Pituitary diseases: long-term clinical consequences

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Chapter 12

The prevalence of the metabolic syndrome is increased in patients with growth hormone deficiency, irrespective of long-term substitution with recombinant human growth hormone

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ABSTRACT

Objectives

Many reports demonstrate improvements in cardiovascular risk factors during growth hormone replacement (rhGH) in adult growth hormone deficiency (GHD). However, it remains to be determined to what extent these changes translate into a reduction of increased cardiovascular morbidity and mortality. The aim of this study was to evaluate the effects of long-term rhGH replacement on the prevalence of the metabolic syndrome.

Design, settings, main outcome measures

The metabolic syndrome was scored using the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) definition in 50 consecutive GHD patients (age 45 ± 9 years), before, after 2, and after 5 years of rhGH replacement and the data of untreated patients were compared to the general population using data from a Dutch population based study (n=1062, age 44 ± 8 years).

Results

Hypertriglyceridemia (46.0% vs. 18.5%, p<0.0001), hypertension (66.0% vs. 35.5%, p<0.0001), and abdominal obesity (38.0% vs. 23.4%, p=0.0178) were more prevalent in untreated patients compared to controls, resulting in a higher prevalence of the metabolic syndrome in patients (38.0% vs. 15.7%, p<0.0001). During rhGH replacement at a mean dose of 0.5 mg ± 0.2 mg/day resulting in IGF-I concentrations in the normal age-adjusted reference range, mean HDL cholesterol increased compared to baseline (p<0.001). However, the prevalence of (components of) the metabolic syndrome did not change after 2 or 5 years of treatment with rhGH.

Conclusion

In this study, the prevalence of the metabolic syndrome in patients with GHD is increased compared to healthy controls, irrespective of rhGH replacement.

INTRODUCTION

Many reports documented the beneficial effects of short-term (1) and long-term (Table 1) recombinant human growth hormone (rhGH) on cardiovascular risk factors in adults with growth hormone deficiency (GHD). In placebo-controlled studies, with a duration ranging from 1 week to 18 months, rhGH treatment was beneficial for lean and fat body mass, total and HDL cholesterol levels and diastolic blood pressure, whereas rhGH negatively influenced plasma glucose and insulin levels (1). Long-term studies have revealed a increase in HDL cholesterol (2-4) and fasting glucose levels (3;5;6), and a decrease in triglyceride levels (3;7). Systolic blood pressure remained unchanged (3;7;8), whereas diastolic blood pressure decreased only in one study (8). The actual data reported in these studies indicate that despite the beneficial effects cardiovascular risk factors remain increased in many patients.

The metabolic syndrome is a cluster of metabolic abnormalities, that identifies persons at high risk for cardiovascular disease (9-11). The aim of this study was to characterize the baseline characteristics of the metabolic syndrome in a cohort of adults with GHD and to evaluate the effect of subsequent rhGH replacement during 5 years on the prevalence of the metabolic syndrome. We hypothesized that long-term rhGH replacement in adults with GHD would ultimately lead to an improved cardiovascular risk profile as assessed by the criteria of the metabolic syndrome.

METHODS

Patients

From October 1994 to April 2000, sixty-four consecutive patients with adult-onset GHD aged 30 to 59 years were enrolled. In 50 patients we could score the presence of the metabolic syndrome at baseline and after 5 years of rhGH replacement, according to the NCEP-ATP III definition (12). The other 14 patients were excluded from analysis, because insufficient data were available to score the prevalence of the metabolic syndrome (n=7) or because rhGH treatment was ended earlier by the patients because of subjective lack of benefit (n=4) or side effects (n=3). No differences were present between the 14 excluded patients and the other 50 patients with respect to age, gender, and BMI.

Treatment Protocol

Patients were prospectively enrolled in an open label treatment protocol. Growth hormone deficiency (GHD) was confirmed in all patients by an insulin tolerance test (nadir blood glucose < 2.2 mmol/) with a peak GH concentration < 3 µg/l. After initial measurements were obtained, all patients were treated with subcutaneous injections of rhGH (Genotropin® Pharmacia/Pfizer or Zomacton® Ferring, Norditropin® NovoNordisk, or Humatrope® Lilly), given subcutaneously

Table 12/1: Observational studies on the effect of recombinant human growth hormone on cardiovascular parameters with a duration of at least 2 year.

Authors	Duration (years)	Numbers (men)	Age	Daily dose	HDL	TG	Glucose	SBP	DBP	Waist circ.	BMI	WH ratio
Colao (7)	2	20 women	18-45	0.077 mg/ kg		↓		=	=		=	
Colao (7)	2	18 men	19-45	0.065 mg/ kg		↓		=	=		↓	
Florakis (5)	2	24 (10)	48	0.4 mg		=	↑					
O'Neal (6)	2	22 (16)	42	0.01 mg/kg	=	=	↑				↑	↓
Garry (27)	3	21 (16)	45.9	0.007 mg/ kg	=	=	=					
Al-Shoumer (28)	4	13 (7)	Median 47	0.008 mg/ kg	=	=	=					
Götherström (3)	5	118 (70)	49	0.48 mg	↑	↓	↑	=	=		↑	
Present study	5	50 (24)	45	0.5 mg	↑	=	=	=	=	=	↑	=
Svensson (4)	7	11 (7)	48	0.61 mg	↑	=	=				=	
Chrisoulidou (8)	7.1	12 (6)	52	0.7 mg	=	=	=	=	↓	=	↑	
Gibney (1;2)	10	10 (7)	38	0.008 mg/ kg	↑	=						

Observational studies on the effect of rhGH on cardiovascular parameters with a duration of at least 2 years. HDL High-density lipoprotein cholesterol; TG Triglycerides; SBP Systolic blood pressure; DBP Diastolic blood pressure; Waist circ. Waist circumference; TC Total cholesterol; BMI Body mass index; WH ratio Waist-to-hip ratio; ↓ Significant decrease; ↑ Significant increase; = No change.

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 physiological serum IGF-I concentrations, within the age-dependent laboratory reference range (IGF-I standard deviation scores (SD scores)). Thereafter, this individualized dose was continued in each patient and adjusted, if necessary, to maintain a normal IGF-I concentration for the duration of the study.

Patients with a functioning adenoma (8 patients with Cushing's disease, 2 patients with acromegaly and 7 patients with prolactinoma) were in long-term remission before entering the study. When secondary amenorrhoea was present for more than 1 year premenopausal women were defined as LH/FSH deficient. In men, LH/FSH deficiency was defined, as a testosterone level below the reference range (8.0 nmol/l). TSH deficiency was defined as a total or free T4 level below the reference range. ACTH deficiency was defined as an insufficient increase in cortisol levels (absolute value <0.55 µmol/l) after a corticotrophin releasing hormone stimulation test or insulin tolerance test. Patients were then treated with hydrocortisone (n=39, mean dosage 25 ± 8 mg/ day, range 10-40 mg/day), L-thyroxine (n=44), testosterone (n=21), and/ or estrogen in combination with prostagens in premenopausal women only (n=18). Conventional substitution therapy was monitored during substitution with rhGH and the respective dosages were adjusted, as required for normalization of clinical and biochemical parameters of pituitary deficiencies. Regular screening for pituitary deficiencies was continued during follow-up. After baseline, additional L-thyroxine substitution was started in 1 patient and additional hydrocortisone was started in 1 patient. Patients were treated with antihypertensive and lipid-lowering medication when needed following standard patient care procedures. During follow-up, lipid-lowering treatment was initiated by the treating physician in 4 of the 50 patients, and antihypertensive medication in 6 of the 50 patients because of additional cardiovascular risk factors.

The study protocol was approved by the local Ethics Committees. All adult patients gave written informed consent to participation in the study.

Study Parameters

The following study parameters were assessed before, after 2 and 5 years of, substitution with rhGH: body weight and height, waist circumference, hip circumference, systolic and diastolic blood pressure (SBP and DBP, respectively), and fasting serum levels of glucose, HDL and TG were measured. Body-mass index (BMI) and waist-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. SBP and DBP were measured using the sphygmomanometric cuff method.

Patients were requested to fast overnight before blood samples were taken for laboratory measurements of lipid profiles, glucose and IGF-I concentrations.

The serum IGF-I (nmol/l) concentration was measured by RIA (INCSTAR Corp., Stillwater, MN) after extraction and purification on ODS-silica columns. The detection limit of this assay is 1.5

nmol/l, and the intra- and inter-assay coefficients of variation were below 11%. Age and gender-adjusted IGF-I data were determined in the same laboratory (13;14). IGF-I was expressed as SD scores for age- and gender-related normal levels.

GH concentrations in the samples of the insulin tolerance test were measured by time resolved immunofluorometric assay (Wallac, Inc, Turku, Finland). Human biosynthetic GH (Pharmacia and Upjohn, Inc, Uppsala, Sweden) was used as standard, calibrated against WHO-IRP 80-505 and the detection limit of this GH assay is 0.01 µg/l with an interassay coefficient of variation of 1.6-8.4%, between 0.1 and 15 µg/l.

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

Control subjects

Control subjects were participants from the Monitoring Project on Risk Factors for Chronic Disease (MORGEN study) organized by he National Institute for Public Health and the Environment (RIVM) (15;16). From 1993 to 1997 age- and sex-stratified random samples were drawn from the municipality registries from three towns in the Netherlands in a cross-sectional study design. The patients were of the same geographical area as the controls. Anthropometry, blood pressure and total and HDL-cholesterol were measured during the survey. Stored plasma samples from subjects participating fasting in the period 1993-1995 were retrieved in 1996 and analyzed for triglyceride concentrations (n=1378). All participants aged 30 years and older were included in the present study (n=1062). Since some of our patients were recruited somewhat later than controls were studied, we investigated whether time-frame of recruitment in our patients influenced the prevalence of the metabolic syndrome. We compared the prevalence of the metabolic syndrome in patients, who started rhGH replacement exactly during the time in which controls were selected (n=31), to patients, who started after the time in which controls were selected (n=19) and found no significant difference in the prevalence of the metabolic syndrome (32% vs. 43%, P=0.285).

Standard enzymatic methods were used to measure HDL-cholesterol and glucose levels. Triglyceride concentrations were measured with Abbott Spectrum clinical analyzer (Abbott Laboratories, Chicago, IL, USA). Blood pressure was measured by Random Sphygmomanometer.

Definition of the Metabolic Syndrome

The metabolic syndrome was scored according to definition of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) (NCEP-ATPIII) published in 2001 (12), which defines the metabolic syndrome as the presence of three or more of the following criteria:

(1) Fasting plasma glucose concentration ≥ 6.1 mmol/l

(2) TG concentration ≥1.69 mmol/l

(3) HDL concentration <1.04 mmol/l in men and <1.29 mmol/l in women
(4) BP ≥130/85 mmHg
(5) Waist circumference >102 cm in men and >88 cm in women

Statistical analysis

Statistical analysis was performed using SAS for Windows, version 9.1 and SPSS for Windows, version 12.0 (SPSS Inc. Chicago, Illinois, USA). Results are expressed as the mean ± SD, unless specified otherwise. Paired samples t-tests or ANOVA with repeated measurements with Bonferroni correction for multiple comparisons were used to assess the differences of continuous variables, when appropriate. Chi-square tests were used to assess the difference in prevalence of the metabolic syndrome between patients and controls. Friedman test for related fractions was used to assess the effect of treatment on the prevalence of the metabolic syndrome. Logistic regression was used to identify indicators of the prevalence of the metabolic syndrome at baseline. General linear model for repeated measurements were used to assess the prevalence of the metabolic syndrome at baseline and after 5 years of treatment taking trend in BMI into account. A p-value of <0.05 was considered to be significant.

RESULTS

Untreated GHD adults compared to controls

Characteristics of patients and controls

Gender was equally distributed in both cohorts (Table 2). There were no differences in age, gender and BMI between controls and patients. The mean maximal GH response during insulin induced hypoglycemia was only 0.3 ± 0.4 µg/l (range 0.1-1.6 µg/l), confirming the diagnosis of severe GHD (17).

Cardiovascular risk factors

Patients had significantly lower fasting glucose concentrations and significantly higher mean TG, SBP, DBP, waist circumference in men, and WH ratio in men and women compared to controls (Table 3).

Comparison of components of the metabolic syndrome

Hypertriglyceridemia (46.0% vs. 18.5%, p<0.0001), hypertension (66.0% vs. 35.5%, p<0.0001) and abdominal obesity (38.0% vs. 23.4%, p=0.0178) were significantly more prevalent in patients, compared to controls (Figure 1).

Table 12/2: Characteristics of patients with adult-onset growth hormone deficiency and controls.

		Patients (n=50)	Controls (n=1062)	P-value
Gender (%)	Male/ Female	48/ 52	52/ 48	NS
Age (years (mean ± SD))		45.2 ± 9.1	43.8 ± 8.0	NS
BMI (kg/ m^2 (mean ± SD))		26.7 ± 4.2	25.7 ± 4.0	NS
Antihypertensive medication (%)		12	17	NS
Lipid-lowering drugs (%)		10	13	NS
Etiology of GHD (%)	Non-functioning pituitary adenoma	24		
	Functioning pituitary adenoma*	34		
	Craniopharyngioma	14		
	Other**	28		
Surgery (%)		78		
Radiotherapy (%)		56		
ADH deficiency (%)		30		
ACTH deficiency (%)		78		
TSH deficiency (%)		88		
LH/ FSH deficiency (%)	Men	88		
	Women	100		

Data are presented as percentages unless specified otherwise. *Prolactinoma, ACTH producing adenoma, GH producing adenoma. **Trauma, hypophysitis, germinoma, epidermoidcyst, Sheehan's syndrome, unknown cause.

Comparison of the metabolic syndrome

The prevalence of the metabolic syndrome was 38% (19/50 patients) vs. 15.7% in controls (p<0.0001). In patients, BMI was a significant indicator of the presence of the metabolic syndrome (OR 1.2, 95% CI [1.0-1.4], p=0.031, Figure 1). The presence of the metabolic syndrome was not dependent on age, gender, etiological diagnosis of GHD, surgery, or radiotherapy (p=0.823, p=0.729, p=0.340, p=0.704, p=0.093, respectively). There were no correlations between calendar time of diagnosis of GHD and the prevalence of the metabolic syndrome or between interval between diagnosis of GHD and start of rhGH replacement.

Effects of long-term substitution with rhGH

RhGH substitution characteristics

After 1 year of rhGH treatment a stable dose of rhGH was maintained and the mean dose after 5 years was 0.5 ± 0.2 mg/day. Mean IGF-I SD scores were –2.0 ± 0.8 at baseline, -0.2 ± 1.8 after 2 years, and 0.8 ± 2.0 after 5 years of rhGH replacement (p<0.001, Table 3).

Table 12/3: Metabolic and anthropometric parameters in adult-onset growth hormone deficient patients after 5 years treatment.

		Baseline controls (n=1062)	Baseline patients (n=50)	2 years treatment patients	5 years treatment patients	P-values between patients (baseline) and controls	P-values patients between baseline and 2 years treatment	P-values between baseline and 5 years treatment
IGF-I SD scores			-2.0 ± 0.8	-0.2 ± 1.8	0.8 ± 1.9		<0.001	0.001
Glucose (mmol/l)		5.4 ± 1.1	4.8 ± 1.2	5.0 ± 0.7	5.3 ± 1.3	<0.0001	NS	NS
HDL (mmol/l)	Men	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	NS	NS	0.081
	Women	1.5 ± 0.4	1.5 ± 0.6	1.6 ± 0.5	1.7 ± 0.6	NS	NS	0.020
TG (mmol/l)		1.3 ± 1.1	1.9 ± 1.1	2.0 ± 1.0	2.1 ± 1.4	<0.0001	NS	NS
Systolic BP (mm Hg)		121 ± 16	128 ± 12	137 ± 19	129 ± 14	0.0004	0.017	NS
Diastolic BP (mm Hg)		79 ± 10	83 ± 8	86 ± 8	82 ± 9	0.0045	NS	NS
Waist circumference (cm)	Men	94.2 ± 10.8	101.5 ± 8.8	98.9 ± 8.3	104.3 ± 9.8	0.0017	NS	0.062
	Women	82.7 ± 11.3	86.8 ± 12.0	87.8 ± 13.3	88.4 ± 12.3	NS	NS	NS
WH ratio	Men	0.91 ± 0.07	0.98 ± 0.05	0.95 ± 0.05	0.99 ± 0.06	<0.0001	0.008	0.042
	Women	0.80 ± 0.07	0.86 ± 0.07	0.85 ± 0.06	0.87 ± 0.06	<0.0001	NS	NS
BMI (kg/ m^2)		25.7 ± 4.0	26.7 ± 4.2	26.7 ± 4.1	27.8 ± 4.7	NS	NS	0.002

Values are expressed as mean ± SD. IGF-I SD scores, IGF-I Standard-Deviation scores; HDL, High-Density-Lipoprotein Cholesterol; TG, Triglycerides; BP, Blood Pressure; WH ratio, waist to hip ratio; BMI Body Mass Index.

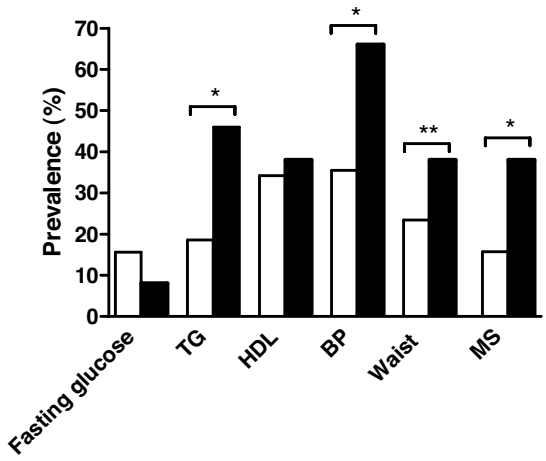

Figure 12/1: The prevalence of (components of) the metabolic syndrome in patients with growth hormone deficiency at baseline compared to healthy controls.
Black bars denote GHD patients at baseline and white bars denote controls; The prevalence of hypertriglyceridemia, hypertension and abdominal obesity were significantly higher in GHD adults compared to controls (*p<0.0001, **p<0.02). The prevalence of the metabolic syndrome was significantly higher in the total cohort (38.0% vs. 15.7%, *p<0.0001). TG, Triglycerides; HDL, High-Density-Lipoprotein cholesterol; BP, Blood Pressure; Waist, Waist circumference; MS, Metabolic syndrome.

Effects of rhGH on cardiovascular risk factors

Fasting glucose and TG levels remained unchanged during follow-up, whereas mean HDL levels increased during follow-up from 1.3 ± 0.5 mmol/l at baseline, to 1.4 ± 0.5 mmol/l after 2 years and to 1.5 ± 0.5 mmol/l after 5 years of rhGH treatment (p<0.001, Table 3). However, when men and women were analysed seperately the increase in HDL in men failed to reach statistical significance (p=0.081). SBP and DBP remained unchanged, except for a transient increase in SBP during the first two years of treatment (128 ± 12 mm Hg at baseline, 137 ± 19 mm Hg after 2 years (p=0.017), and 129 ± 14 mm Hg after 5 years of treatment). Mean BMI increased from 26.7 ± 4.2 kg/ m^2 to 27.8 ± 4.7 kg/ m^2 (p=0.002). Mean waist circumference remained unchanged, except for a slight increase in men after 5 years of treatment which failed to reach statistical significance (p=0.062). This increase was also reflected in the increase in waist-to-hip ratio only seen in men during follow-up (0.98 ± 0.05 at baseline to 0.99 ± 0.06 after 5 years of treatment, p=0.042).

Effects of rhGH on components of the metabolic syndrome

After 2 and after 5 years of rhGH replacement, the prevalence of the components of the metabolic syndrome remained unchanged (Figure 2, Table 4). The decrease in prevalence of low HDL levels, (38% at baseline, 42% after 2 years to 20% after 5 years) failed to reach statistical significance (p=0.068).

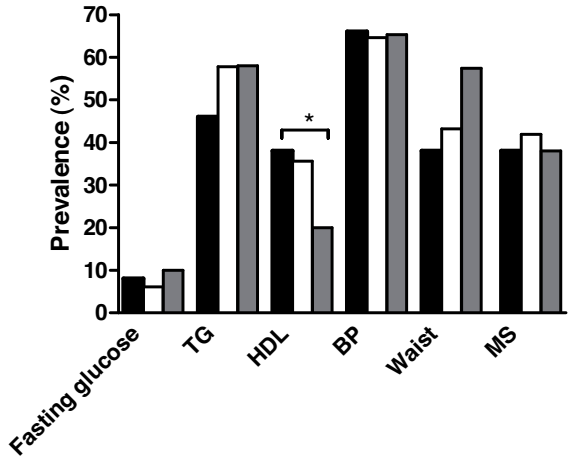

Figure 12/2: The prevalence of (components of) the metabolic syndrome in patients with growth hormone deficiency at baseline, after 2 and after 5 years of substitution of rhGH. Black bars denote GHD patients at baseline; White bars denote patients after 2 years of substitution with rhGH and grey bars denote patients after 5 years of substitution with rhGH. The prevalence of an abnormal low HDL decreases after 5 years of substitution with rhGH (*p=0.068).

Effects of rhGH on the prevalence of the metabolic syndrome

After 2 years of rhGH treatment the prevalence of the metabolic syndrome was 42% and after 5 years the metabolic syndrome was still present in 19 patients (38.0%, NS in a Friedman test for related fractions, Figure 2).

Influence of age, gender, BMI and etiological diagnosis of GHD

When adjusted for the increase in BMI during the period, the prevalence estimate for the metabolic syndrome did not change during 5 years of treatment with rhGH (39.6% at baseline vs. 36.4% after 5 years; p=0.71).

There were no differences in age, gender, BMI, etiological diagnosis of GHD, and applied treatments (radiotherapy or surgery), mean dose of rhGH after 5 years, and mean change in

Table 12/4: Prevalence of components of the metabolic syndrome in adult onset growth hormone deficient adults before, after 2 years and after 5 years treatment.

	Baseline	2 years treatment	5 years treatment	P-values treatment*
Increased fasting glucose (%)	8.0	6.1	10.0	0.717
Increased BP (%)	66.0	64.6	65.3	0.913
Decreased HDL cholesterol (%)	38.0	35.6	20.0	0.068
Increased TG levels (%)	46.0	57.8	58.0	0.084
Increased waist circumference (%)	38.0	43.2	57.4	0.741
Metabolic syndrome (%)	38.0	41.9	38.0	0.846

Values are expressed as percentages. BP, Blood pressure; HDL, High-Density-Lipoprotein Cholesterol; TG, Triglycerides; *Friedman test for related fractions.

IGF-I levels between patients who acquired the metabolic syndrome (n=9), who were relieved from the metabolic syndrome (n=9), or who were stable during follow-up (metabolic syndrome present (n=10) or absent (n=22)).

One of the 8 patients with Cushing's disease had the metabolic syndrome at baseline and after 5 years none of the patients treated for Cushing's disease had the metabolic syndrome.

There were no significant differences in the prevalence of the metabolic syndrome at any time-point between patients with or without ACTH deficiency and patients with or without TSH deficiency, or between patients with or without LH/ FSH deficiency. Logistic regression revealed no statistically significant influence of increasing number of anterior pituitary deficiency or increasing hydrocortisone dose on the prevalence of the metabolic syndrome at any time point during follow-up.

DISCUSSION

In this study, patients with GHD have a more than twofold increased prevalence of the metabolic syndrome, when compared to the general population. This increase is predominantly due to increased prevalences of hypertension, abdominal obesity and hypertriglyceridemia among patients with GHD. Long-term rhGH treatment increased HDL cholesterol concentrations, whereas fasting glucose and triglyceride concentrations remained unchanged in accordance with previous observations (references summarized in Table 1). However, rhGH treatment did not reduce the high prevalence of other cardiovascular risk factors assessed by the criteria of the metabolic syndrome.

The rationale for treatment with rhGH is to improve the metabolic abnormalities and psychological well-being, with the expectation to, ultimately, normalize life expectancy. The results of placebo-controlled trials with rhGH on cardiovascular risk factors were recently evaluated in a meta-analysis (1). In those studies (with a duration ranging from 1 week to 18 months) rhGH treatment was beneficial for lean and fat body mass, total and HDL cholesterol levels and diastolic blood pressure, but negatively influenced plasma glucose and insulin levels (1). Moreover, the weighted mean change, especially in total cholesterol, LDL cholesterol levels and diastolic blood pressure, was restricted to a maximum of only 0.3 mmol/l, 0.5 mmol/l, and 1.8 mm Hg, respectively (1). It remains unclear, to what extend these relative small changes would translate into a net beneficial effect on cardiovascular risk.

Some factors may have influenced the effect of rhGH in our study. The data obtained after 5 years of follow-up were not only affected by rhGH treatment, but also by age and BMI. In our control population an increase of 5 years in age was associated with a significant increase in prevalence of the metabolic syndrome from 15.7% to 20.9% (data not shown). However, this does not affect our conclusions with respect to the limited effects of rhGH treatment, since the prevalence of the metabolic syndrome remained much higher in GHD patients, irrespective of

the duration of follow-up and rhGH treatment.Additional adjustment for the trend in BMI did not affect our conclusions. Moreover, after two years of rhGH replacement, in which the BMI did not increase, the prevalence also remained unaffected by rhGH replacement. However, we cannot exclude the possibility that rhGH replacement was able to stabilize the prevalence of the metabolic syndrome and prevented an increase in prevalence of cardiovascular risk factors, associated with the observed increase in BMI and age. Although BMI significantly increased during follow-up, but waist circumference and waist-to-hip ratio remained unchanged. The increase in BMI in patients receiving rhGH replacement for 5 years is consistent with a previous reports in GHD adults (3;6;8). Moreover, with linear regression in our control population, an increase in BMI of 0.5 kg/ m^2 after a 5-year age increase was estimated. Thus, it appears that increasing age of GHD adults is associated with an increase in BMI, irrespective of rhGH replacement, just like in the normal population.

Waist circumference transiently decreased in men during follow-up, but remained unchanged after 5 years of rhGH replacement compared to baseline. This is in line with findings of a large short-term studies by Filipsson et al. and of Abs et al. in which waist circumference decreased after 1 year and 2 years of rhGH treatment, respectively (18;19), as well as with findings of one long-term study in which waist circumference was unchanged after 7 years of rhGH replacement (8). Thus, it seems that short-term rhGH replacement is able to induce favorable changes in waist circumference but unable to prevent the increase in waist circumference due to ageing as is seen in healthy adults.

The high prevalence of the metabolic syndrome could also be related to the complex syndrome of anterior pituitary deficiencies. All patients received adequate replacement therapies for pituitary insufficiencies prior to the start of study except for GHD. Moreover, conventional substitution therapy was carefully monitored during substitution with rhGH and the respective dosages were adjusted, as required for normalization of clinical and biochemical parameters of pituitary deficiencies. The prevalence of the anterior pituitary deficiencies in our cohort is comparable to the prevalence found in a large study of long-term rhGH replacement in GHD adults by Götherström et al. (3). In our study, 94% of patients had a deficiency of at least one anterior pituitary hormone compared to 92% in the study of Götherström et al. and 78% in our study had at least three other deficiencies besides GHD compared to 68% in the study of Götherström et al. (3). Although the prevalence of pituitary deficiencies might influence the prevalence of the metabolic syndrome in these patients, we did not find any differences between patients with or without various deficiencies. This might be related to the limited number of patients included in the present study.

Recently, it has been shown by Filipsson et al. that dose of glucocorticoids in the treatment of ACTH deficiency influences body mass index, triglycerides, LDL and total cholesterol in a dose-dependent manner, whereas it did not affect treatment response to rhGH replacement (20). In our limited number of patients and limited range of hydrocortisone doses used, we

were unable to show such a relationship between the metabolic syndrome and hydrocortisone dose.

The underlying diseases that caused GHD could also influence our results. Patients with Cushing's disease are known to have a high prevalence of cardiovascular risk factors, even after successful long-term cure of Cushing's disease (21). On the other hand, Feldt-Rasmussen et al. found no differences in waist-to-hip ratio, body mass index, triglycerides, and total, LDL and HDL cholesterol between patients with GHD due to previous treatment for Cushing's disease compared to patients with GHD due to other aetiologies (22). In our limited number of patients, we were unable to demonstrate differences in the prevalence of the metabolic syndrome between patients treated for Cushing's disease or acromegaly and patients treated for non-functioning pituitary adenomas, or between patients with producing pituitary adenomas compared to patients with non-functioning adenomas.

In our study, in four patients lipid-lowering treatment was started during follow-up and in six patients antihypertensive medication. The exclusion of these patients from the analysis of lipid parameters or systolic and diastolic blood pressure measurements, respectively, did not affect our observations. Recently, Grundy et al. proposed to take the medication use into account (23). We therefore chose to perform a second analysis in which we also scored antihypertensive and lipid-lowering medication in patients and controls. The comparison with controls remained unchanged (38% vs. 16.5%, $p<0.0001$) as well as the prevalence after 5 years of substitution with rhGH (38% at baseline vs. 43% after 5 years, NS vs. baseline).

The concept of the metabolic syndrome is subject to debate, because the pathophysiological basis of the proposed syndrome is unclear (24), and because the combination of cardiovascular risk factors does not add to the risk related to the individual risk factors (25). Nonetheless, this current debate does not affect our conclusions, because we also focus on the prevalence of the individual, well-recognized cardiovascular risk factors, which all individually have been associated with increased cardiovascular morbidity and mortality in the general population (9;10;25).

It needs to be established whether adult GHD patients with the metabolic syndrome have the same risks for cardiovascular morbidity and mortality compared with those with the metabolic syndrome in the general population. It remains to be studied whether the prognostic significance of the metabolic syndrome in these patients with GHD is the same as in the healthy general population. Moreover, the pathogenesis of the metabolic syndrome might be different in our patients compared to the general population. For example the effect of GHD and rhGH replacement on insulin sensitivity might influence the prevalence of the metabolic syndrome in our patients. Data so far on insulin resistance during rhGH replacement are conflicting, but some studies have pointed towards an improved insulin sensitivity during long-term rhGH replacement (4), which could be attributed to favourable changes in body composition (26). Furthermore, it remains to be studied in prospective trials if GHD adults may benefit from more

aggressive antihypertensive and lipid-lowering therapy and life style intervention to reverse the metabolic abnormalities seen in the adult GHD syndrome.

In conclusion, the prevalence of the metabolic syndrome in our GHD adults is significantly higher compared to the general population, irrespective of rhGH treatment. Apparently, appropriate substitution of rhGH and other hormones in adult patients with GHD is insufficient to improve this adverse cardiovascular risk profile.

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