

Effects of 7 Years of Growth Hormone Replacement Therapy in Hypopituitary Adults*

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ABSTRACT

Short-term studies of GH replacement in adult hypopituitarism have usually demonstrated beneficial effects on body composition and circulating lipids, with neutral or occasionally adverse effects on glucose tolerance. Fasting hyperinsulinemia has been reported. GH effects on cardiac function have been variable. The effects of long-term GH therapy, taking into account the consequences of increasing age, are not fully known. Thirty-three hypopituitary, initially middle-aged adults were studied over a 7-yr period; 12 patients took GH therapy (mean, 0.7 mg daily) continuously (group A); 11 took GH for only 6–18 months, a minimum of 5 yr previously (group B); and 10 patients never received GH therapy (group C). Other pituitary replacement was maintained. Effects on anthropometry, body composition (by bioimpedance analysis, total body potassium, and dual energy x-ray absorptiometry), circulating lipids, glucose and insulin concentrations, cardiac 2-dimensional and Doppler echocardiography, and exercise tolerance were assessed before and after the treatment period. Continuous GH therapy had no significant effect on body weight, but it prevented the increase in waist circumference and waist to hip ratio

that occurred in the patients without GH substitution (waist to hip ratio, group A, 0.87 ± 0.08 at baseline, 0.85 ± 0.09 at 7 yr; group B, 0.89 ± 0.11 at baseline, 0.94 ± 0.11 at 7 yr; $P < 0.005$ for GH effect; group C, 0.87 ± 0.10 at baseline, 0.92 ± 0.10 at 7 yr; $P < 0.005$ for GH effect). A GH-induced decrease in subscapular skinfold thickness was also observed. By bioimpedance analysis, GH therapy caused an increase in total body water and fat-free mass, and a decrease in the percent body fat. Although changes occurred with time in all groups, no significant additional GH therapy effects were observed on glucose tolerance, insulin concentrations, lipid levels, cardiac dimensions, echocardiographic diastolic function, or exercise tolerance. In conclusion, prolonged GH substitution in middle-aged hypopituitary adults causes a sustained improvement in body composition. Other benefits, e.g. on lipid levels and exercise tolerance, were not apparent at 7 yr when comparisons were made with GH-untreated hypopituitary controls. Potentially adverse effects on glucose tolerance and insulinemia did not develop with prolonged GH therapy. (*J Clin Endocrinol Metab* 85: 3762–3769, 2000)

THE ADULT GH deficiency syndrome, described in recent years (1, 2), includes generalized and visceral obesity, reduced lean body mass and increased fat mass, reduced exercise performance, and abnormalities of circulating lipids. Beneficial effects of GH replacement have been reported in short-term studies (3, 4) with most consistent findings in body composition (reduction in fat mass and increase in fat-free mass) and lipid metabolism (reduction in total cholesterol levels). Data on cardiac indexes indicated improvement in diastolic function (5), which was not always sustained (6). Longer-term studies are complicated by the fact that body composition and metabolism, cardiac structure, and exercise tolerance change with age even in normal subjects (7). To assess the long-term effects of GH replacement therapy, information is also required over a number of years in those treated conventionally without GH therapy.

We have therefore investigated changes over 7 yr in body composition, aspects of metabolism, and cardiac status in GH-replaced and GH-untreated hypopituitary adults.

Subjects and Methods

Patients

Thirty-three hypopituitary patients (all GH deficient) were studied before and after 7.1 (mean; range, 5.9–8.5) yr of follow-up. The patients had initially participated in other studies from our department (8–10). They were divided into 3 groups: group A, 12 patients who had been treated continuously with GH (mean, 0.7 mg/day at recall) for 7 yr, having started treatment in a randomized controlled trial (11); group B, 11 patients who were treated with GH for 6–18 months as part of the randomized controlled trial, but opted to stop GH therapy and did not receive GH therapy during the following 5 yr; and group C, 10 patients who were initially investigated but never treated with GH.

Patients were recruited from the Endocrine Clinic at St. Mary's Hospital and adjacent hospitals. Hypopituitarism resulted mainly from pituitary adenomas (Table 1). Most had adult-onset GH deficiency (2 patients in group A, 2 in group B, and 1 in group C had childhood-onset GH deficiency). GH deficiency at baseline was defined as GH values less than 3 ng/mL in response to insulin-induced hypoglycemia (mostly) or clonidine test. They were all stable on cortisol, T_4 , sex steroids, fludrocortisone, and desmopressin (where appropriate) and were assessed clinically and biochemically every 6 months.

The three groups at the outset were similar with respect to age, body mass index (BMI), and duration of hypopituitarism. The reasons for

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TABLE 1. Clinical characteristics of the study patients at recall

	Group A	Group B	Group C
No. of patients (F/M)	12 (6/6)	11 (5/6)	10 (4/6)
Age (yr)	52 ± 10	53 ± 14	61 ± 10
BMI (kg/m ²)	30 ± 6	31 ± 5	29 ± 4
Duration of HP (yr)	20 ± 9	15 ± 7	23 ± 15
Diagnosis			
Chromophobe adenoma	3	2	5
Craniopharyngioma	2	4	2
Prolactinoma	2	3	1
Cushing's/Nelson syndrome	2	1	0
Sheehan's syndrome	0	0	2
Idiopathic HP	1	0	0
Other ^a	2	1	0
Treatment			
Surgery (TC/TS)	11 (5/6)	11 (6/5)	7 (2/5)
Radiotherapy	7	11	8
Replacement therapy			
Cortisol	10	8	10
T ₄	11	8	8
Sex steroids	11	9	7
Fludrocortisone	2	1	0
Desmopressin	3	2	1
GH (mg/day)	0.7 ± 0.3		

Data are the mean ± SD or median (range). F/M, Females/males; TC/TS, transcranial/transphenoidal surgery.

^a Group A, a meningioma and a dysgerminoma; Group B, a pinealoma.

stopping GH treatment in group B had been lack of subjective improvement or transient deterioration of glucose tolerance while taking GH. The patients in group C opted not to have GH therapy because they disliked injections or because they felt sufficiently well without additional treatment.

The Parkside Health Authority ethics committee approved the protocol, and patients gave informed written consent.

Study protocol and methods

Investigations at baseline and at follow-up were: 1) anthropometry [height, weight, BMI, waist and hip circumference with calculated waist to hip ratio (W/H), and skinfold thicknesses]; 2) body composition by total body potassium (TBK), bioimpedance analysis (BIA) and dual energy x-ray absorptiometry (DXA); 3) blood tests after an overnight fast and after positioning an iv cannula for measurement of total and high density lipoprotein (HDL) cholesterol and triglyceride, insulin-like growth factor I (IGF-I), nonesterified fatty acids (NEFA), and a 3-h 75-g oral glucose tolerance test with glucose and insulin estimations at 30-min intervals; and 4) echocardiography and exercise tests.

All patients attended the Metabolic Day Ward at St. Mary's Hospital. General clinical examination was performed. Weight and height were measured while the subject was wearing light indoor clothes without shoes. W/H was measured as the narrowest waist to the widest hip circumference. Skinfold thicknesses at the triceps and subscapular areas were measured using a Tanner and Whitehouse skinfold caliper (Holtain Ltd., Crosswell, UK).

TBK was measured in 24 patients by ⁴⁰K counting in a whole body counter situated at the Medical Research Council Cyclotron Unit, Hammersmith Hospital (London, UK), as described previously (9, 12). Patients were measured for 30 min in a whole body counter with 10 sodium iodide scintillation detectors, housed in a shielded room made of 15-cm-thick, low activity steel. TBK was calculated by comparing the patient's net potassium count with counts from a known quantity of potassium in a reference phantom. This number was then adjusted for body habitus using a calibration factor (12) related to height and weight. During the course of the study, two detectors were changed. Their efficiencies were cross-calibrated with those of the original detectors, and adjustments were made accordingly. Later measurements on a standard phantom were consistent with the counts in earlier studies.

Fat-free mass (FFM; kilograms) was calculated from TBK (millimoles)

using the following sex-specific formulas (13): males: FFM = (TBK × 7.55/1000) + 27.98; females: FFM = (TBK × 10.14/1000) + 18.23.

Electrical impedance was measured in 25 patients using a Holtain body composition analyzer (Holtain Ltd.) with an alternating current of 50 KHz, 800 μA and following the instructions given by the manufacturer. The same apparatus was used throughout. The patients were tested while supine after voiding. Total body water (TBW) was calculated from the measured impedance using the following formula (14): TBW = [(height²/impedance) × 0.585] + 1.825. FFM was then calculated from TBW by assuming 73% hydration of FFM (15): (FFM = TBW/0.73).

Body composition was assessed by DXA in 20 patients using a Lunar Corp. absorptiometer (DPX-L, Lunar Corp., Madison, WI). Although the computer software changed during the study period, baseline and repeat data were analyzed using the latest software (version 1.35). Body composition estimations by DXA involved differential attenuation by tissues of transmitted photons of two energies (16). The soft tissue mass was partitioned into nonskeletal FFM (lean tissue mass) and body fat mass (BFM) using an equation derived from calibrating water-fat and tissue-fat mixtures.

For TBK and BIA, body composition was analyzed using a two-compartment model: body weight = FFM + BFM. FFM was calculated from TBK or TBW, and BFM was calculated by subtracting FFM from body weight. For DXA, a three-compartment model was used (body weight = bone mineral content + lean tissue mass + BFM). The mass of each compartment was measured directly by the scanner. FFM was then calculated as the sum of lean tissue mass and bone mineral content.

Plasma glucose was measured with a hexokinase method. Insulin was measured by RIA using a polyethylene glycol-accelerated second antibody method (17). Interassay precision was less than 5% for values between 86.8–1547.7 pmol/L. Serum IGF-I was measured after acid-ethanol extraction by RIA (18). Total cholesterol and triglycerides were measured by an enzymatic method (19). HDL cholesterol was analyzed enzymatically after dextran sulfate precipitation (20). Low density lipoprotein (LDL) cholesterol was calculated using the Friedwald equation (21). NEFA was also measured by an enzymatic method (22). Blood samples after collection were stored at –60 °C. For all laboratory methods, the same assay was employed at baseline and at follow-up. Within- and between-batch precisions were monitored throughout the study using frozen plasma and serum pools and commercially available lyophilized sera, and by participation in national quality control schemes where available.

Twenty-two of the patients underwent two-dimensional and Doppler echocardiography. Left ventricular (LV) mass was determined with an area × length method that has been validated in man (23). For this calculation two echocardiographic views are required: a parasternal short axis view of the LV at the papillary muscle tip level to assess the cross-sectional area of the myocardium and the apical four-chamber view that maximizes the distance from the mitral valve annulus to the LV apex to determine the length of the ventricle. LV mass was then calculated from the algorithm LV mass = 1.04(5/6(A1 × L1) – 5/6(A2 × L2)), where A1 and A2 represent the epicardial and endocardial areas, respectively, measured by planimetry, and L1 and L2 represent the lengths of the LV from the mitral annulus to the epicardial and endocardial borders, respectively. LV mass index was determined by dividing LV mass by body surface area. Pulsed Doppler examination of transmittal flow was recorded with reference to the two-dimensional echocardiographic image (24). The peak flow velocities of the early and atrial waves were measured from the three consecutive cardiac cycles displaying the highest measurable velocity profiles. The ratio of the early and atrial peak flow velocities (E/A) was used as an index of left ventricular filling. The isovolumic relaxation time (IVRT) was measured from the apical five-chamber view by placing the continuous wave Doppler beam between the mitral and aortic valve junction. The time interval between the end of the aortic velocity envelope and the onset of the early filling wave was taken to represent the IVRT (24).

Exercise assessment was performed in 21 of the 22 patients who had echocardiographic studies by a symptom-limited, graded multistage treadmill exercise testing using Bruce's standard protocol (7 stages, each of 3-min duration). The tests took place in a temperature- and humidity-controlled environment with standard safety precautions. Heart rate and blood pressure were measured at the end of each stage. The test was stopped if patients complained of excessive shortness of breath, leg weakness, or exhaustion.

Statistical analysis

Data are expressed as the mean (\pm SD) or median (range) where appropriate. The area under the curve (AUC) for glucose and insulin was calculated using the trapezoidal rule.

The primary analysis was of the change with GH therapy *vs.* that without GH. Secondary analyses were performed on baseline *vs.* follow-up measurements. The differences in the change over 7 yr between groups were analyzed using the Mann-Whitney test (where two groups were compared) or the Kruskal-Wallis test (where three groups were compared). Comparisons at baseline *vs.* follow-up were performed using Student's paired *t* test or the Wilcoxon test where appropriate.

Results

For anthropometry and for carbohydrate and lipid metabolism, the three groups (A, B, and C) are described separately, and also when groups B and C have been combined (as group D). Because of the smaller numbers of subjects participating in the body composition and heart studies, groups B and C have been amalgamated as group D for statistical evaluation.

Anthropometry

Weight and BMI increased significantly, but the increase over 7 yr was similar in all groups (Table 2). W/H did not change significantly in group A, but it tended to increase in group B and increased significantly in group C (0.87 ± 0.10 to 0.92 ± 0.10 ; $P < 0.005$). The change in W/H over the study period was significantly different between groups A and B ($P < 0.005$) as well as groups A and C ($P < 0.005$). Waist circumference increased significantly in groups B and C, and the increase was significantly greater when groups B and C were combined (group D) compared with that in group A ($P < 0.05$). Skinfold thickness in the subscapular area decreased significantly in group A (29.5 ± 7.4 to 23.5 ± 8.2 mm; $P < 0.005$), but not in the other two groups, and the change was not significantly different between these groups. The change in subscapular skinfold thickness assumed statistical significance when group A was compared with group D ($P < 0.05$; Table 2).

Body composition

By BIA, TBW increased significantly in group A (38.5 ± 9.9 to 45.4 ± 9.5 kg; $P < 0.005$; Table 3), but not in group D. The

changes in groups A and D were significantly different ($P < 0.005$). FFM increased significantly in group A (53.5 ± 13.5 to 62.2 ± 13.0 kg; $P < 0.005$), and this increase in FFM was significantly greater than that in group D. BFM decreased in group A and increased in group D, but the changes were not significant, and the changes between the two groups did not achieve statistical significance ($P = 0.06$). The percentage of body fat showed a similar pattern as BFM, but the changes over time between groups A and D were significantly different ($P < 0.05$).

Using TBK, FFM in group A increased significantly (49.7 ± 8.7 to 52.8 ± 9.1 kg; $P < 0.0005$), whereas no significant change was seen in group D (Table 4). The change with time did not differ significantly between groups, and there was no significant change in BFM or percent body fat using this methodology.

In the smaller number of subjects in whom body composition was assessed by DXA, FFM did not change significantly in group A, but it decreased in group D (63.9 ± 14.0 to 60.2 ± 12.6 kg; $P < 0.05$; Table 5). BFM and percent body fat increased significantly in both groups using this methodology, but the changes did not differ significantly between the groups.

Carbohydrate and lipid metabolism

At baseline, four patients in group A and three patients each in groups B and C were found to have impaired glucose tolerance. One patient in group C was diagnosed as having borderline type II diabetes. Impaired glucose tolerance was present at follow-up in four patients in group A, two in group B, and two in group C. Diabetes was present in two patients in group B and three patients in group C.

No significant changes were seen in fasting glucose in any of the groups (Table 6). Fasting insulin levels increased significantly in groups B and D, but no GH effect was observed. The 75-g oral glucose tolerance test AUC for glucose was similar in each group, and the changes in glucose tolerance with time did not differ significantly between groups. The AUC for insulin increased significantly in all groups, but to a similar extent in each. IGF-I levels increased significantly in group A [12.4 (range, 9.2 – 18.1) to 29.1 (16.5 – 41.9) nmol/L] and decreased significantly in groups B and C. IGF-I levels

TABLE 2. Anthropometric indexes at baseline and repeat visit for each group

	Group A		Group B		Group C		Group D (B + C)	
	Baseline	Repeat	Baseline	Repeat	Baseline	Repeat	Baseline	Repeat
Wt (kg)	81.2 \pm 18.9	87.3 \pm 23.7 ^a	87.1 \pm 15.8	91.2 \pm 17.0 ^a	80.6 \pm 19.4	86.1 \pm 18.7 ^a	84.2 \pm 17.3	88.9 \pm 17.5 ^b
Ht (m)	1.70 \pm 0.13	1.70 \pm 0.13	1.73 \pm 0.11	1.73 \pm 0.11	1.71 \pm 0.10	1.71 \pm 0.10	1.72 \pm 0.10	1.72 \pm 0.10
BMI (kg/m ²)	28.1 \pm 4.7	30.0 \pm 6.2 ^a	29.1 \pm 4.2	30.6 \pm 4.7 ^a	27.2 \pm 4.0	28.9 \pm 4.4 ^a	28.3 \pm 4.1	29.9 \pm 4.5 ^b
Waist (cm)	90.5 \pm 11.7	91.6 \pm 13.3	94.4 \pm 12.5	100.5 \pm 11.7 ^a	90.7 \pm 13.2	95.6 \pm 13.0 ^a	92.8 \pm 12.6	98.3 \pm 12.2 ^{b,c}
W/H	0.87 \pm 0.08	0.85 \pm 0.09	0.89 \pm 0.11	0.94 \pm 0.11 ^d	0.87 \pm 0.10	0.92 \pm 0.10 ^{b,d}	0.88 \pm 0.10	0.93 \pm 0.11 ^{a,c}
Triceps ST (mm)	21.9 \pm 8.7	23.7 \pm 9.8	25.3 \pm 8.5	22.2 \pm 8.2	23.7 \pm 8.7	21.9 \pm 7.8	24.6 \pm 8.4	22.1 \pm 7.8
Subscapular ST (mm)	29.5 \pm 7.4	23.5 \pm 8.2 ^b	31.9 \pm 8.5	30.1 \pm 8.5	29.2 \pm 10.9	26.8 \pm 11.2	30.7 \pm 9.5	28.6 \pm 9.7 ^c

Data are the mean \pm SD. BMI, Body mass index; W/H, waist to hip ratio; ST, skinfold thickness.

^a $P < 0.05$, baseline *vs.* repeat in each group.

^b $P < 0.005$, baseline *vs.* repeat in each group.

^c $P < 0.05$, for the changes in group D being significantly different from those in group A.

^d $P < 0.005$, for the changes in groups B or C being significantly different from those in group A.

TABLE 3. Body composition assessed by BIA

	Group A (n = 12)		Group D (n = 13)	
	Baseline	Return	Baseline	Return
Total body water (kg)	38.5 ± 9.9	45.4 ± 9.5 ^a	44.8 ± 8.8	43.3 ± 7.3 ^b
Fat-free mass (kg)	53.5 ± 13.5	62.2 ± 13.0 ^a	60.9 ± 11.3	59.3 ± 10.0 ^b
Body fat mass (kg)	27.4 ± 8.1	25.1 ± 18.1	26.4 ± 9.4	30.9 ± 10.9
% Body fat	33.8 ± 5.8	27.1 ± 12.4	29.9 ± 8.8	33.7 ± 7.8 ^c

Data are the mean ± SD.

^a $P < 0.005$, baseline vs. repeat in each group.

^b $P < 0.005$, for the changes with time in group D being significantly different from those in group A.

^c $P < 0.05$, for the changes with time in group D being significantly different from those in group A.

TABLE 4. Body composition assessed by TBK

	Group A (n = 11)		Group D (n = 13)	
	Baseline	Repeat	Baseline	Repeat
Fat-free mass (kg)	49.7 ± 8.7	52.8 ± 9.1 ^a	53.1 ± 7.8	54.4 ± 6.7
Body fat mass (kg)	27.9 ± 10.6	29.8 ± 13.7	34.3 ± 9.2	34.3 ± 9.8
% Body fat	35.2 ± 8.1	34.8 ± 9.8	38.8 ± 5.3	38.1 ± 5.3

Data are the mean ± SD.

^a $P < 0.0005$ for baseline vs repeat in each group.

TABLE 5. Body composition assessed by DXA

	Group A (n = 8)		Group D (n = 12)	
	Baseline	Repeat	Baseline	Repeat
Fat-free mass (kg)	59.0 ± 18.2	58.1 ± 19.0	63.9 ± 14.0	60.2 ± 12.6 ^a
Body fat mass (kg)	24.2 ± 13.6	30.9 ± 15.0 ^b	24.4 ± 7.9	30.3 ± 8.7 ^b
% Body fat	28.8 ± 13.4	34.6 ± 12.4 ^b	27.8 ± 8.8	33.5 ± 8.7 ^b

Data are the mean ± SD.

^a $P < 0.05$, baseline vs. repeat in each group.

^b $P < 0.0005$, baseline vs. repeat in each group.

at follow-up were in the age-related normal range in all subjects in group A (ranging between 0–2 SD score).

No significant changes were observed in serum triglyceride and HDL cholesterol levels. Total cholesterol decreased significantly in all three groups [group A, 6.3 ± 1.8 to 5.4 ± 1.0 mmol/L ($P < 0.05$); group B, 7.3 ± 2.0 to 5.7 ± 1.4 mmol/L ($P < 0.005$); group C, 7.6 ± 1.8 to 6.0 ± 1.2 mmol/L ($P < 0.05$)], and a similar decrease was noted in LDL cholesterol. The change in cholesterol with time did not differ significantly between the groups. Fasting NEFA concentrations showed a downward trend in all groups, significant only in group B. No GH effect was observed.

Echocardiographic data

IVRT and left ventricular mass index did not change significantly in either group A or D (Table 7). The E/A decreased significantly in group A (1.31 ± 0.28 to 1.07 ± 0.33; $P < 0.05$), but the changes with time were not significantly different in the two groups.

Heart rate, blood pressure, and exercise testing

Resting heart rate increased in group D (69 ± 7 to 86 ± 14 beats/min; $P < 0.05$; Table 8), but there was no significant difference between groups A and D. Resting systolic blood pressure increased significantly in group D (128 ± 17 to 139 ± 20 mm Hg; $P < 0.05$), but there was a similar, although nonsignificant, increase in group A. Resting diastolic blood pressure decreased in group A (84 ± 9 to 74 ± 12; $P < 0.05$),

but the change with time did not differ significantly between the groups. The exercise time achieved did not change significantly in either group. Maximal exercise heart rate also did not change significantly in either group. The maximal rate-pressure product decreased in both groups, significantly only in group A, but the changes in each group were not significantly different. Three subjects in group D and one in group A had 1 mm of lateral ST depression at peak exercise. None of these patients had chest pain. No subject had 2 mm or more ST depression during exercise.

Other changes over the study period

Minor changes in treatment occurred in the 7-yr period in all groups. The most common alterations were the requirement for T_4 (one patient in each group started T_4 replacement during that period) and for sex hormone replacement (one patient in group A and one in group C). Four patients started hypotensive therapy over the 7 yr of follow-up (one in group A, two in group B, and one in group C). Their exclusion did not change the statistical significance of any measurement. Treatment alterations were distributed evenly throughout the groups.

Discussion

Most previous studies of GH therapy have reported on the effects of 6–18 months of treatment (3, 4, 25). The best studies are placebo-controlled trials, but as the placebo requires sc injections, longer-term studies have not been undertaken.

TABLE 6. Glucose tolerance and lipids for each group

	Group A		Group B		Group C		Group D	
	Baseline	Return	Baseline	Return	Baseline	Return	Baseline	Return
F glucose (mmol/L)	4.9 ± 0.4	5.2 ± 0.7	5.0 ± 0.7	5.3 ± 1.0	5.0 ± 0.7	5.2 ± 0.9	5.0 ± 0.7	5.2 ± 0.9
AUC-G (mmol/L·h)	41.5 ± 6.5	43.3 ± 8.3	42.4 ± 7.9	43.4 ± 15.2	46.1 ± 13.9	52.2 ± 19.5	44.2 ± 11.0	47.6 ± 17.5
F insulin (pmol/L)	18.5 (2.2–62.3)	30.4 (14.8–230.6)	22.2 (2.2–162.4)	43.0 (2.2–298.1) ^a	48.2 (20.0–146.8)	50.1 (3.0–167.6)	36.3 (2.2–162.4)	46.7 (2.2–298.1) ^a
AUC-I (pmol/L·h)	1208 (200–3845)	2983 (801–13292) ^a	1236 (713–6729)	2431 (1223–20360) ^a	2089 (362–5321)	2508 (239–7878) ^a	1742 (362–6729)	2494 (239–20360) ^a
IGF-I (nmol/L)	12.4 (9.2–18.1)	29.1 (16.5–41.9) ^b	11.8 (2.8–19.4)	5.8 (2.4–13.0) ^c	9.2 (6.9–22.7)	3.7 (2.0–11.5) ^c	9.8 (2.8–22.7)	5.0 (2.0–13.0) ^b
T-cholesterol (mmol/L)	6.3 ± 1.8	5.4 ± 1.0 ^a	7.3 ± 2.0	5.7 ± 1.4 ^c	7.6 ± 1.8	6.0 ± 1.2 ^a	7.5 ± 1.9	5.8 ± 1.2 ^b
Triglycerides (mmol/L)	1.7 ± 1.0	1.9 ± 1.2	1.6 ± 0.4	1.8 ± 0.6	1.4 ± 1.0	1.3 ± 0.6	1.5 ± 0.7	1.6 ± 0.6
LDL-cholesterol (mmol/L)	4.3 ± 1.4	3.3 ± 0.7 ^a	5.4 ± 1.9	3.9 ± 1.5 ^c	5.5 ± 1.7	4.0 ± 1.1 ^a	5.5 ± 1.8	3.9 ± 1.3 ^b
HDL-cholesterol (mmol/L)	1.3 ± 0.6	1.3 ± 0.5	1.2 ± 0.5	1.1 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.4
NEFA (μmol/L)	470.8 ± 171.8	347.2 ± 199.1	495.2 ± 191.9	352.1 ± 195.0 ^a	469.4 ± 173.9	408.0 ± 249.4	482 ± 178	380 ± 219 ^a

Data are the mean ± SD or median (range). AUC, Area under the curve; F, fasting; G, glucose; I, insulin; T, total; chol, cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; IGF-I, insulin-like growth factor-I; NEFA, nonesterified fatty acids.

^a $P < 0.05$, baseline vs. repeat in each group.

^b $P < 0.0005$, baseline vs. repeat in each group.

^c $P < 0.005$, baseline vs. repeat in each group.

The long-term GH effects have been therefore investigated by comparison with baseline (26, 27). Such a protocol cannot take account of changes that occur anyway with time in the absence of GH therapy. Only one previous study has investigated the effects of prolonged (10 yr) GH therapy in adult GH deficiency, using as controls GH-untreated patients (28). The features of the postulated GH deficiency syndrome described in the present report (body composition, glucose tolerance and insulinemia, lipid status, and cardiac function) all change with age. We have compared the changes with continuous GH therapy with those in patients who either never received GH treatment or who took it for only a short time. The patients who had opted never to receive GH and those who stopped therapy did so out of choice, reflecting contentment with their conventional treatment, aversion to injections, or lack of perceived benefit with GH. This study design is inappropriate to investigate GH effects on quality of life. However, the measurements reported here are unlikely to be affected by patient self-selection. The groups were initially comparable, tending to be overweight and to have mildly elevated cholesterol and triglyceride levels, as reported previously in hypopituitarism (8, 10, 29).

We have combined some of the data at follow-up for those patients who never received GH treatment with those who took it for 6–18 months, at least 5 yr beforehand. This is justified as the biological actions of GH revert on cessation of long-term GH therapy within several months, at least for body composition and muscle strength (30).

Assay methodology was maintained the same for all laboratory measurements, and precision was ensured by, among others, participation in national quality control schemes. For the body composition studies, BIA was performed with the same apparatus throughout, whereas TBK measurements were performed in the same center using the same apparatus calibrated with a standard phantom. The DXA studies were performed with the same precautions, and although the computer software changed, baseline data were reanalyzed using the new software. Data are reported using all three methods of body composition analysis in view of the limitations of all methods (9, 31). The cardiac Doppler and echocardiographic data were ascertained by different observers, but the measurements reported are those affected least by observer bias.

Previous shorter-term studies have demonstrated an effect of GH to decrease central body fat, measured as W/H, or using DXA or magnetic resonance imaging techniques (25, 32). The effect of GH on body weight has usually been neutral. GH has increased lean and decreased fat mass in these studies. Effects on glucose tolerance and insulinemia have been variable, although a transient increase in fasting blood glucose and persistent hyperinsulinemia have been reported (33). A GH-induced decrease in cholesterol has been observed (25, 26), with an increase in HDL cholesterol in some studies (27).

The dose of GH was similar to that used by other investigators (4, 34). Optimal GH dosage regimens are uncertain, and none mimics the normal diurnal GH profile. Most investigators now use regimens that aim to maintain IGF-I levels in the age-related normal range. The IGF-I fall in our untreated groups was perhaps greater than might have been

TABLE 7. Echocardiographic data

	Group A (n = 12)		Group D (n = 10)	
	Baseline	Repeat	Baseline	Repeat
IVRT (ms)	97.8 ± 17.1	89.1 ± 14.4	103.0 ± 20.4	103.3 ± 29.3
LVMI (g/m ²)	96.7 ± 18.8	97.7 ± 14.3	89.7 ± 14.7	100.4 ± 23.5
E/A	1.31 ± 0.28	1.07 ± 0.33 ^a	1.06 ± 0.36	0.92 ± 0.39

Data are the mean ± SD. IVRT, Isovolumic relaxation time; LVMI, left ventricular mass index; E/A, peak early to late left ventricular filling ratio.

^a $P < 0.05$ for baseline vs repeat in each group.

TABLE 8. Exercise testing

	Group A (n = 11)		Group D (n = 10)	
	Baseline	Repeat	Baseline	Repeat
Heart rate (beats/min)				
Resting	72 ± 12	78 ± 13	69 ± 7	86 ± 14 ^a
Maximal	167 ± 22	156 ± 21	163 ± 25	158 ± 17
Blood pressure (mm Hg)				
Resting SBP	128 ± 16	136 ± 24	128 ± 17	139 ± 20 ^a
Maximal SBP	196 ± 30	185 ± 21	188 ± 30	182 ± 27
Resting DBP	84 ± 9	74 ± 12 ^a	81 ± 10	82 ± 10
Maximal DBP	97 ± 18	87 ± 12	92 ± 18	91 ± 10
Maximal HR × SBP	32,655 ± 5,735	28,658 ± 4,373 ^a	30,825 ± 7,701	28,470 ± 4,473
Exercise time (min)	11.0 ± 3.0	10.8 ± 2.7	8.2 ± 3.0	9.5 ± 2.4

Data are the mean ± SD. HR, Heart rate; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

^a $P < 0.05$, baseline vs. repeat at each group.

expected with time in a normal population (35), but we did not study a normal control group.

The most striking effect of prolonged GH therapy was to prevent the increase in waist circumference and W/H that occurred in conventionally treated patients. This presumably reflects an effect of GH to limit the central body fat deposition that occurs with age (36). Using the Framingham model, the GH-induced difference in W/H would in other circumstances represent a 3–4% decrease in the incidence of coronary heart disease over 10 yr (37). A GH-induced decrease in subscapular skinfold thickness was also observed. No GH effect was observed on body weight. Prolonged GH therapy increased FFM assessed by BIA. Similarly, an increase in FFM was observed using TBK, in keeping with the findings in one previous long-term study (28), although the change we observed with GH was not significantly greater than that in GH-untreated subjects using this methodology. No significant change in FFM was observed using DXA. BIA may overestimate FFM with GH treatment due to an increase in tissue hydration (31), but the increase observed with both BIA and TBK suggests that it is real. Sustained changes in body fat mass with prolonged GH treatment were not observed consistently with the different methodologies. By BIA, a reduction in the proportion of body fat was observed in the GH-treated vs. untreated subjects, but this was not confirmed with TBK or DXA.

Although total and LDL cholesterol decreased in both GH-treated and untreated subjects, no significant GH effect was observed. This is contrary to some (38, 39), but not all (34), previous studies. Gibney *et al.* (28) found no difference in total cholesterol in GH-treated and untreated patients with long-term treatment, but reported a decrease in LDL cholesterol only in the GH-treated subjects. The reason for the fall with time in all of the groups in our study, when an

increase with age might have been expected, is uncertain. During the course of the study, information on cardiovascular risk in hypopituitarism was published (40, 41) and clinical practice altered to advise on lifestyle. This could account for the fall in cholesterol in our study [and the rise in HDL cholesterol in the study by Gibney *et al.* (28)]. However, total adiposity was not affected. The lipid changes cannot be attributed to other medications, as treatment changes were minimal. In keeping with the literature (28, 38, 42, 43), triglyceride levels did not change significantly despite the reduction in central body fat. HDL cholesterol and NEFA were similarly unaffected.

Concerns regarding an adverse effect on glucose tolerance with prolonged GH therapy have not been substantiated, although glucose tolerance may deteriorate in the first few months of GH replacement (33). The number of subjects studied was, however, relatively small, and further data are required. Fasting insulin tended to increase, but was unaffected by GH therapy, and although insulin levels after oral glucose increased with time, no additional GH treatment effect was apparent.

The small increase in resting systolic blood pressure in both GH-treated and untreated groups (statistically significant only in the untreated) probably reflects the fact that the subjects were 7 yr older. The decrease in resting diastolic blood pressure in the GH-treated patients was significant ($P < 0.05$), but was not significantly affected by GH. A decrease in diastolic blood pressure has previously been observed in some (39, 43), but not all (6, 44), shorter-term studies. Left ventricular hypertrophy is a powerful predictor of morbidity and mortality in the population (45). The possibility that prolonged GH treatment might induce left ventricular hypertrophy has not been confirmed. On Doppler studies, abnormal diastolic function (decreased E/A and in-

creased IVRT) has been reported in hypopituitarism (5) and was unaffected by 12 months of GH replacement (6). In the current study, E/A declined with time (significantly in group A), but the IVRT did not change, and no GH effect was observed. E/A decreases normally with age, and IVRT increases (46), but GH therapy had no influence.

With exercise testing, the heart rate-systolic blood pressure product decreased after 7 yr, significantly in the GH-treated group. No GH therapy effect was observed. This rate-pressure product reflects the maximum oxygen consumption (MVO_2) and is an indicator of exercise capacity (47). Maximum exercise heart rate also correlates with MVO_2 (47). In the present study there was a nonsignificant decrease in maximal heart rate in both groups, with no GH therapy effect. Exercise time on the treadmill did not change significantly in either group. Thus, although short-term GH treatment increases exercise capacity (48), no persistent GH-induced changes were observed over 7 yr.

In conclusion, GH treatment induced a sustained decline in waist circumference, W/H, and subscapular fat together with an increase in body water and FFM and a decline in percentage of body fat by BIA. No significant effects on carbohydrate metabolism, insulinemia, lipid concentrations, or cardiac function were observed.

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References

- Cuneo RC, Salomon F, McGauley GA, Sönksen PH. 1992 The growth hormone deficiency syndrome in adults. *Clin Endocrinol (Oxf)*. 37:387–397.
- Lamberts SWJ, Valk NK, Binnerts A. 1992 The use of growth hormone in adults: a changing scene. *Clin Endocrinol (Oxf)*. 37:111–115.
- Salomon F, Cuneo RC, Hesp R, Sönksen PH. 1989 The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med*. 321:1797–1803.
- Bengtsson B-Å, Edén S, Lonn L, et al. 1993 Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab*. 76:309–317.
- Shahi M, Beshyah SA, Hackett D, Sharp PS, Johnston DG, Foale RA. 1992 Myocardial dysfunction in treated adult hypopituitarism: a possible explanation for increased cardiovascular mortality. *Br Heart J*. 67:92–96.
- Beshyah SA, Shahi M, Foale R, Johnston DG. 1995 Cardiovascular effects of prolonged growth hormone replacement in adults. *J Intern Med*. 237:35–42.
- Toogood AA, Adams JE, O'Neil PA, Shalet SM. 1996 Body composition in growth hormone deficient adults over the age of 60 years. *Clin Endocrinol (Oxf)*. 45:399–404.
- Beshyah SA, Henderson A, Niththyanathan R, Sharp P, Richmond W, Johnston DG. 1994 Metabolic abnormalities in growth hormone-deficient adults. II. Carbohydrate tolerance and lipid metabolism. *Endocrinol Metab*. 1:173–180.
- Beshyah SA, Freemantle C, Thomas E, Page B, Murphy M, Johnston DG. 1995 Comparison of measurements of body composition by total body potassium, bioimpedance analysis, and dual-energy x-ray absorptiometry in hypopituitary adults before and during growth hormone treatment. *Am J Clin Nutr*. 61:1186–1194.
- Beshyah SA, Freemantle C, Thomas E, et al. 1995 Abnormal body composition and reduced bone mass in growth hormone deficient hypopituitary adults. *Clin Endocrinol (Oxf)*. 42:179–189.
- Beshyah SA, Freemantle C, Shahi M, et al. 1995 Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. *Clin Endocrinol (Oxf)*. 42:73–84.
- Spinks TJ, Bewley DK, Ranicar ASO, Joplin GF. 1977 Measurement of total body calcium in bone disease. *J Radioanal Chem*. 37:345–355.
- Boddy K, King PC, Hume R, Weyers E. 1972 The relationship of total body potassium to height, weight and age in normal adults. *J Clin Pathol*. 25:512–517.
- Kushner RF, Schoeller DA. 1986 Estimation of total body water by bioelectrical-impedance analysis. *Am J Clin Nutr*. 44:417–424.
- Pace HV, Rathbun EN. 1945 Studies on body composition, body water and chemically combined nitrogen content in relation to fat content. *J Biol Chem*. 158:685–691.
- Mazess R, Barden HS, Bisek JP, Hanson J. 1990 Dual-energy x-ray absorptiometry for total and regional bone-mineral and soft-tissue composition. *Am J Clin Nutr*. 51:1106–1112.
- Hampton SM, Morgan LM, Tredger JA, Cramb R, Marks V. 1986 Insulin and C-peptide levels after oral and intravenous glucose. *Diabetes*. 35:612–616.
- Teale JD, Marks V. 1986 The measurement of insulin like growth factor 1: Clinical applications and significance. *Ann Clin Biochem*. 23:413–424.
- Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. 1974 Enzymatic determination of total serum cholesterol. *Clin Chem*. 20:470–475.
- Warnick GR, Benderson J, Albers JJ. 1982 Dextran sulphate-Mg²⁺ precipitation procedure for quantitation of high-density lipoprotein cholesterol. *Clin Chem*. 28:1379–1388.
- Friedwald WT, Levy RI, Fredrickson DS. 1972 Estimation of the concentration of low-density-lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 18:499–502.
- Elphick MC. 1968 Modified colirimetric ultramicrometric method for estimating NEFA in serum. *J Clin Pathol*. 21:567–570.
- Reichek N, Helak J, Plappert T, St. John Sutton M, Weber KT. 1983 Anatomic validation of left ventricular mass estimates from clinical two-dimensional echocardiography: initial results. *Circulation*. 67:348–352.
- Nishimura RA, Abel MD, Hatle LK, Tajik AJ. 1989 Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. II. Clinical studies. *Mayo Clin Proc*. 64:181–204.
- Cuneo RC, Judd S, Wallace JD, et al. 1998 The Australian Multicenter Trial of Growth Hormone (GH) Treatment in GH-Deficient Adults. *J Clin Endocrinol Metab*. 83:107–116.
- Al-Shoumer KAS, Page B, Thomas E, Murphy M, Beshyah SA, Johnston DG. 1996 Effects of four years' treatment with biosynthetic human growth hormone (GH) on body composition in GH-deficient hypopituitary adults. *Eur J Endocrinol*. 135:559–567.
- Johannsson G, Rosén T, Lindstedt G, Bosaeus I, Bengtsson B-Å. 1996 Effects of 2 years of growth hormone treatment on body composition and cardiovascular risk factors in adults with growth hormone deficiency. *Endocrinol Metab*. 3:3–12.
- Gibney J, Wallace JD, Spinks T, et al. 1999 The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. *J Clin Endocrinol Metab*. 84:2596–602.
- De Boer H, Blok GJ, Voerman HJ, Phillips M, Schouten JA. 1994 Serum lipids in growth hormone deficient men. *Metabolism*. 43:199–203.
- Ogle GD, Moore B, Lu PW, Craighead A, Briody JN, Cowell CT. 1994 Changes in body composition and bone density after discontinuation of growth hormone therapy in adolescence: an interim report. *Acta Paediatr*. 399(Suppl):3–7.
- De Boer H, Blok GJ, Van der Veen EA. 1995 Clinical aspects of growth hormone deficiency in adults. *Endocr Rev*. 16:63–75.
- Snel YEM, Brummer RJM, Doerga ME. 1995 Adipose tissue assessed by magnetic resonance imaging in growth hormone-deficient adults: the effect of growth hormone replacement and a comparison with control subjects. *Am J Clin Nutr*. 61:1290–1294.
- O'Neal DN, Kalfas A, Dunning PL, et al. 1994 The effects of 3 months of recombinant growth hormone (GH) therapy on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults: a minimal model analysis. *J Clin Endocrinol Metab*. 79:975–983.
- Edén S, Wiklund O, Oscarsson J, Rosén T, Bengtsson B-Å. 1993 Growth hormone treatment of growth hormone deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. *Arterioscler Thromb*. 13:296–301.
- Corpas E, Harman SM, Blackman MR. 1993 Human growth hormone and human aging. *Endocr Rev*. 14:20–39.
- Toogood AA, Shalet SM. 1998 Ageing and growth hormone status. *Clin Endocrinol Metab*. 12:281–296.
- Megnien JL, Denarie N, Cocaul M, Simon A, Levenson J. 1999 Predictive value of waist-to-hip ratio on cardiovascular risk events. *Int J Obes Relat Metab Disord*. 23:90–97.
- Vahl N, Jorgensen JOL, Hansen TB, et al. 1998 The favourable effects of growth hormone (GH) substitution on hypercholesterolaemia in GH-deficient adults are not associated with concomitant reductions in adiposity. A 12-month placebo-controlled study. *Int J Obes Relat Metab Disord*. 22:529–536.
- Johannsson G, Marin P, Lonn L, et al. 1997 Growth hormone treatment of

- abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. *J Clin Endocrinol Metab.* 82:727-734.
40. **Rosén T, Bengtsson B-Å.** 1990 Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet.* 336:285-288.
 41. **Markussis V, Beshyah SA, Fisher C, Sharp P, Nicolaidis AN, Johnston DG.** 1992 Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet.* 340:1188-1192.
 42. **Al-Shoumer KAS, Gray R, Anyaoku V, et al.** 1998 Effects of four years' treatment with biosynthetic human growth hormone (GH) on glucose homeostasis, insulin secretion and lipid metabolism in GH-deficient adults. *Clin Endocrinol (Oxf).* 48:795-802.
 43. **Caidhal K, Edén S, Bengtsson B-Å.** 1994 Cardiovascular and renal effects of growth hormone. *Clin Endocrinol (Oxf).* 40:393-400.
 44. **Christiansen JS, Jorgensen JOL, Thuesen L.** 1996 Cardiovascular aspects of growth hormone replacement therapy in adults. *Endocrinol Metab.* 3(Suppl A):19-22.
 45. **Kannel WB.** 1992 Left ventricular hypertrophy as a risk factor in arterial hypertension. *Eur Heart J.* 13(Suppl D):82-88.
 46. **Spirito P, Maron BJ.** 1988 Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J.* 59:672-679.
 47. **Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL.** 1974 Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation.* 50:1179-1189.
 48. **Rutherford OM, Jones DA, Round JM, Buchanan CR, Preece MA.** 1991 Changes in skeletal muscle and body composition after discontinuation of growth hormone treatment in growth hormone deficient young adults. *Clin Endocrinol (Oxf).* 34:469-475.