

CLINICAL STUDY

Fifteen years of GH replacement improves body composition and cardiovascular risk factors

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Abstract

Objective: Few studies have determined the effects of more than 5–10 years of GH replacement in adults on body composition and cardiovascular risk factors.

Design/patients: In this prospective, single-center, open-label study, the effects of 15 years of GH replacement on body composition and cardiovascular risk factors were determined in 156 hypopituitary adults (93 men) with adult-onset GH deficiency (GHD). Mean age was 50.5 (range 22–74) years at study start. Body composition was measured using dual-energy X-ray absorptiometry. **Results:** The mean initial GH dose of 0.55 (S.E.M. 0.03) mg/day was gradually lowered to 0.40 (0.01) mg/day after 15 years. The mean serum IGF1 SDS increased from –1.53 (0.10) at baseline to 0.74 (0.13) at study end ($P < 0.001$ vs baseline). Lean soft tissue (LST) increased to 3% above the baseline level at study end ($P < 0.001$). After a 9% decrease during the first year of treatment ($P < 0.001$ vs baseline), body fat (BF) started to increase and had returned to the baseline level after 15 years. Serum levels of total cholesterol and LDL-cholesterol decreased and serum HDL-cholesterol level increased. Fasting plasma glucose increased from 4.4 (0.1) at baseline to 4.8 (0.1) mmol/l at study end ($P < 0.001$). However, blood HbA1c decreased from 5.0 (0.1) to 4.6 (0.1) % ($P < 0.001$).

Conclusions: Fifteen-year GH replacement in GHD adults induced a transient decrease in BF and sustained improvements of LST and serum lipid profile. Fasting plasma glucose increased whereas blood HbA1c was reduced.

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Introduction

GH-deficient (GHD) adults have abnormal body composition (1), impaired lipid profile (1), decreased insulin sensitivity (1), and increased cardiovascular morbidity and mortality (2, 3). Within the first year of treatment, GH replacement therapy normalizes the alterations in body composition through a reduction in body fat (BF) and an increase in lean mass (4, 5, 6). The increase in lean mass is sustained for up to 10 years during GH replacement (7, 8). However, BF gradually returns toward baseline values during prolonged GH replacement (7, 8), which could possibly be an effect of the normal aging of the patients (8).

GH replacement improves serum lipid profile with a decrease in serum LDL-cholesterol (LDL-C) and, in most studies, an increase in serum HDL-cholesterol (HDL-C) (7, 8, 9, 10). Depending on the duration of GH replacement and the dose of GH administered, serum triglyceride (TG) level may be increased, unchanged, or decreased (7, 8, 9, 10).

The effect of GH on glucose homeostasis is still controversial. Both unchanged (4) and increased (8, 9, 10, 11) fasting plasma glucose concentrations have been observed. The acute insulin antagonist effect of GH could be one mechanism underlying the deterioration of glucose homeostasis seen during the first months of GH replacement (12). During long-term GH replacement, insulin sensitivity has either continued to be decreased (4, 13), returned to the baseline level (14), or increased compared with baseline (15). A fixed low GH dose of 0.1 mg increased insulin sensitivity compared with unchanged insulin sensitivity with a standard dose aiming at normalizing insulin-like growth factor 1 (IGF1) (16). In one study, 7 years of GH replacement provided protection against the normal age-related decline in insulin sensitivity (12), possibly as a result of the improvements in body composition (12).

The effects of GH replacement on body composition and cardiovascular risk factors after more than 10 years of treatment have not been previously studied. However, we demonstrated that 15 years of GH replacement

induced sustained increases in total body and lumbar (L2–L4) spine bone mineral content (BMC) and bone mineral density (BMD), whereas femur neck BMC and BMD increased up to 7 years of GH replacement and then decreased toward baseline levels (17). As GHD is a chronic disease and GH replacement may continue over decades, long-term studies are of importance. The aim of this prospective, single-center, open-label study was to evaluate the effects of 15 years of GH replacement in 156 hypopituitary adults on body composition and cardiovascular risk factors.

Materials and methods

Patients

In this study, 156 consecutive GHD adults (93 men) with a mean age of 50.5 (range 22–74) years were included in 1990–1996. All patients had adult-onset pituitary disease and all had known pituitary disease or other anterior pituitary hormonal deficiencies. The pituitary deficiency was mainly caused by pituitary tumors and/or their treatment (Tables 1 and 2). The patients had been treated with pituitary surgery ($n=73$), surgery and radiotherapy ($n=47$), radiotherapy alone ($n=13$), and no treatment ($n=23$).

Most patients had multiple anterior pituitary hormonal deficiencies (Tables 1 and 2). Possibly due to late effects of radiotherapy, several patients had more pituitary hormonal deficiencies at study end compared with baseline (Tables 1 and 2). In 145 of the patients, the diagnosis of GHD was based on a peak GH $<3 \mu\text{g/l}$ during a stimulation test (insulin ($n=137$), GHRH ($n=5$), and glucagon ($n=3$)). In nine patients, the diagnosis was based on a 24-h GH profile (sampling every 30 min). In two patients, both having a known anterior pituitary disease and three additional hormonal deficiencies, the diagnosis was based on a low serum

IGF1 level. When required, patients received adequate and stable therapy with glucocorticoids, thyroid hormone, and desmopressin. All the testosterone-deficient men received testosterone therapy. However, at baseline, 60% (34 out of 57) of the estrogen-deficient women received estrogen replacement therapy.

Twenty-one of the patients died during the study period (cerebral infarction ($n=3$), myocardial infarction ($n=3$), pneumonia ($n=3$), sudden death of unknown cause ($n=3$), renal cancer ($n=1$), subarachnoid hemorrhage ($n=1$), chronic obstructive pulmonary disease ($n=1$), perimyocarditis ($n=1$), pulmonary embolism ($n=1$), coronary artery disease ($n=1$), sepsis ($n=1$), dementia ($n=1$), and cortisol deficiency during gastroenteritis ($n=1$)). Thirteen (62%) of the patients who died had previously been treated with pituitary irradiation therapy. Eighteen patients discontinued GH replacement (lack of compliance ($n=9$), old age ($n=3$), colon cancer ($n=1$), stroke ($n=1$), epilepsy after stroke ($n=1$), pulmonary cancer ($n=2$), and chronic lymphocytic leukemia ($n=1$)). Eight patients were lost to follow-up because they moved to other cities or abroad. Thus, 109 of the 156 patients completed the 15 years of GH replacement. The total number of patient years was 1971. All patients were, however, retained in the statistical analysis according to the intention-to-treat approach used.

For patients receiving medical therapy for hypertension, hypercholesterolemia, or diabetes, the last value before treatment (measures of blood pressure, lipid profile, or glucose metabolism) was carried forward in the statistical analysis.

Study protocol

This is an ongoing, prospective, open-label treatment trial. The first 64 patients initially received a weight-based GH dose of $11.9 \mu\text{g/kg}$ per day (0.25 IU/kg per week). During the first years of treatment, the GH dose was gradually lowered and individualized when the weight-based dose regimen was abandoned. In the remaining 92 patients, the dose of GH was individualized from the beginning, with the aim of normalizing serum IGF1 concentration and body composition in each patient (18).

At baseline, and after each year of GH replacement until 5 years, and then after 7, 10, 12, and 15 years, physical and laboratory examinations were performed including measurements of body composition. Dose titration and safety monitoring were performed every third month during the first year and every sixth month thereafter. Body weight was measured in the morning to the nearest 0.1 kg, and body height was measured to the nearest 0.01 m. BMI was calculated as the weight in kilograms divided by the height in meters squared. No effort was made to influence the patients' physical activity level during the study period.

Table 1 Causes of pituitary deficiency in the study population of 156 (93 men) adults with adult-onset GHD.

	Men (<i>n</i>)	Women (<i>n</i>)	Total (<i>n</i>)
Non-secreting pituitary adenoma	53	22	75
Secreting pituitary adenoma	15	19	34
Craniopharyngioma	9	7	16
Empty sella	4	3	7
Sheehan's syndrome	0	3	3
Idiopathic	2	3	5
Pituitary apoplexia	2	1	3
Sarcoidosis	2	2	4
Traumatic brain injury	1	1	2
Other pathology ^a	5	2	7
Total	93	63	156

GHD, GH deficiency.

^aContains one patient with a meningioma, one with histiocytosis X, one with a cholesteatoma, one with an ependymoma, one with a dysgerminoma, one with a granular cell tumor, and one with APS2.

Table 2 Number of pituitary deficiencies at baseline and after 15 years of GH replacement (study end) in the study population of 156 (93 men) adults with adult-onset GHD.

Type of deficiency	Baseline (n)			Study end (n)		
	Men	Women	Total	Men	Women	Total
Isolated GHD	11	2	13	4	1	5
1 Additional deficiency	10	10	20	3	7	10
2 Additional deficiencies	12	9	21	17	7	24
3 Additional deficiencies	60	42	102	69	48	117
Diabetes insipidus	25	17	42	26	20	46

GHD, GH deficiency.

Ethical considerations

Informed consent was obtained from all patients. The study was approved by the Regional Ethics Review Board at the University of Gothenburg and the Swedish Medical Products Agency (Uppsala, Sweden).

Body composition

Dual-energy X-ray absorptiometry (DXA) was used to measure lean soft tissue (LST), BF, and trunk fat (TF) as described previously (19). Appendicular LST (ALST) was calculated as the sum of LST in the arms and legs and used to estimate skeletal muscle mass (20). From the start of the study until the end of 1999, a LUNAR DPX-L scanner was used (Scanex, Helsingborg, Sweden). Software versions were changed several times (from 1.1 to lastly 1.35), version 1.33 being used during the major part of this period of the study. In-house precision error on the scanner used, as determined from duplicate examinations in ten healthy subjects, was 1.5% for LST.

From January 2000, a LUNAR Prodigy scanner (Scanex) was used. Software versions were upgraded several times during data collection, from version 5.70 to 8.10. The precision of the scanner was estimated from repeated measurements on different days in 30 subjects with coefficient of variation (CV) of LST being 1.1%. Before the change of scanner in the end of 1999, the old and new DXA machines were compared by measurements on the same day on both machines in 30 subjects. No significant differences in body composition parameters were found.

Biochemical analysis

All biochemical analyses were performed at the Sahlgrenska University Hospital Laboratory, which is accredited according to international standards by the Swedish Board for Accreditation and Conformity Assessment (Swedac). Serum IGF1 concentration, until June 2004, was determined by a hydrochloric acid-ethanol extraction RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Interassay and intra-assay CV were 5.4 and 6.9% respectively at a mean serum IGF1 level of 126 µg/l and 4.6 and 4.7% respectively at mean serum IGF1 level of 327 µg/l. From

June 2004 to August 2006, serum IGF1 concentration was determined using a chemiluminescence immunoassay (Nichols Advantage; Nichols Institute Diagnostics) (21). From September 2006, serum IGF1 level was determined using an automated chemiluminescent assay system (IMMULITE 2500, Diagnostic Products Corp., Los Angeles, CA, USA). The WHO NIBSC 1st IRR 87/518 standard was used for calibration throughout the study period. The individual serum IGF1 values were compared with age- and sex-adjusted values obtained from a reference population (22), and the individual IGF1 SDS were then calculated (23).

Serum levels of total cholesterol (TC), HDL-C, and TGs were measured using enzymatic methods (8). LDL-C was calculated according to Friedewald's formula adjusted to SI units (24). Serum LDL-C was excluded in patients with serum TG > 4.3 mmol/l. Blood glucose was measured with the glucose-6-phosphate dehydrogenase method (Kebo Lab, Stockholm, Sweden) until April 1998. From May 1998, plasma glucose was measured with a hexokinase method (Roche Diagnostics Scandinavia AB). All blood glucose values obtained before May 1998 were converted to plasma glucose values using a multiplication factor of 1.11. Blood HbA1c was determined by HPLC (Waters, Millipore AB, Solna, Sweden).

Statistical analysis

The descriptive statistical results are presented as the mean and s.e.m. For all variables, within-group differences were calculated using a repeated-measures ANOVA, with all data obtained from all time points, and with time as the independent variable. *Post hoc* analysis was performed using Student–Newman–Keuls test. Gender differences and differences between women receiving or not receiving estrogen replacement were calculated by a two-way ANOVA with gender or estrogen treatment as the independent variables. In order to eliminate the baseline differences, data were transformed into percent change or change from baseline before the between-group analyses.

All analyses were performed according to the intention-to-treat principle (using the carry forward principle). A two-tailed $P < 0.05$ was considered significant.

Results

GH dose, serum IGF1, and BMI

The dose of GH prescribed at the baseline visit was 0.55 (0.03) mg/day (Table 3). The dose was then gradually reduced to 0.40 (0.01) mg/day at study end. Mean IGF1 SDS (adjustment for age and gender) was above the normal range during the first 3 years, but after that, it was within the normal range (± 2 s.d.). There was no change in height or weight whereas BMI increased from 27.7 kg/m² at baseline to 28.3 kg/m² at study end ($P < 0.01$). Systolic blood pressure increased whereas diastolic blood pressure was unchanged.

DXA body composition

LST increased by 3% during the first year of GH replacement and was then stable throughout the study period (Fig. 1). Also, LST expressed as a percentage of body weight increased significantly ($P < 0.001$; Table 4). ALST increased up to 10 years of GH replacement ($P < 0.05$) and then decreased toward the baseline value.

Total BF decreased by 9% during the first year of treatment ($P < 0.001$), was still below the baseline level after 10 years ($P < 0.01$), but had returned to the baseline level at study end (Fig. 1). However, total BF expressed as a percentage of body weight was still significantly below the baseline level at study end ($P < 0.01$; Table 4). TF decreased by 10% during the first year ($P < 0.001$), stayed below the baseline level up to 5 years ($P < 0.001$), and then increased to 6% above the baseline level after 15 years ($P < 0.001$; Fig. 1).

Lipids and glucose

There were sustained decreases in serum levels of TC and LDL-C (both $P < 0.001$ vs baseline; Table 4). Serum HDL-C concentration increased ($P < 0.001$ vs baseline).

There was no change in serum TG level. Fasting plasma glucose level increased throughout the study period ($P < 0.001$), whereas blood HbA1c level decreased ($P < 0.001$).

Diabetes mellitus

Four patients (two men) had diabetes mellitus (DM) type 2 at baseline. During the study period, 12 patients (nine men) were diagnosed and treated for DM type 2 (within 5 years, $n = 2$; after 5–10 years, $n = 7$; after > 10 years, $n = 3$). Five (42%) of these 12 patients had previously been treated with pituitary irradiation therapy. At baseline, the patients who later developed DM type 2 had higher body weight (96.4 vs 81.3 kg; $P < 0.01$), BF (35.3 vs 26.6 kg; $P < 0.01$), TF (18.1 vs 14.1 kg; $P < 0.01$), fasting plasma glucose (5.1 vs 4.4 mmol/l; $P < 0.001$), and serum TG level (2.3 vs 1.7 mmol/l; $P < 0.05$).

Gender differences

Except for the first year of treatment, women received a higher GH dose than men ($P < 0.001$). The mean initial GH dose was 0.59 (0.04) mg/day in men and 0.48 (0.04) mg/day in women ($P = 0.06$), whereas at study end, the dose was 0.37 (0.01) and 0.44 (0.02) mg/day respectively ($P < 0.01$). IGF1 SDS increased from -1.30 (0.13) at baseline to 0.88 (0.18) after 15 years of GH replacement in men and from -1.89 (0.15) to 0.53 (0.18) in women ($P < 0.001$ men vs women). At baseline, women had a higher serum TC level (6.3 (1.4) vs 5.8 (0.13) mmol/l, $P < 0.05$) and higher serum HDL-C level (1.4 (0.06) vs 1.1 (0.03) mmol/l, $P < 0.001$) than men. Similar differences in serum lipid profile were seen after 15 years of GH replacement (data not shown). In women, the decrease in serum LDL-C was marginally greater than that in men ($P < 0.05$; data not shown). There was no gender difference in the treatment effect in terms of other

Table 3 The dose of GH during 15 years of GH replacement in 156 GHD adults and the effects of this treatment on serum IGF1 concentration, IGF1 SDS, height, weight, BMI, and blood pressure. All values are shown as the mean (s.e.m.).

	Baseline (n=156)	1 year (n=154)	3 years (n=146)	5 years (n=136)	7 years (n=135)	10 years (n=125)	12 years (n=117)	15 years (n=109)	P value (10–15 years)
Dose of GH (mg/day)	0.55 (0.03)	0.56 (0.02)	0.56 (0.02) [‡]	0.47 (0.02) [‡]	0.44 (0.01) [‡]	0.42 (0.01) [‡]	0.41 (0.01) [‡]	0.40 (0.01) [‡]	<0.001
Serum IGF1 (µg/l)	109 (5)	307 (10) [‡]	294 (9) [‡]	269 (9) [‡]	241 (8) [‡]	204 (7) [‡]	185 (7) [‡]	183 (7) [‡]	<0.001
IGF1 SDS	-1.53 (0.10)	2.49 (0.21) [‡]	2.32 (0.17) [‡]	1.91 (0.17) [‡]	1.48 (0.15) [‡]	0.89 (0.19) [‡]	0.61 (0.13) [‡]	0.74 (0.13) [‡]	NS
Height (cm)	172.3 (0.8)	172.6 (0.8)	172.6 (0.8)	172.4 (0.8)	172.1 (0.8)	171.7 (0.8)	171.6 (0.9)	171.5 (0.9)	NS
Weight (kg)	82.5 (1.3)	82.0 (1.3)	82.8 (1.3)	83.1 (1.3)	83.7 (1.3)	83.3 (1.3)	83.3 (1.3)	83.5 (1.3)	NS
BMI (kg/m ²)	27.7 (0.4)	27.5 (0.4)	27.7 (0.4)	27.9 (0.4)	28.2 (0.38) [*]	28.2 (0.4) [*]	28.2 (0.4) [‡]	28.3 (0.4) [‡]	NS
SBP (mmHg)	123.4 (1.3)	122.2 (1.3)	125.3 (1.4)	124.5 (1.3)	127.1 (1.4)	130.5 (1.5) [‡]	131.7 (1.5) [‡]	133.4 (1.5) [‡]	<0.05
DBP (mmHg)	78.0 (0.9)	75.4 (0.9)	76.1 (0.8)	75.4 (0.9)	76.0 (0.8)	77.5 (0.8)	79.4 (0.8)	79.3 (0.8)	<0.01

The statistical analyses are based on a one-way ANOVA followed by Student–Newman–Keuls *post hoc* test. P values (10–15 years) are based on the statistical analysis between the 10- and 15-year values. * $P < 0.05$, [†] $P < 0.01$, and [‡] $P < 0.001$ (for the dose of GH vs initial GH dose; for other variables vs baseline). NS, non-significant; GHD, GH deficiency; SBP, systolic blood pressure; DBP, diastolic blood pressure; IGF1, insulin-like growth factor 1.

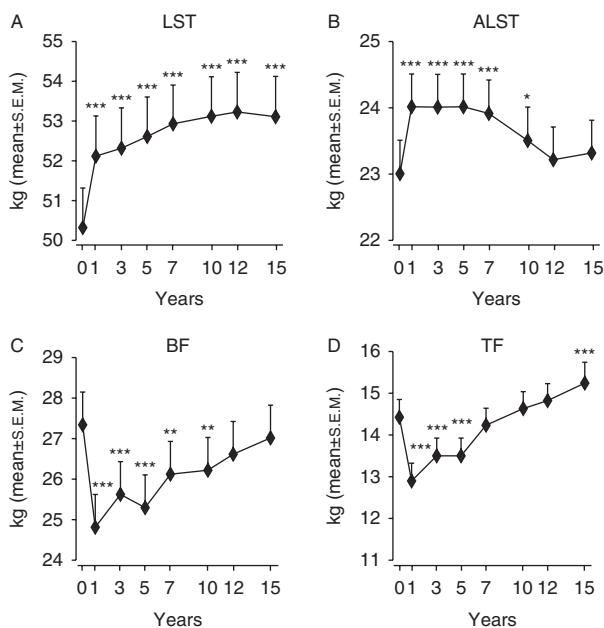


Figure 1 Effects of 15 years of GH replacement in 156 adults with adult-onset GHD on (A) LST, (B) ALST, (C) BF, and (D) TF as measured using dual-energy X-ray absorptiometry (DXA). All values are shown as the mean (s.e.m.). The statistical analyses are based on a repeated-measures ANOVA followed by Student–Newman–Keuls *post hoc* test. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ vs baseline. LST, lean soft tissue; ALST, appendicular lean soft tissue; BF, body fat; TF, trunk fat.

serum lipid levels, plasma glucose, blood HbA1c, blood pressure, or body composition (data not shown).

Women on estrogen replacement vs women without estrogen replacement

Of the 57 gonadotropin-deficient women, 34 (60%) at study start and 15 (26%) at study end received estrogen replacement therapy. The reason for fewer women receiving estrogen replacement at study end compared with baseline was discontinuation because of age. The women receiving estrogen replacement at baseline were younger (estrogen, mean age 45.3 (1.8) years vs not estrogen, 58.9 (2.0) years; $P < 0.001$). Women on estrogen replacement therapy received a higher dose of GH than women without estrogen replacement ($P < 0.001$). There was no difference in the baseline level or the treatment response in any variable studied between women with or without estrogen replacement at baseline.

Discussion

This single-center study is the longest and largest observational study of the effects of GH replacement on body composition and cardiovascular risk factors in patients with adult-onset GHD. The results demonstrate

that 15 years of GH replacement induced a transient decrease in BF and sustained improvements of LST and serum lipid profile.

The first 64 patients initially received a weight-based dose of GH, which was gradually lowered and individualized, whereas the remaining patients received individualized GH replacement from the beginning. This resulted in supraphysiological IGF1 SDS values during the first 3 years of treatment, but during the remaining part of the study, mean IGF1 SDS was within the normal range (± 2 s.d.). The 15 years of GH replacement increased BMI as observed in other studies (8, 9, 10). This suggests that BMI increases during long-term GH replacement as in the general population during a 15-year period (25).

There was a sustained increase in total LST. By contrast, ALST, used as an estimate of skeletal muscle mass (20), returned to the baseline level after 10 years of GH replacement. This is in accordance with our previous results on muscle strength, which after an initial increase decreases with age as in the background population (26). Previous studies have shown a greater effect of GH on proximal compared with distal lean mass (27), which might be in line with our results of increased total LST but unchanged ALST after 15 years of GH replacement. However, whether the increase in proximal (mainly trunk) lean mass after 15 years represents increases in muscle tissue, visceral organs, and/or connective tissue cannot be determined using DXA.

During the first year of GH replacement, in line with the results of previous short-term studies (4, 6) and a recent meta-analysis (5), total body and TF decreased. After the initial decrease, total BF gradually returned to the baseline level, whereas TF was even above the baseline level at study end. This is in line with increased abdominal fat mass in relation to peripheral fat mass seen in normal aging (28). Although BF returned to the baseline level, total BF expressed as a percentage of body weight was still significantly below the baseline level at study end. This suggests that 15 years of GH replacement has, after correction for body weight, a sustained effect on the relative amount of BF.

Improvements in serum lipid profile, with increased HDL-C and decreased TC and LDL-C, were sustained. This is likely not explained by the transient improvements in body composition. Direct effects of GH on lipid metabolism are supported by previous studies. GH increases the expression of LDL receptors (29) and enhances the catabolism of LDL (30). GH administration may increase the turnover of LDL to a higher degree than indicated by changes seen in serum LDL-C concentrations (31), and GH increases very LDL-apolipoprotein B turnover (32). Furthermore, as we have previously observed (8), fasting blood glucose increased whereas blood HbA1c was reduced. Although the meaning of this finding is unclear, it could suggest that insulin sensitivity was approximately unchanged.

Table 4 Effects of 15 years of GH replacement in 156 adults with adult-onset GHD on body composition corrected for body weight, serum lipid profile, fasting plasma glucose, and blood HbA1c. All values are shown as the mean (S.E.M.).

	Baseline (n=156)	1 year (n=154)	3 years (n=146)	5 years (n=136)	7 years (n=135)	10 years (n=125)	12 years (n=117)	15 years (n=109)	P value (10–15 years)
Body composition									
LST/weight (%)	62.2 (0.7)	65.2 (0.8)***	64.6 (0.8)***	64.8 (0.8)***	64.5 (0.8)***	64.3 (0.8)***	64.2 (0.8)***	63.7 (0.8)***	<0.01
ALST/weight (%)	28.3 (0.4)	29.8 (0.4)***	29.5 (0.4)***	29.5 (0.4)***	29.2 (0.4)***	28.8 (0.4)***	28.6 (0.4)	28.5 (0.4)	<0.01
BF/weight (%)	33.7 (0.8)	30.9 (0.8)***	31.5 (0.8)***	31.0 (0.8)***	31.7 (0.8)***	32.0 (0.8)***	32.3 (0.8)***	32.7 (0.8)**	<0.001
TF/weight (%)	20.7 (0.4)	18.9 (0.4)***	19.3 (0.5)***	19.5 (0.6)***	20.2 (0.5)*	20.5 (0.6)	20.5 (0.6)	21.2 (0.7)**	<0.001
Serum lipids									
TC (mmol/l)	6.0 (0.1)	5.8 (0.1)*	5.7 (0.1)***	5.5 (0.1)***	5.5 (0.1)***	5.4 (0.1)***	5.4 (0.1)***	5.5 (0.1)***	NS
LDL-C (mmol/l)	4.0 (0.1)	3.7 (0.1)***	3.6 (0.1)***	3.4 (0.1)***	3.4 (0.1)***	3.3 (0.1)***	3.2 (0.1)***	3.3 (0.1)***	NS
HDL-C (mmol/l)	1.2 (0.03)	1.3 (0.03)	1.3 (0.03)*	1.3 (0.03)*	1.3 (0.03)*	1.4 (0.07)***	1.4 (0.04)***	1.4 (0.04)***	NS
TG (mmol/l)	1.7 (0.1)	1.8 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)	NS
Glucose metabolism									
Glucose (mmol/l)	4.4 (0.05)	4.7 (0.05)***	4.6 (0.05)**	4.6 (0.05)**	4.7 (0.06)***	4.8 (0.06)***	4.8 (0.05)***	4.8 (0.06)***	NS
HbA1c (%)	5.0 (0.04)	5.0 (0.05)	4.9 (0.05)	4.8 (0.05)	4.7 (0.06)***	4.6 (0.07)***	4.6 (0.06)***	4.6 (0.06)***	NS

The statistical analyses are based on a repeated-measures ANOVA followed by Student–Newman–Keuls *post hoc* test. P values (10–15 years) are based on the statistical analysis between the 10- and 15-year values. GHD, GH deficiency; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TGs, triglycerides; LST/weight, lean soft tissue as a percentage of body weight; ALST/weight, appendicular lean soft tissue as a percentage of body weight; BF/weight, body fat as a percentage of body weight; TF/weight, trunk fat as percentage of body weight.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs baseline

In further support of unchanged insulin sensitivity, serum TG level, which is inversely correlated with insulin sensitivity (31), was unchanged.

At baseline, four patients had DM type 2. GHD adults not receiving GH replacement are insulin resistant (33, 34) and may therefore be at increased risk of developing DM type 2. In two recently published studies based on international surveillance databases, patients with obesity and disturbed metabolic profile at baseline were at increased risk of diabetes (35, 36). One of the studies showed a higher overall risk of diabetes, in particular during the first year of GH replacement (36), and the other study showed a diabetes incidence that was similar or slightly increased compared with the background population (35). In our study, in which most patients received a low dose of GH at initiation of therapy, only two patients developed DM type 2 during the first 5 years of GH replacement. However, another nine patients developed DM type 2 during the remaining study period, suggesting that a proportion of GHD patients will develop DM type 2 with increasing duration of GH replacement and increasing age of the patients. In line with the results of the aforementioned studies (35, 36), the patients who developed DM type 2 were more obese and had more disturbed glucose at baseline. In a general population in Sweden aged 20–100 years, the incidence of DM type 2 was 378 cases per 100 000 and year (37). With this incidence, eight GHD patients would be expected to develop DM type 2, which indicates an increased risk in our patients compared with the normal population. Furthermore, in a Swedish multi-center study, the prevalence of diabetes was increased in GHD women but not in GHD men on GH replacement, partly attributed to reduced physical

activity and increased BMI in the GHD women (38). Therefore, whether increased risk of DM type 2 in adult GHD is due to impaired metabolic baseline status and sedentary life-style or whether the risk is accelerated by GH replacement needs to be determined in more detail in further studies.

During the study period, 21 patients died, equivalent to one death in 94 patient years. In one study from our center, there was one death in 180 patient years (39). One study based on the global KIMS database and one Dutch national study has observed a mortality rate of one death per 130–140 patient years, which was slightly higher than that expected in the background population (40, 41). Thus, the mortality rate was higher in this study but the patients were older at baseline and the mean follow-up time in the other studies was shorter, 4–6 years (39, 40, 41). Furthermore, whether the improvements in cardiovascular risk factors seen during the 15 years of GH replacement will result in reduced mortality from cardiovascular diseases (CVD) remain to be proven. In previous studies of hypopituitary patients not receiving GH replacement, all-cause mortality was almost doubled compared with that of the general population, mainly due to increased CVD mortality (2, 3). The mortality in hypopituitary patients receiving GH replacement in the Dutch national study and the KIMS study was 27 and 13% respectively higher than that of the background population (40, 41). CVD mortality remained increased in women in the Dutch national study (40, 41) whereas in the KIMS study, cerebrovascular but not cardiovascular mortality was increased (40, 41). Taken together, this could indicate that the beneficial effects of GH replacement on cardiovascular risk factors might

reduce CVD mortality, although all-cause mortality could still be increased compared with that in the general population. However, larger studies are needed to determine in more detail whether GH replacement can reduce the increased overall and cardiovascular mortality seen in untreated GHD.

Sixty (38%) of our patients had received pituitary irradiation therapy (combined surgery and radiotherapy, $n=47$, and radiotherapy alone, $n=13$), and 96 (62%) of our patients had not received radiotherapy. Thirteen (62%) of the 21 patients who died during the study period had previously received radiotherapy and five (42%) of the 12 patients who developed DM type 2 during the study period had previously received radiotherapy. Although the importance of previous radiotherapy needs to be evaluated in larger studies than the present one, these data might suggest that previous radiotherapy is a risk factor for increased mortality in hypopituitary patients whereas previous radiotherapy does not appear to be a major determinant of the risk of DM type 2 during GH replacement therapy.

Women received, in line with previous studies (8, 9, 42), a higher GH dose than men. Except for a marginally more beneficial reduction of serum LDL-C level in women, there were no gender differences in the treatment responses in any variables reflecting body composition or metabolic indices. This suggests similar responsiveness to long-term GH replacement in these variables if women receive a higher dose of GH than men. Gonadotropin-deficient women on estrogen replacement received a higher GH dose compared with those not receiving estrogen. However, the treatment response was similar in the two groups.

A limitation of the study is that there was no untreated control group. Furthermore, at the end of 1999, the DXA machine used was changed. The new DXA was, however, found to give similar estimates of body composition parameters as the old one. Finally, the assays for measurements of glucose and IGF1 were changed during the study period. Based on measurements in the local laboratory, a conversion factor of 1.11 was used to transfer blood glucose values to plasma glucose values. In terms of the IGF1 measurements, the WHO NIBSC 1st IRR 87/518 standard was used for calibration throughout the study period.

In conclusion, 15 years of GH replacement in hypopituitary adults resulted in a sustained increase in LST whereas most other changes in body composition were transient, possibly at least to some extent due to the normal aging of the patients. The improvements in lipid profile were sustained and taking into consideration the relatively small changes in body composition at study end, this indicates direct GH effects on lipid metabolism. The effects on glucose metabolism were conflicting, but possibly, glucose homeostasis was approximately unchanged. The risk of DM type 2 is, however, probably increased in obese GHD adults with impaired glucose homeostasis at baseline. Future larger

studies are needed to investigate whether the increased mortality seen in hypopituitary adults not receiving GH (2, 3) can be affected by GH replacement.

Declaration of interest

G Johannsson has received lecture fees from Pfizer, Novo Nordisk, Merck Serono, and Eli Lilly and is a member of the SAB for KIMS Pfizer. B-Å Bengtsson has previously received a research grant from Pharmacia/Pfizer. All other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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