, who developed atrial fibrillation. Perhaps, in contrast to the experience in children, caution should be used when increasing the dosage of thyroid hormones in adults given GH replacement.

Use of the amino-terminal peptide of procollagen-III as an indicator of the effects of GH on collagen metabolism and of osteocalcin as an indicator of bone effects was first reported from this laboratory in studies of GHD children (40–42). The concentration changes with time in the amino-terminal collagen-III peptide in our patients agree with the findings in children (43–45). Also, the continued increase in mean osteocalcin concentrations throughout the study is in accordance with the observations in children (41, 46, 47) and shows that, in adults also, GH treatment has marked effects on bone and connective tissue. It is known that bone mineral content is decreased in GHD (3), and it is possible that long term treatment of GHD adults with GH may normalize these changes.

To our knowledge, there is only a single report on serum PTH concentrations during GH therapy (48). In that 7-day study of GH administration to healthy elderly volunteers, there was no discernible effect on serum calcium concentrations, but urinary calcium excretion increased. Serum PTH concentrations increased, as did the concentrations of phosphate, 1,25-dihydroxyvitamin D, and osteocalcin. We found a decrease in intact PTH concentrations after 6 and 26 weeks concomitant with increased total calcium concentrations. The latter may be a result of increased formation of 1,25-hydroxyvitamin D, a process stimulated by GH. This conceivably

promoted intestinal calcium absorption during our longer study period.

Side-effects due to fluid retention were a major problem in the present study, which prompted us to discontinue treatment in the first patient and lower the dose of GH in four subjects. Similar observations were made by Salomon *et al.* (5), who used the same dose of GH that we did. Side-effects were not observed in the study by Jörgensen *et al.* (6), who used similar doses of GH.

The dose (0.5 U/kg·week = 0.026 mg/kg·day) chosen in this study was similar to the dose currently used to treat GHD children. IGF-I concentrations increased markedly during treatment, and in several patients, the concentrations of IGF-I were above the upper reference limits, suggesting that the dose used was too high for replacement therapy of adults. The reduced dose given to four subjects produced IGF-I concentrations within the normal range, and symptoms of fluid retention disappeared. Possibly, a dose of 0.25 U/kg·week GH is more appropriate for replacement therapy in adults.

Over the last few years, much attention has been focused on different aspects of "quality of life," and several instruments have been developed to assess such factors. In the present study, which was initiated in 1987, the CPRS and SCL-90 scales were chosen because they covered a wide spectrum of psychopathology. Reliability tests have shown the CPRS scale to give good correlations between different raters (17), and it has also been found to be satisfactory in studies of nonpsychiatric patients (48, 49). Similarly, the SCL-90 scale has been widely used in studies of psychiatric symptoms in chronic disease (50) and endocrine disorders (51). Several studies have demonstrated an impaired quality of life in adults with GHD from childhood (52), and similar observations have been made in patients with adult-onset GHD (53). In line with the present results, GH treatment of adults with GHD has been reported to improve various aspects of well-being and mood (53, 54). Since GH treatment resulted in marked changes in body composition and, in some instances, fluid retention, it is possible that these effects were related to such noticeable changes despite the double blind design of the study.

We have previously shown that patients with hypopituitarism, despite adequate replacement therapy with corticosteroids and L-T_4, have decreased life expectancy due to increased mortality rate in cardiovascular disease (29). The changes in fat mass and fat distribution in response to GH replacement, as seen in the present study, could be beneficial with respect to the long term prognosis of these patients (15, 28). There are several important questions highlighted in the present study that require more long term trials of GH treatment. Future prospective studies should be of sufficient duration and include a large number of patients in order to clarify whether GH replacement decreases mortality rate and morbidity in GHD adults. The observed beneficial effects of GH treatment are of sufficient magnitude to consider treatment of GHD adults at the present state. However, due to the financial costs of such treatment, it is as yet unlikely that all adult patients with GHD can receive such therapy.

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