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The Effects of 10 Years of Recombinant Human Growth Hormone (GH) in Adult GH-Deficient Patients

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ABSTRACT

The long term effects of GH replacement in adult GH-deficient (GHD) patients have not yet been clarified. We studied 21 GHD adults who originally took part in a randomized, double blind, placebo-controlled trial of GH treatment in 1987. After completion of that trial, 10 patients received continuous GH replacement for the subsequent 10 yr, whereas 11 did not. A group of 11 age- and sex-matched normal controls were also studied in 1987 and 1997. Lean body mass, as assessed by total body potassium measurement and computed tomography scanning of the dominant thigh, increased in the GH-treated group ($P < 0.01$ for both) only ($P < 0.05$ between groups for total body potassium). Low density lipoprotein cholesterol decreased in the GH-treated group ($P < 0.05$) only. Carotid intima media thickness was significantly greater ($P < 0.05$) in the untreated group than in the GH-treated group. Assessment of psychological well-being using the Nottingham Health Profile revealed improvement in overall score, energy levels, and emotional reaction in the GH-treated group compared with those in the untreated group ($P < 0.02$). In conclusion, GH treatment for 10 yr in GHD adults resulted in increased lean body and muscle mass, a less atherogenic lipid profile, reduced carotid intima media thickness, and improved psychological well-being. (*J Clin Endocrinol Metab* **84:** 2596–2602, 1999)

IN RECENT years the condition of adult GH deficiency (GHD) has come to be accepted as a well defined clinical syndrome consisting of altered body composition (1–5), altered lipid profile with increased low density lipoprotein (LDL) cholesterol and decreased high density lipoprotein (HDL) cholesterol (6–9), reduced muscle strength (10), and a reduced sense of psychological well-being (11). Replacement with recombinant human GH results in rapid improvements in body composition (1–5), lipid profile (5, 8, 12–14), and psychological well-being (15, 16). Improvements in physical strength (10, 17) have been shown in open studies lasting 1 yr or more.

To date, no assessment has been made of more long term effects of GH replacement. Placebo-controlled trials have been conducted only up to 18 months (18). Similar studies of longer duration may be seen as unethical in the light of demonstrated benefit. Uncontrolled trials suffer from many problems of interpretation. In this study we report on a cohort of 21 patients with adult GHD, initially studied in 1987 (1), 10 of whom have been receiving long term GH replacement and 11 of whom have not. The objectives of the study were firstly to assess whether the benefits of GH replacement with regard to body composition and strength, endocrine and lipid profile, and psychological well-being are maintained over a 10-yr period, and secondly to determine whether there is any evidence in this cohort of patients of different prevalence of atherosclerosis between those subjects who received and those who did not receive GH over this time.

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Materials and Methods

Study design

Data presented here are from a 10-yr follow-up study of adult GHD subjects who took part in a 6-month, double blind, placebo-controlled trial of GH therapy in 1987 (1). Observations were made at baseline and after 10 yr for 10 patients who had been treated with GH since the original trial and 11 who were not (see Fig. 1). Body composition was also assessed at baseline and after 10 yr in a group of age-, sex-, and body mass index-matched controls. Subjects were studied as out-patients after an overnight fast. Ethical approval was given by the West Lambeth Health Authority. All patients gave written informed consent.

Subjects

All patients had severe GHD for at least 12 months before 1987 (peak serum GH response to insulin tolerance test, <3 mU/L). Patients were considered to have been treated continuously (GH-treated group) if they had taken GH for at least 9 of the intervening yr and had been taking it continuously for 1 yr before being studied; they were considered not to have been treated if they had taken GH for less than 1 of the intervening yr and had not been taking it during the year before being studied (untreated group). Using these criteria, 10 patients had been treated with GH continuously, and 11 had not. Of the 24 original patients in the 1987 study, 1 patient did not fit into either category and was therefore excluded from this study, and 2 patients were lost to follow-up. Of the patients in the GH-treated group, 5 had been in the original GH group, and 5 had been in the placebo group (see Fig. 1). Of the 11 patients in the untreated group, 5 were originally in the GH group, and 6 were in the placebo group. Some of the subjects had been attending the hospital regularly since the original visit, whereas others were recalled for the first time since the original trial. We did not assess changes in diet or exercise over the 10-yr period. There had been no changes in replace-

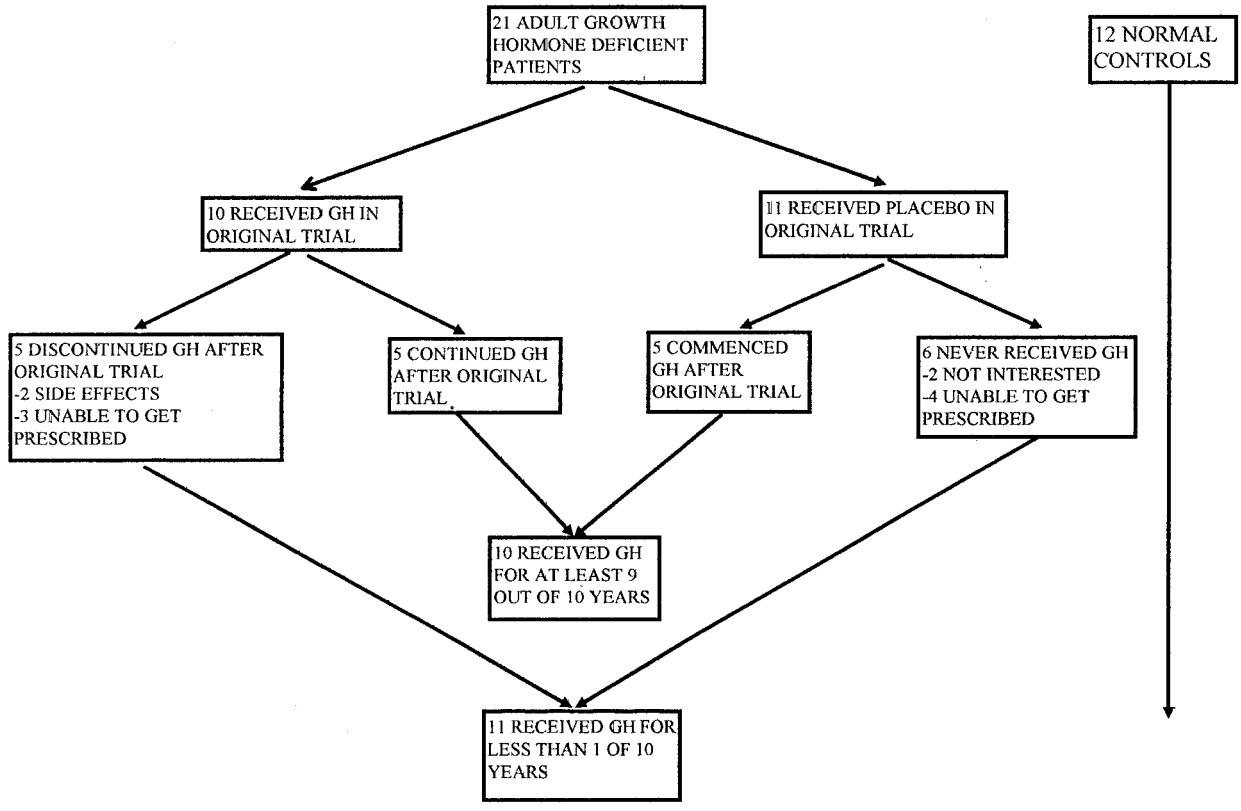

FIG. 1. At baseline (1987), patients were randomized to treatment with either GH (0.075 IU/kg·day) or placebo for 6 months. After the trial, 10 patients received GH for at least 9 yr, and 11 received it for not more than 1 yr. Body composition only was also studied in 12 normal controls at baseline and 10 yr.

TABLE 1. Baseline characteristics of the study population

Characteristic	GH-treated group	Untreated group	Controls
Mean age (yr) at baseline	38	39.3	40
Range	21–48	21–51	24–53
Male/female	7/3	8/3	8/3
Original diagnosis			
Cushing's disease	4	2	
Prolactinoma, chromophobe adenoma	4	8	
Idiopathic hypopituitarism	2	0	
Replacement treatment			
Corticosteroid	9	9	
T_4	9	9	
Gonadal steroids	9	9	
Desmopressin	1	2	
Fludrocortisone	2	0	
Ht (cm) at baseline (SD)	171 (9.6)	168 (4.5)	173 (4.2)
Wt (kg) at baseline (SD)	75.3 (15.7)	83.5 (15.9)	80.1 (13.3)
Cigarette smokers	3	3	

ment dose of hormones other than GH since the original trial. Those subjects who continued taking GH did not differ either at baseline or in response to GH in the original trial from those who stopped taking it in terms of height, weight, body mass index, body composition, psychological status, or insulin-like growth factor I (IGF-I) level. Reasons for not taking GH were inability to get it prescribed (n = 6), perceived side-effects (n = 2), and lack of interest (n = 3). Patient characteristics are shown in Table 1. Those subjects receiving GH treatment were self injecting GH at a mean dose of 0.025 IU/kg·day, sc, at bedtime. Arthralgia and fluid retention were the only documented side-effects and were limited to the first 6 months of treatment.

Analytic methods

All samples were analyzed separately at baseline and at the 10 yr point. Insulin was measured by double antibody RIA [within-assay coefficient of variation (CV), 6%]. IGF-I was measured by double antibody RIA after acid-ethanol extraction, using a commercially available reagent pack (Amersham Pharmacia Biotech, Arlington Heights, IL). Free T_4 and T_3 were measured in a Chiron Corp. ACS:180 analyzer with a chemiluminescent end point (within-assay CV, <5%). Plasma cholesterol and triglycerides were measured with a Cobas centrifugal analyzer (Roche, Welwyn Garden City, UK; within-assay CV, <5%). HDL cho-

lesterol was measured enzymatically (Roche Molecular Biochemicals) after precipitating the apolipoprotein B-containing particles with dextran sulfate/magnesium chloride (within-assay CV, <5%). LDL cholesterol was calculated using the Friedewald formula when the level of triglycerides was less than 4 mmol/L and was determined by sequential NaCl density gradient ultracentrifugation on a Centrikon Kantra TI 2070 using a TF7.45.6 rotor when the level of triglycerides was greater than 4 mmol/L (within-assay CV, <5%). IGF-I levels and lipid profile were reanalyzed in stored serum samples from the original study (baseline) and did not differ from the results originally obtained (between-assay CV, <10% for all).

Body composition and strength testing

Total body potassium was measured as the naturally occurring radioisotope of potassium (K^{40}) in a whole body potassium counter as previously described (1). The whole body counters used on both occasions were calibrated against each other and did not differ (CV between scanners, <2%). Computed tomography (CT) of the thigh was measured in the original study using a Somatom DRH CT scanner (Siemens, Munich, Germany) and a Phillips Tomoscan AV CT scanner at the 10 yr point. Scans were taken at a point midway between the greater trochanter and the joint space of the knee, as assessed by a scout film. Total muscle and fat cross-sectional areas were calculated using Hounsfield numbers 20 to −100 and −150 to 0, respectively. Strength was measured in three separate muscle groups (elbow flexion, shoulder abduction, and hip abduction) by a single observer using a hand-held dynamometer as previously described (19). (The same instrument was used at both time points.) The mean of three values was taken for each measurement, and the sum of the measurements was used for analysis.

Cardiovascular investigations

Arterial blood pressure was recorded in the sitting position after at least 30 min of rest. At least two measurements were taken, and the mean value was recorded. Echocardiography was performed as previously described (20). The same echocardiographer, blinded to the treatment patients had received, performed the measurements in 1987 and 1997. Studies were performed in the original study using a Hewlett-Packard Co. machine (model 77020 AC, Palo Alto, CA) and at the later time point using a Vingmed CFM800 machine (Horten, Norway). Carotid Doppler ultrasonography was performed by an ultrasonographer blinded to the patient's treatment group on the extracranial carotid arteries using an Acuson XP10 ultrasound system, with 7- and 5-MHz linear probes in the high resolution color B mode. Measurements of the thickness of the intima and media were taken from longitudinal scans at the distal common carotid arteries, the origin of the internal carotid arteries, and the origin of the external carotid arteries bilaterally, and the mean value was determined.

Psychological assessment

The Nottingham Health Profile was administered at both time points to assess psychological well-being and quality of life.

Statistical analysis

Characteristics of the groups at baseline were compared using unpaired Student's *t* tests. Paired *t* tests were used to compare the within-group response to long term treatment or placebo. Unpaired *t* tests were used to compare changes between groups and to compare variables that were only measured at the 10 yr point. ANOVA was used where more than two groups were compared. Nonnormally distributed data were transformed logarithmically or by square route as appropriate. All comparisons were two tailed. $P < 0.05$ was taken as statistically significant.

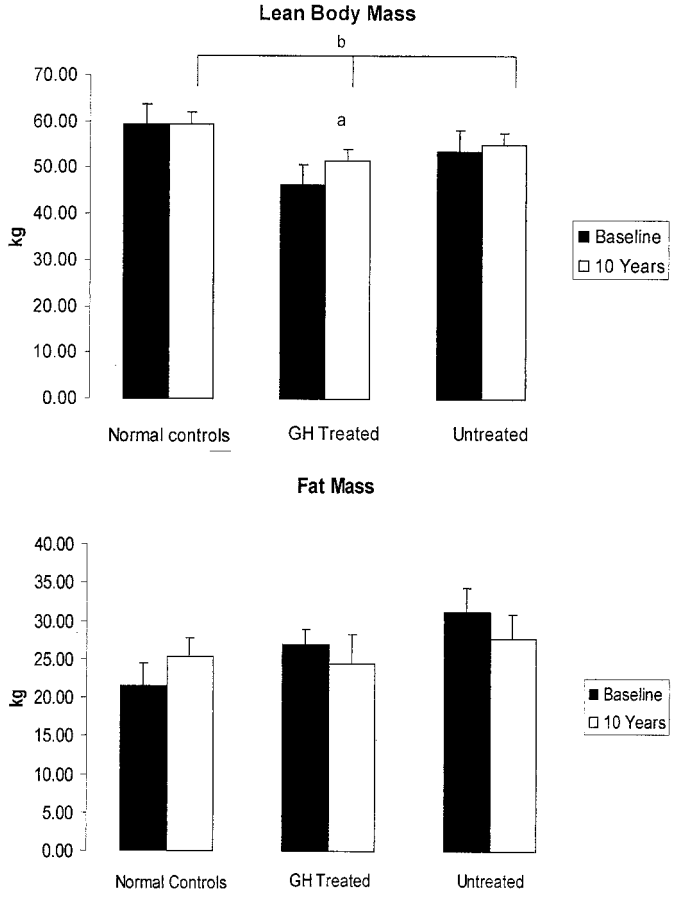

FIG. 2. Lean body mass and fat mass assessed by total body potassium measurement at baseline and 10 yr in the GH-treated and untreated groups and in the normal control group. a, $P < 0.02$ *vs.* baseline; b, $P < 0.05$ between groups.

TABLE 2. Hormone and plasma lipid concentration at baseline and 10 yr in GH-deficient adults who received (GH-treated group) and did not receive (untreated group) GH replacement over this time

	GH-treated group		Untreated group	
	Baseline	10 yr	Baseline	10 yr
IGF-I (nmol/L)	12.3 ± 3	26.9 ± 4[a,b]	12.1 ± 19	12.1 ± 1.7
Free T_3 (pmol/L)	4.9 ± 0.4	4.3 ± 0.3	4.8 ± 0.4	4.3 ± 0.3
Free T_4 (pmol/L)	18.3 ± 2.2	15.4 ± 1.5	16.4 ± 2.5	15.1 ± 1.9
Insulin (mu/L)	11.2 ± 1.9	13.5 ± 2	15.5 ± 4.5	14.8 ± 3.3
Total cholesterol (mg/dL)	228 ± 15.5	232 ± 15.5	220 ± 11.6	255 ± 27
Triglyceride (mg/dL)	186 ± 44.3	239 ± 70.8	195 ± 0.2	310 ± 79.7
HDL cholesterol (mg/dL)	30.9 ± 3.9	54.1 ± 3.9[c]	30.9 ± 3.7	46.4 ± 3.9[c]
LDL cholesterol (mg/dL)	159 ± 11.6	130 ± 7.7[d]	143 ± 11.6	146 ± 19.3

Values are the mean ± SEM.
[a] $P < 0.001$ *vs.* baseline value.
[b] $P < 0.02$, change from baseline *vs.* change from baseline in the untreated group.
[c] $P < 0.01$ *vs.* baseline value.
[d] $P < 0.05$ *vs.* baseline value.

TABLE 3. Body composition and strength at baseline and 10 yr in GH-deficient adults who received (GH-treated group) and did not receive (untreated group) GH replacement over this time

	GH-Treated group		Untreated group		Normal controls	
	Baseline	10 yr	Baseline	10 yr	Baseline	10 yr
BW (kg)	73.8 ± 4.9	75.9 ± 5.4	80.4 ± 4.7	80.9 ± 5.5	80.8 ± 4	84.6 ± 4.4
Lean body mass (kg)	46.5 ± 4.2	51.4 ± 4.9[a,b]	53.7 ± 4.2	54.9 ± 5	59.4 ± 2.2	59.3 ± 2.7
Fat mass (kg)	26.9 ± 1.9	24.5 ± 2.2	31.2 ± 3	27.7 ± 3.6	21.4 ± 2.9	25.3 ± 3.1
Thigh muscle area (cm^2)	121.4 ± 12	134.1 ± 16.1[c]	143.9 ± 15.1	140.7 ± 13.7		
Strength testing[d] (Newtons)	534 ± 29	497 ± 29	575 ± 15	486 ± 34[a]		

Values are the mean ± SEM.
[a] $P < 0.02$ *vs.* baseline value.
[b] $P < 0.02$, change from baseline *vs.* change from baseline in the untreated group and the normal control group.
[c] $P < 0.05$ *vs.* baseline value.
[d] Strength testing is expressed as the sum of mean strength measurements in each of three muscle groups (see text).

TABLE 4. Blood pressure and echocardiographic findings at baseline and 10 yr in GH-deficient adults who received (GH-treated group) and did not receive (untreated group) GH replacement over this time

	GH-treated group		Untreated group	
	Baseline	10 yr	Baseline	10 yr
Systolic blood pressure (mm Hg)	113.7 ± 2.9	123.0 ± 3	118.0 ± 4.6	123.4 ± 7.8
Diastolic blood pressure (mm Hg)	78.5 ± 4.3	79.2 ± 2.8	77.2 ± 2.5	74.2 ± 3.5
End diastolic diameter (cm)	4.9 ± 0.1	5.1 ± 0.2	5.0 ± 0.2	5.1 ± 0.1
End systolic diameter (cm)	3.3 ± 0.2	3.2 ± 0.2	3.1 ± 0.1	3.2 ± 0.1
Left ventricular mass (g)	193.8 ± 15.5	225.7 ± 22.7	222.0 ± 16.2	234.3 ± 22.2

Values are the mean ± SEM.

Results

Endocrine, metabolic, and lipid profile

IGF-I increased in the GH-treated group ($P < 0.0001$) and did not change in the untreated group ($P < 0.001$ between groups). There was no significant change in thyroid hormone levels in either group. Fasting glucose, insulin, and C peptide levels did not change in either group. Total cholesterol and triglycerides did not change in either group. LDL cholesterol decreased significantly ($P < 0.05$) in the GH-treated group and remained the same in the untreated group. HDL cholesterol increased significantly in both groups ($P < 0.01$; Table 2).

Body composition and strength testing

There was no increase in weight in either the GH-treated group or the untreated group. Lean body mass, measured by total body potassium, increased ($P < 0.02$) over the 10-yr period in the GH-treated group, whereas there was no change in the untreated group or in the normal control group ($P < 0.05$ between groups). There was no change in fat mass in any of the three groups (Fig. 2). There was a significant increase in the total cross-sectional muscle area of the dominant thigh as assessed by CT in the GH-treated group ($P < 0.05$), whereas there was no change in the untreated group. The sum of strength measured in three different muscle groups declined significantly in the untreated group ($P < 0.02$), whereas there was no change in the GH-treated group (Table 3).

Cardiovascular investigations

There was no change in systolic blood pressure, diastolic blood pressure, or echocardiographic findings in either group (Table 4). Carotid intima media thickness was increased in the untreated group compared to that in the GH-treated group ($P < 0.05$; Fig. 3).

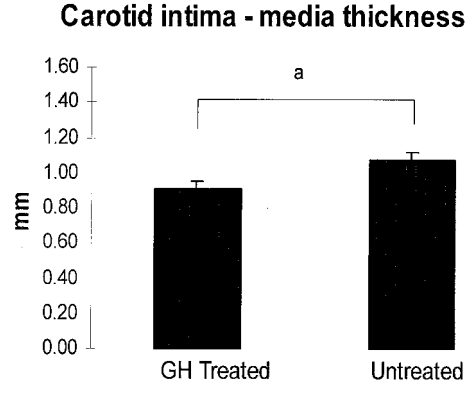

FIG. 3. Mean carotid intima media thickness assessed at the 10 yr point only in the GH-treated and untreated groups. a, $P < 0.05$ between groups.

Psychological status

There was an improvement from baseline in energy level, emotional reaction, and overall score ($P < 0.02$ for all) in the GH-treated group when assessed by the Nottingham Health Profile (Fig. 4). There was no change in the untreated group ($P < 0.02$ between groups). Other variables remained unchanged (Table 5).

Discussion

Since the identification of the syndrome of GHD in adults, repeated studies have demonstrated that patients with this condition are at a marked disadvantage compared to age- and sex-matched controls in terms of body composition (1–5)

and strength (10), lipid profile (6–9), and psychological well-being (11). There is evidence to suggest that adults with hypopituitarism (excluding those with a history of Cushing's disease or acromegaly) receiving conventional full pituitary hormone replacement other than GH have an increased mortality rate, largely attributable to increased atherosclerosis (6, 21). GHD may have a role in this increase, possibly mediated by increased abdominal adiposity and dyslipidemia. Studies evaluating the replacement of rhGH in GHD adults have shown marked short term improvements in body composition (1–5), lipid profile (8, 12–14), and psychological well-being (15, 16). Longer term (up to 4 yr) uncontrolled studies have shown an improvement in muscle strength (10, 17) and have shown that beneficial effects on lean body mass (17) and lipid profile (22, 23) are maintained over this time. The questions remain of whether these benefits are sustained over a more prolonged period and whether the observed improvement in body composition and lipid profile is ultimately reflected in reduced atherosclerosis and mortality rate.

The present study attempted to answer these questions by comparing two matched groups of GHD patients: one group who had been treated for 10 yr and one group who had not. Body composition in both groups was compared with that in age-matched controls. The two groups were well matched at baseline and had all taken part in one of the first reported trials of GH replacement (1). Although this was not a formal randomized trial, we were fortunate that the reasons for not continuing GH were largely logistical or due to inability to obtain the treatment prescribed. We were also fortunate that there was no difference in the response of any of the variables measured in the original study between those who received and those who did not receive long term GH replacement. Finally, an equal distribution of those who received GH or placebo first in the original study within the different long term treatment groups excludes this as a possible confounding variable. One additional strength of the study design was an attempt to control for the effect of normal aging on changes in body composition, by studying matched control subjects at the same time points 10 yr apart.

Arguably, the most striking effect of starting GH replacement is the increase in lean body mass and the reduction in fat mass. Studies have consistently shown a mean increase in lean body mass averaging between 2–5.5 kg that occurs within several months of initiation of therapy and is associated with a similar reduction in fat mass. Our results suggest that this increase in lean body mass is maintained over a 10-yr period in GH-treated patients. The maintained increase in lean body mass is demonstrated by two independent techniques: total body potassium measurement and cross-sectional muscle area of the dominant thigh and is reflected in a reduced decline in muscle strength. Although muscle strength declined in both groups, the decline in strength in the GH-treated group was attenuated by a margin similar to the increase in lean body mass in this group. Fat mass, however, did not change in either the GH-treated or the untreated group after 10 yr. This may reflect the fact that

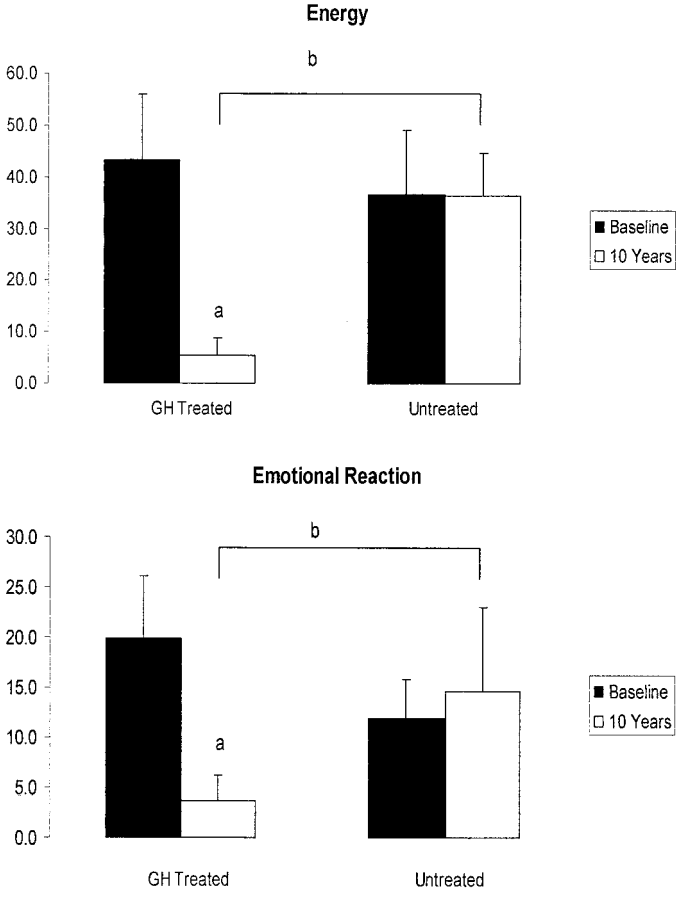

FIG. 4. Energy level and emotional reaction assessed by the Nottingham Health Profile at baseline and 10 yr in the in the GH-treated and untreated groups. a, $P < 0.02$ *vs.* baseline. b, $P < 0.02$ between groups.

TABLE 5. Nottingham Health Profile at baseline and 10 yr in GH-deficient adults who received (GH-treated group) and did not receive (untreated group) GH replacement over this time

	GH-treated group		Untreated group	
	Baseline	10 yr	Baseline	10 yr
Average	18.8 ± 6.1	7.5 ± 2.5[a]	14.6 ± 3.7	18.8 ± 4.5
Subsection score				
Mobility	4.9 ± 1.9	5.9 ± 3.7	3.3 ± 1.6	11.2 ± 4.6
Pain	0.0 ± 0.0	4.8 ± 4.8	3.5 ± 2.4	7.8 ± 3.0
Sleep	5.2 ± 2.7	14.5 ± 6.1	15.0 ± 6.6	29.9 ± 11.7
Energy	43.3 ± 12.6	5.3 ± 3.5[a]	36.4 ± 12.6	36.3 ± 8.3
Social	9.1 ± 4.9	4.0 ± 2.7	17.9 ± 8.9	13.1 ± 8.6
Emotional	19.8 ± 6.3	3.7 ± 2.6[a]	11.9 ± 3.9	14.6 ± 8.4

Values are the mean ± SEM.
[a] $P < 0.02$ *vs.* baseline value, $P < 0.02$, change from baseline *vs.* change from baseline in the untreated group.

fat mass is more influenced by lifestyle and environmental factors than lean body mass and thus over a 10-yr period would require larger numbers of subjects to demonstrate a significant change. It is important to note, however, that total body potassium measurement gives a value for whole body fat only and does not give any indication of how fat is distributed. Further studies are required to investigate whether the specific effect of GH of reducing visceral fat is maintained independently of its effect on whole body fat. Previous studies (24) have demonstrated an increase in left ventricular mass after GH replacement. We were unable to repeat this finding in the current study. There are three possible explanations for this discrepancy. Firstly, this effect may not be maintained over an extended time course. Secondly, the relatively low dosage of GH that the patients in this study had been receiving may not produce this effect. Finally, this study may have had inadequate power to detect such an effect, especially as different equipment was used at the different time points.

The effect of GH replacement on the lipid profile in this study is very similar to the findings of previous short and long term studies. There was a reduction in LDL cholesterol in the GH-treated group that was not seen in the untreated group. The increase in HDL cholesterol in both groups, although less marked in the untreated group, may in part reflect long term recovery from original disease and possibly the change in lifestyle (lower fat, higher fiber, less smoking, more exercise) that has occurred over this 10-yr period. Other cardiovascular risk factors, specifically blood pressure, glucose, and insulin, remained effectively unchanged in both groups.

Ultrasound-determined carotid intima media thickness has been demonstrated in epidemiological surveys to be a useful marker of both cardiovascular and cerebrovascular atherosclerosis (25, 26). It has previously been shown that adults with hypopituitarism on full hormone replacement other than GH have increased carotid intima media thickness compared to age- and sex-matched controls, who, other than pituitary disease, have a similar risk factor profile for atherosclerosis (27). This study shows a significant difference in carotid intimal medial thickness between GH-treated and untreated groups who are closely matched for age, sex, systolic and diastolic blood pressure, and cigarette-smoking characteristics. This may be at least partly explained by the improvement in lipid profile seen in the GH-treated group. It is possible that GHD may influence atherogenesis through other mechanisms, namely via increased serum fibrinogen and plasminogen activator inhibitor activities (9), or by reduced nitric oxide production (28). Whether long term GH treatment in GHD adults results in reduced cardiovascular or all-cause mortality is unknown, but the current findings are supportive of this hypothesis.

Both groups of patients were assessed with the Nottingham Health Profile. Although this questionnaire is designed for use in patient groups with more disabling illness and may not be ideal for assessing more subtle changes in psychological status, it has been the most widely used instrument to address the psychological effects of GHD and subsequent replacement. Studies using the Nottingham Health Profile have demonstrated that GHD adults score higher (more psychological disturbance) than peers matched for age, gender, marital status, and socioeconomic group in terms of energy, emotional reaction, social isolation, and overall psychological well-being (11). After randomized, double blind, placebo-controlled trials of GH treatment, significant improvements have been seen in energy levels and emotional reaction (16). However, in one of the longer studies addressing this issue, improvements were found for 2 yr after commencement of treatment but reverted to baseline levels in the third year of treatment (29). The current study demonstrates a sustained improvement in energy levels, emotional reaction, and overall psychological well-being that was not seen in the untreated group.

In summary, this study has shown that 10 yr of GH replacement in adult GH-deficient patients results in a sustained improvement in lean body mass, a reduced decline in muscle strength, an improved lipid profile, reduced carotid intima media thickness, and an improvement in energy levels and emotional reaction. Further studies are needed to investigate whether GH replacement will result in a reduction or normalization of mortality rates in GH-deficient adults.

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