CLINICAL STUDY

Sustained effects of recombinant GH replacement after 7 years of treatment in adults with GH deficiency

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Abstract

Context: The goal of GH replacement with recombinant human GH (rhGH) is to ameliorate symptoms, signs, and complications of adult GH deficiency (GHD) in the long term. To determine whether the observed short-term beneficial effects of rhGH treatment are sustained in the long term, we evaluated biochemical and anthropometric parameters after 7 years of rhGH replacement.

Patients and methods: After 2, 5, and 7 years of rhGH replacement, 63 adult GHD patients (30 men, 52 adult-onset GHD) were assessed. IGF-I increased during rhGH replacement, and a stable dose of rhGH was reached within 1 year of rhGH substitution. Thereafter, this individualized dose was continued.

Results: Plasma levels of total cholesterol and low-density lipoprotein cholesterol decreased even after 5 years of rhGH replacement (11% decrease, $P < 0.001$; 22% decrease, $P < 0.001$ respectively). High-density lipoprotein cholesterol levels increased during 7 years of rhGH replacement (1.4 ± 0.5 mmol/l at baseline vs 1.7 ± 0.5 mmol/l after 7 years, $P < 0.001$), whereas triglyceride concentrations remained unchanged. Fasting glucose levels increased during follow-up, mainly during the first 2 years of rhGH replacement (4.4 ± 0.7 mmol/l to 5.0 ± 1.0 mmol/l, $P < 0.001$). Body mass index increased during follow-up, whereas waist circumference and waist-to-hip ratio remained unchanged. Diastolic blood pressure decreased ($P = 0.002$), but when patients using antihypertensive medication were excluded this decrease did not reach significance ($P = 0.064$). Systolic blood pressure remained unchanged.

Conclusion: The beneficial effects of rhGH replacement, described after short-term rhGH replacement, are sustained in the long term up to 7 years.

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Introduction

Adult growth hormone (GH) deficiency (GHD) is characterized by an adverse cardiovascular metabolic profile: increased serum concentrations of serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and triglycerides (TG), decreased serum concentrations of high-density lipoprotein (HDL) cholesterol, and an altered body composition reflected in reduced muscle strength and mass, visceral obesity, and decreased bone mass (1). The goal of recombinant human GH (rhGH) replacement is to ameliorate symptoms and signs of the adult GHD syndrome. Short-term (up to 24 months) replacement therapy with rhGH decreases the plasma concentrations of LDL cholesterol, TC, also fat mass and diastolic blood pressure, and increases lean body mass, fasting glucose and insulin concentrations (2). Since GHD in general is an irreversible condition which requires long-term replacement, the question arises, whether these short-term changes are sustained during long-term rhGH replacement.

Götherström *et al.* reported results of 5 years of rhGH replacement in 118 patients, and documented decreases in TC, LDL cholesterol, TG, glycosylated hemoglobin, and body fat, and increases in HDL cholesterol and lean body mass (3). However, only three small studies have reported a follow-up duration of more than 5 years (maximum number of 12 patients, summarized in Table 3 (4–6)). To determine whether the beneficial effects of rhGH treatment are sustained in the long term in a larger cohort, we evaluated the effects of 7 years rhGH replacement on biochemical parameters and anthropometric parameters in our cohort of GHD adults.

Subjects and methods

Patients

We prospectively enrolled 88 consecutive patients with GHD (Table 1). After the initiation of treatment, 20 patients discontinued after a mean duration of rhGH

Table 1 Baseline characteristics of the total cohort and the 63 patients who completed 7 years of recombinant human growth hormone (rhGH) replacement.

	Total cohort (n=88)	Patients who completed 7 years (n=63)
Gender (M/F (n))	44/44	30/33
Age (years ± s.d.)	46.8 ± 14.0	46.7 ± 14.3
Age at onset (AO/CO (n))	71/17	52/11
BMI (kg/m ²)	25.9 ± 3.4	25.5 ± 3.3
Etiological diagnosis of GHD (n)		
Non-functioning adenoma	28	19
Functioning adenoma	17	14
Craniopharyngeoma	13	8
Cerebral malignancy	6	4
Sheehan's syndrome	4	4
Idiopathic	13	10
Other causes	5	4
Surgery (TS/TC (n))	37/25	30/14
Radiotherapy (n)	36	26
Anterior pituitary deficiencies (n)		
TSH/LH-FSH/ACTH/ADH	75/76/69/23	52/53/47/15

M, male; F, female; AO, adult onset; CO, childhood onset; BMI, body mass index; GHD, growth hormone deficiency TS, transsphenoidal; TC, transcranial; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; ACTH, adrenocorticotrophic hormone; ADH, anti-diuretic hormone.

treatment of 3.2 years (range 0.7–6.3 years), 2 patients died (acute cardiac arrest and acute stroke), and 3 were lost to follow-up (Fig. 1). Sixty-three patients completed 7 years of rhGH replacement. Baseline characteristics of the patients who did not complete the study did not differ from the patients who completed the study (gender/age/body mass index (BMI)/age at onset of GHD/etiological diagnosis/surgery/radiotherapy/pituitary deficiencies). Biochemical and anthropometric efficacy parameters were studied in these 63 patients who completed the 7 years of rhGH replacement. During follow-up, 1 patient, a 29-year-old male, with idiopathic GHD and a BMI of 37.5 kg/m² developed diabetes 7 years after the start of rhGH replacement. Biochemical and anthropometric

efficacy parameters were studied separately in seven patients who stopped after completion of 2 years of rhGH replacement and in five patients who stopped after completion of 5 years of rhGH replacement (eight patients dropped out before the first efficacy evaluation). There were no differences in responses to rhGH replacement for any of the efficacy parameters between the seven patients who stopped after 2 years and the patients who continued after 2 years. The response to rhGH replacement during 5 years was also the same for the five patients who stopped after 5 years and patients who continued after 5 years.

Treatment Protocol

Prior to the start of rhGH treatment, the diagnosis of GHD was established by a peak GH concentration < 3 µg/l during an insulin tolerance test (nadir blood glucose < 2.2 mmol). Patients were then prospectively enrolled in an open-label treatment protocol.

All patients were treated with s.c. injections of rhGH (Genotropin Pharmacia/Pfizer, Zomacton Ferring, or Norditropin NovoNordisk, Humatrope Lilly), given every evening. The initial dose of rhGH was 0.2 mg/day, which was individually adjusted each month in the first half year to achieve serum insulin-like growth factor-I (IGF-I) concentrations within the age-dependent laboratory reference range, aimed at SDS between 0 and +2. Thereafter, this individualized dose was continued for the duration of the study (see Fig. 2).

Mean basal IGF-I concentration was 9.1 ± 4.6 nmol/l and increased to 16.4 ± 6.4 nmol/l after 2 years (P<0.0001). At 5 years IGF-I was 22.2 ± 9.4 nmol/l (P<0.0001 vs basal and 2 years) and at 7 years 25.5 ± 9.9 nmol/l (P=0.05 vs 5 years). Fluid-related side effects were noticed in nine patients (14% of patients) only during the first and second year of rhGH replacement.

When secondary amenorrhea was present for more than 1 year, premenopausal women were defined as being luteinizing hormone (LH)/follicle-stimulating

Figure 1 Flow sheet of 88 consecutive growth hormone deficiency (GHD) adults enrolled in the open-label observational study. Other reasons for discontinuation consisted of non-specific complaints, pregnancy, no coverage of insurance, patient's mistake, severe depression, unknown (n=3). FU, follow-up.

Figure 2 Dose of recombinant human GH (rhGH) replacement used during 7 years. After 1 year, a stable daily dose was reached and after 7 years mean daily dose was 0.5 ± 0.3 mg. * $P < 0.001$ compared with baseline.

hormone (FSH) deficient. In men, LH/FSH deficiency was defined by a testosterone level below the reference range (8.0 nmol/l). Thyroid-stimulating hormone (TSH) deficiency was defined as total thyroxine (T_4) or free T_4 level below the reference range. Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insufficient increase in cortisol levels (absolute value < 0.55 μ mol/l) after a corticotropin-releasing hormone stimulation test or the insulin tolerance test. Patients received replacement therapy with hydrocortisone, L- T_4 , testosterone in men, and/or estrogen (15 females on oral estrogen replacement therapy and 2 on transdermal estrogens) in combination with progestagens in premenopausal women only. There were 17 premenopausal women and 17 postmenopausal women. Substitution therapy was monitored during replacement with rhGH and the respective dosages were adjusted as required. Thyroid hormone replacement dosing was started with 0.1 μ g/day and dose titration was based on clinical response and serum free T_4 concentrations within the reference range. In all patients with childhood-onset GHD, rhGH replacement was stopped for at least 3 months prior to retesting GH reserve, applying adult cut-off values.

Patients were treated with lipid-lowering medication and antihypertensive medication according to the discretion of their attending physicians. Two patients were already treated with lipid-lowering drugs at baseline and in seven additional patients, lipid-lowering drugs treatment was initiated during follow-up. All patients used statins. Four patients were already treated with antihypertensive medication at baseline and in seven additional patients antihypertensive treatment was initiated during follow-up. The antihypertensive medication consisted of diuretics, β -adrenoreceptor blockage drugs, calcium-antagonists, angiotensin-converting enzyme inhibitors, angiotensin type II receptor

antagonist and central acting antihypertensive medication, and combinations thereof.

Efficacy parameters

The following efficacy parameters were assessed before the start, and after 2, 5, and 7 years of rhGH replacement:

- Biochemical parameters: fasting levels of glucose, total cholesterol, HDL cholesterol, and TG. LDL cholesterol concentrations were calculated using the Friedewald formula. Patients were requested to fast overnight before blood samples were taken for laboratory measurements of lipid profiles and glucose.
- Anthropometric parameters: body weight and height, waist circumference, hip circumference, systolic and diastolic blood pressures (SBP and DBP respectively) were measured. BMI and waist-to-hip (WH) ratio were calculated. Body weight was measured to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.001 m. The BMI was calculated as weight in kilograms divided by the square of height in meters.

Assays

At baseline, during the first year, and at 2 and 5 years serum IGF-I (nmol/l) concentration was measured by RIA (INCSTAR Corp., Stillwater, MN, USA) after extraction and purification on octadecasilyl-silica columns. The detection limit of this assay is 1.5 nmol/l, and the inter-assay coefficient of variation was below 11%.

During the last 2 years of the study, a new assay was introduced. The serum IGF-I concentration (nanograms/milliliter) was measured using an immunometric technique on an Advantage Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The lower limit of detection was 6.0 ng/ml and intra-assay variation ($n = 250$) was 8.0 and 6.0% at mean plasma levels of 30 and 450 ng/ml respectively. Inter-assay variation was 8.7, 5.8, and 6.5% at mean IGF-I plasma levels of 33, 174, and 445 ng/l respectively ($n = 115$). The concentrations were converted to SI units by dividing by 7.65.

A Hitachi 747 autoanalyzer (Roche) was used to quantify serum concentrations of glucose, TC, and TG. HDL cholesterol was measured with a homogenous enzymatic assay (Hitachi 911, Roche). In 2003, the Hitachi 747 was replaced by a modular P 800 with no change in the chemistry components.

Statistics

Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS, Inc., Chicago, IL, USA).

Table 2 Biochemical and anthropometric parameters in GHD adults before and after 7 years of rhGH replacement.

	Baseline	7 years or rhGH replacement	P value
IGF-I (nmol/l)	9.1±4.6	25.5±9.9	<0.001
Fasting glucose (mmol/l)	4.4±0.7	5.0±1.0	<0.001
TC (mmol/l)	6.4±1.2	5.6±1.0	<0.001
LDL (mmol/l)	4.7±1.1	3.5±0.9	<0.001
HDL (mmol/l)	1.4±0.5	1.7±0.5	<0.001
TG (mmol/l)	1.6±0.9	1.7±1.2	NS
BMI (kg/m ²)	25.5±3.3	27.1±3.9	<0.001
Waist circumference (cm)	92.2±11.8	94.8±11.9	NS
WH ratio	0.9±0.08	0.9±0.08	NS
SBP (mmHg)	131.3±16.4	132.9±19.3	NS
DBP (mmHg)	84.0±9.2	80.1±8.2	0.002

IGF-I, insulin-like growth factor; LDL, lowdensity lipoprotein; HDL, high density lipoprotein; BMI, body mass index; TC, total cholesterol; TG, triglycerides; WH ratio, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Results are scored as the mean±s.d., unless specified otherwise. Independent samples *t*-tests and ANOVA repeated measurements with Bonferroni correction for multiple comparisons were used, when appropriate. Logarithmic transformation of the data was used to limit dispersion of the variance. *P* value <0.05 was assumed to represent a significant difference.

Results

Fasting plasma glucose levels significantly increased during follow-up by 15% ($P<0.001$, Table 2) due to a significant increase within the first 2 years (Fig. 3).

TC levels significantly decreased during follow-up by 11% ($P<0.001$, Table 2). Compared with baseline, this decrease became significant after 5 years of rhGH replacement ($P=0.006$) and decreased further thereafter (Fig. 3). LDL cholesterol concentrations significantly decreased during follow-up ($P<0.001$, Table 2, Fig. 3). HDL cholesterol significantly increased during follow-up compared with baseline ($P<0.001$, Table 2), due to an increase between 2 and 5 years (Fig. 3). After 5 years treatment, the increase of HDL cholesterol was only borderline statistically significant ($P=0.052$).

Since a subset of the patients (9/63=14%) were on lipid-lowering medication at any time point during follow-up, the data are also analyzed for the cohort free of lipid-lowering medication at any time point. The pattern of change remained unaffected for TC, HDL cholesterol, and TG. For LDL cholesterol, the decrease became significant only after 5 years, and continued to decrease thereafter. In those patients using lipid-lowering medication, the degree of change for TC was significantly greater compared

Figure 3 Fasting glucose levels significantly increased when baseline and 7 years were compared ($P<0.001$). Plasma levels of total cholesterol, low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol during 7 years of rhGH replacement in all patients. Total cholesterol and LDL cholesterol significantly decreased after 7 years ($P<0.001$). HDL cholesterol significantly increased ($P<0.001$). * $P<0.05$ compared with baseline. † $P<0.05$ compared with baseline. ‡ $P<0.05$ compared with baseline. § $P<0.05$ compared with previous time point.

with those who were not (-0.2 ± 0.1 mmol/l vs -0.1 ± 0.1 mmol/l respectively, $P=0.007$).

BMI significantly increased by 6% ($P<0.001$, Table 2), mainly due to an increase between 2 and 5 years (Fig. 4). Waist circumference and WH ratio remained unchanged (Table 2). SBP did not change during follow-up (Table 2, Fig. 4). Exclusion of the patients using antihypertensive medication ($n=11$) did not affect the conclusions. DBP decreased during follow-up in all patients ($P=0.002$, Table 2), but this decrease failed to reach statistical significance when patients using antihypertensive medication were excluded ($P=0.064$).

Influence of gender

The dose of rhGH was significantly higher in women compared with men at all time points. At the 2 years evaluation, men used 0.42 ± 0.9 mg and women 0.60 ± 0.22 mg ($P=0.002$). At 5 years the doses were 0.42 ± 0.10 and 0.66 ± 0.26 mg ($P<0.001$) and at 7 years 0.36 ± 0.10 and 0.66 ± 0.26 mg ($P<0.001$) respectively. We found no differences in treatment effects of any of the biochemical and anthropometric parameters between men and women.

Influence of age

At the start of the study, 35 patients (56%) were younger than 50 years and 28 (44%) between 50 and 75 years of age. As was expected, older patients had a higher BMI, waist circumference, WH ratio, LDL cholesterol, TC, TG, fasting glucose, SBP, and DBP compared with younger patients (data not shown). The individualized rhGH dose used in older patients was significantly lower compared with younger patients (0.4 ± 0.2 mg/day compared with 0.6 ± 0.3 mg/day, $P=0.012$). Age was not a significant covariate of the IGF-I response to treatment. The differences in LDL and total cholesterol concentrations after 7 years of rhGH replacement were higher in the older patients compared with the younger patients (-1.4 ± 0.9 mmol/l compared with -0.9 ± 1.0 mmol/l for LDL cholesterol, $P=0.020$, and -1.3 ± 1.0 mmol/l compared with -0.4 ± 0.9 mmol/l for TC, $P=0.001$). The mean change in TG was -0.4 ± 0.9 mmol/l in older patients compared with 0.5 ± 1.5 mmol/l in younger patients ($P=0.006$). Younger patients had a larger increase in BMI compared with older patients (2.2 ± 2.7 kg/m² compared with 0.9 ± 1.7 kg/m² respectively, $P=0.036$). The mean change in DBP was larger in older patients compared with younger patients (-6.7 ± 8.0 compared with -1.7 ± 9.2 mmHg, $P=0.033$). There

Figure 4 Body mass index (BMI) significantly increased during follow-up when baseline and 7 years were compared ($P<0.001$ respectively). Waist circumference remained unchanged. Systolic blood pressure remained unchanged when baseline and 7 years were compared ($P=0.483$). Diastolic blood pressure significantly decreased when baseline and 7 years were compared ($P=0.002$), but the decrease failed to reach significance when patients using antihypertensives were excluded ($P=0.064$). † $P<0.05$ compared with baseline. § $P<0.05$ compared with baseline. § $P<0.05$ compared with previous time point.

were no age differences in the response of HDL cholesterol, glucose, waist circumference, WH ratio, or SBP to 7 years of rhGH replacement.

Discussion

In this large single-center study, we described the effects of 7 years of rhGH replacement with a stable individualized dose in adult GHD patients on biochemical and anthropometric parameters. We demonstrated that the beneficial changes on TC, HDL cholesterol levels, and DBP were sustained even after 7 years of treatment, whereas the anthropometric parameters, except BMI, remained unchanged.

Short-term effects of rhGH on biochemical cardiovascular risk factors have been reported in many studies, including a recent meta-analysis, restricted to placebo-controlled trials. These studies conclude that rhGH replacement therapy was beneficial for TC and HDL cholesterol levels, but had a negative influence on glucose and insulin concentrations (2). Long-term observational studies are rather scarce. Götherström *et al.* published their results of rhGH replacement therapy during 5 years in a cohort of 118 patients (3). We identified only three other studies with a follow-up of more than 5 years, comprising 33 patients in total, which described biochemical and anthropometric changes after GH substitution (4, 5, 7).

Fasting glucose increased in our study in accordance with a weighted mean increase of 0.2 mmol/l demonstrated in the meta-analysis of short-term studies (2), and the increase in fasting glucose found in the largest

observational study (3). However, during long-term studies in a limited number of patients, only a transient increase in fasting glucose during the first year of the study was observed (7, 8). This discrepancy with the increase in the meta-analysis and the increase in the largest observational study might be explained by the number of patients included. The increase of fasting glucose is probably due to the direct GH-induced insulin resistance (9).

In our study, the decrease in TC and LDL cholesterol levels was manifest during the first 5 years of rhGH replacement and continued even to decrease thereafter. This is consistent with the mean weighted changes during short-term rhGH replacement calculated in the meta-analysis and with the changes found by Götherström *et al.* during 5 years of rhGH replacement (2, 3). In the studies of 7 years or longer, summarized in Table 3, LDL cholesterol concentrations persistently decreased, but TC decreased in only one study (4). HDL cholesterol levels significantly increased after 5 years of rhGH replacement, mainly due to the increase after 2 years. However, no increase was found in short-term studies included in the meta-analysis, which is consistent with our findings that HDL cholesterol increased mainly after 3 years of rhGH (2). Similar to the present findings, HDL cholesterol levels increased in three out of the five long-term studies summarized in Table 3 (3, 5, 6). TG concentrations remained unchanged in our study, and in all long-term studies, except for a minimal decrease observed by Götherström *et al.* (3).

The effects on blood pressure were minimal. DBP decreased after 7 years of rhGH replacement, but this effect was abolished when patients on antihypertensive

Table 3 Summary of long-term studies (longer than 4 years) of effectivity of rhGH replacement therapy in GHD adults.

Authors	Numbers treated with rhGH (men)	Mean age at baseline	Mean dose	Duration (years)	Outcome
Al-Shoumer (8)	13 (7)	47 (24–65)	0.7 mg/day	4	TC ↓, LDL ↓, Fasting insulin ↑ TG and HDL unchanged. Fasting glucose ↑ in 1 st year, thereafter return to pretreatment values
Götherström (3)	118 (70)	49.3 ± 1.0 S.E.M.	Initially 0.98 mg/day, lowered to 0.48 mg/day	5	TC ↓, LDL ↓, HDL ↑, TG ↓, Fasting glucose ↑ LBM ↑, body fat ↓
Svensson (6)	11 (7)	48.0	Initially 1.1 mg/day, lowered to 0.61 mg/day	7	HDL ↑, LDL ↓ TG and TC unchanged. Fasting glucose ↑ transiently during 1 st year. BF ↓, FFM ↑
Chrisoulidou (4)	12 (6)	52 ± 10	0.7 mg/day	7	TC ↓, LDL ↓ Fasting glucose, fasting insulin, TG, and HDL unchanged Subscapular skinfold ↓, Total body water ↑, FFM ↑, BF ↓, weight ↑, BMI ↑
Gibney (5)	10 (7)	38	0.0075 mg/kg per day	10	Resting SBP unchanged, resting DBP ↓ LDL ↓, HDL ↑ TG and TC unchanged LBM ↑
Our study	63 (30)	46.7 ± 14.0	0.5 mg/day	7	Fasting glucose ↑, TC ↓, LDL ↓, HDL ↑ TG unchanged BMI ↑, waist ↑, DBP ↓

TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; BF, body fat; FFM, fat-free mass; LBM, lean body mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; Waist, waist circumference; ↓, significant decrease; ↑, significant increase.

medication were excluded. SBP remained unchanged. In line with these findings, only one other long-term study reported beneficial changes on DBP with SBP remaining unaffected (4).

BMI significantly increased during follow-up, but waist circumference and WH ratio remained unchanged. The increase in BMI in patients receiving rhGH replacement for 7 years is consistent with a previous report in only 12 adults, in which both treated and untreated GHD adults showed an increase in BMI after 7 years (4). It appears that increasing age of GHD adults is associated with an increase in BMI, irrespective of rhGH replacement, like in the normal population (10). However, favorable changes in body composition (increase in fat free mass and decrease in body fat mass) were reported in four out of the five long-term studies (3–6). Waist circumference, a more sensitive parameter reflecting visceral adipose tissue remained unaffected.

The question to be addressed is whether our observations were affected by the subgroup of patients using lipid-lowering and/or antihypertensive medication. Excluding patients using lipid-lowering drugs did not affect our observations for TC, HDL cholesterol, and TG levels. For LDL cholesterol, the decrease manifested after 5 years, and thereafter. However, as expected, the decrease in TC was significantly greater in patients using lipid-lowering drugs. Conversely, when patients using antihypertensive medication were excluded, the decrease in DBP was no longer significant ($P=0.064$). The favorable clinical effects on the lipid profile might be attributed to the patients who were withdrawn from the study. However, such effect was not demonstrable in a detailed subanalysis. Patients became substantially older during this study, which may have negatively affected various studied parameters. On the other hand, IGF-I continued to increase during this study, which might be due to age-related increased responsiveness to GH replacement. It is therefore conceivable that part of the ongoing favorable effects that we describe here are due to the effect of IGF-I.

The consequence of the increase in fasting glucose in terms of cardiovascular morbidity of mortality remains to be determined, but it has been established that there is a graded positive correlation between fasting glucose levels and the subsequent 12-year occurrence of cardiovascular events, even apparent for glucose levels below the diabetic threshold (11, 12).

The clinical relevance of these long-term effects of rhGH on lipids can best be discussed in view of the previously documented beneficial changes of lipid-lowering drugs (especially statins). In our study, TC and LDL cholesterol levels decreased with a mean change of 0.8 (11% decrease) and 1.0 mmol/l (22% decrease) respectively. In patients treated for hypercholesterolemia, cardiovascular mortality risk reduces by 15% for every 10% points of cholesterol lowering by conventional lipid-lowering drugs (13). Whether lowering of TC levels in GHD adults is associated with the same magnitude of

reduction in cardiovascular mortality remains to be established. In patients with risk factors for cardiovascular disease, lipid-lowering should be targeted at LDL cholesterol below 2.6 mmol/l, TC below 5.2 mmol/l, and HDL cholesterol above 1.6 mmol/l (14). Since patients with hypopituitarism are at increased risk for cardiovascular mortality (15, 16), we applied these targets to our population on rhGH replacement alone ($n=53$). Target goals were reached on rhGH replacement alone in 8 out of 49 patients with elevated LDL cholesterol concentrations for LDL cholesterol, in only 11 out of 44 patients with elevated TC concentrations for TC, and in 17 out of 40 patients with low HDL cholesterol for HDL cholesterol. It should be noted that the recently published clinical practice guideline for evaluation and treatment of adult GHD did not incorporate guidelines for cholesterol or blood pressure (17).

In conclusion, persistent beneficial changes are present even after 7 years of rhGH treatment. However, given the magnitude of these changes on lipid concentrations by rhGH alone and the fact that adults with panhypopituitarism are at high risk of (cardiovascular) mortality, we propose that these patients should be carefully monitored according to a multimodality approach in addition to rhGH replacement.

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