CLINICAL STUDY

Dose-, IGF-I- and sex-dependent changes in lipid profile and body composition during GH replacement therapy in adult onset GH deficiency

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Abstract

Objective: Patients with GH deficiency of adult onset (GHDA) exhibit dyslipidaemia and increased cardiovascular morbidity. GH replacement potently reduces body fat and serum lipids in GHDA. In recent years, lower GH doses have been introduced. The purpose of this analysis was to explore the response relationship between GH doses, lipids and body composition.

Design: Two consecutive, randomized 12-month GH replacement studies covering placebo and three different doses of GH (0.5, 1.0 and 1.7 IU/m² per day). Low and intermediate doses were IGF-I titrated.

Patients: Fifty-eight patients with severe GHDA, not previously treated with GH and stably substituted for other endocrine deficiencies, were included in the study.

Methods: Serum lipoproteins, serum IGF-I and body composition analysis by dual energy X-ray absorptiometry (DXA) were used.

Results: Fifty-seven percent of patients exhibited low density lipoprotein (LDL) cholesterol levels above 4.16 mmol/l, corresponding to the American Heart Association threshold of 160 mg/dl. GH treatment resulted in significant decreases in total and LDL cholesterol, with no significant change in high density lipoprotein cholesterol or triglycerides. The low dose induced no significant changes in lipid levels, whereas the medium dose reduced LDL cholesterol and the high dose decreased both LDL and total cholesterol. The effects depended significantly on the GH dose and the level of IGF-I obtained, but not on gender. GH replacement induced dose-dependent reductions in fat mass and sex-dependent increases in lean mass.

Conclusions: GH given for 1 year at a dosage between 0.5 and 1.7 IU/m² per day reduced fat mass in a dose-dependent manner, increased lean body mass and lowered total and LDL cholesterol in patients with severe GHDA. Low dose GH treatment with normal IGF-I levels induced smaller changes compared with high dose therapy, and may need a longer treatment time.

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Introduction

As a group, patients with growth hormone (GH) deficiency of adult onset (GHDA) exhibit an adverse lipid profile, central obesity, impaired cardiac function and increased mortality due to cardiovascular and cerebrovascular disease (1–5). GH has potent lipolytic effects with increases in mobilization of free fatty acids and in hepatic low density lipoprotein (LDL) receptor expression (6). At the same time, GH decreases endogenous cholesterol synthesis (7).

Initial studies of the effects of GH on lipids and body composition used comparatively high doses, based on patient weight or body surface, which were derived from experience with GH substitution in children. However, the current consensus (8, 9) is to use lower GH

doses associated with – and preferably titrated against – normal insulin-like growth factor (IGF) levels.

GH has known positive effects on cardiovascular risk factors, quality of life and bone mineral density. While circumstances exist where placebo may be used even if a proven treatment is available, clinicians must consider carefully whether the World Medical Association's exemptions to article 29 of the Helsinki Declaration are met (10). New dose finding studies assessing the dose–response relationship between a range of GH doses and placebo may perhaps not be forthcoming. Instead, we have added a new low and intermediate dose study to complement our findings regarding the effects of high dose, IGF-I unadjusted GH therapy for 12 months on lipid levels (11) and body composition (12) in previously untreated, severe GHDA.

The two consecutive studies shared inclusion criteria, set-up and equipment and, taken together, cover the full clinical spectrum of GH doses as well as placebo. The purpose of the present analysis was to explore the dose–response relationship between GH doses, serum lipids and body composition in men and women. Specifically, we wanted to pursue the hypothesis that low dose GH treatment induces improvements in lipid status of similar magnitude to that achieved by the former high dose regime.

Study population and methods

Study design

The present investigation consisted of two consecutive double-blind, randomized studies, with shared inclusion criteria. Study A (11) used a traditional height- and weight-based dosing regime, where an initial dose of 2 IU/m² per day GH ($\approx 14 \mu\text{g/kg}$ per day; ‘high dose’; HD) was compared with placebo for 12 months. Therapy was initiated with 25% of the target dose, and increased in steps of 25% at 14-day intervals. In this study, doses were reduced only in case of side-effects. In the new study B, the effects of 0.5 IU/m² per day GH ($\approx 4 \mu\text{g/kg}$ per day; ‘low dose’; LD) and 1.5 IU/m² per day ($\approx 9 \mu\text{g/kg}$ per day; ‘medium dose’; MD) were compared. In this study the aim was to maintain serum IGF-I within the physiological range (13). Doses were reduced if serum IGF-I rose above the maximum limit of the age-adjusted reference range (two standard deviations above the age-specific mean) or if patients developed side-effects, but doses were not increased if IGF-I levels were low during therapy.

Study population

The population studied consisted of 58 patients with GHDA of at least 1 year’s duration (Table 1). The pyridostigmine–GH-releasing hormone test was used for diagnosing GH deficiency. A GH response of 20 mU/l was chosen as the cut-off for the diagnosis (14), but 80% of the patients had GH responses of less than 10 mU/l. The stimulated GH response did not differ between the four study groups ($P = 0.48$, Kruskal–Wallis test). No patients had previously been treated with GH. Patients were fully substituted for other endocrine deficiencies, and the doses had been stable for at least a year. Their hormone replacement was continued unchanged throughout the study. There was a tendency for the female patients to be older (median 48.4 years) than the males (44.5 years, $P = 0.18$). The difference was not significant in any of the four groups ($P = 0.08$ in the placebo-treated group to $P = 0.95$ in the HD group), nor did the four groups themselves differ in age ($P = 0.57$, Kruskal–Wallis test).

All patients received written and oral information and gave their consent in writing before entry to the

study. The studies were approved by the local ethics committees (refs 91/239 and 95/190) and conducted in accordance with the Helsinki II Declaration.

GH injections and compliance

Norditropin (Novo Nordisk, Lyngby, Denmark) was taken as daily s.c. self-injections at bedtime. The placebo formulation was prepared by Novo Nordisk and was identical in appearance to the GH preparation. Patient compliance was monitored by collecting all vials. In addition, patients were asked to report the number of missed injections at each visit. In the following, we refer to the GH dose in terms of the average dose received by the patient during the course of the study rather than the dose assigned at randomization.

Body composition

Total and regional body composition (fat mass, lean body mass (LBM) and percent body fat) was measured using a Hologic QDR-2000 densitometer (Waltham, MA, USA) in single-beam mode.

Serum lipoproteins

Total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglycerides (TG) were measured enzymatically using a Cobas Integra analyzer and reagents from Roche Diagnostics (both Hvidovre, Denmark). LDL was derived indirectly (described in 15): $\text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/2.2)$. No patients had TG levels above 4 mmol/l.

Serum IGF-I

Serum IGF-I was measured after extraction with HCl–ethanol. After centrifugation, the supernatant was diluted 1:40 in assay buffer and measured in an immuno-fluorometric sandwich assay using the Delphia principle and an AutoDelphia reader (Wallac, Turku, Finland). The detection limit was 2.5 ng/l. Intra- and interassay variations were less than 5% and 10% respectively.

Statistics

Correlations were evaluated by Spearman rank correlation analysis, between-group differences by the Kruskal–Wallis test and paired comparisons using Wilcoxon tests. A 95% confidence level was applied throughout. Dose–response relationships were investigated in two steps. First, a general tendency over all four treatments groups was tested by linear regression with robust standard errors and adjustment for baseline values. Secondly, the dose–response relationships were investigated within the three active treatment groups by the same method. In the event of a significant

Table 1 Clinical characteristics.

Study group	Sex	Age (years)	BMI	Diagnosis	Surgery/irradiation	Additional substitution
HD	F	46	33.2	Epidermoid cyst	Both	D + E + H + L
	F	48	25.1	Meningeoma	S	H + L
	F	49	24.2	Pituitary adenoma	S	
	F	51	35.7	Pituitary adenoma	S	
	F	57	24.4	Pituitary adenoma	S	
	M	31	24.3	Paraganglioma	Neither	H + L + T
	M	38	33.3	Pituitary adenoma	Both	D + H + L + T
	M	43	23.1	Pituitary adenoma	S	H + L
	M	46	30.7	Craniopharyngeoma	S	H + L + T
	M	49	25.1	Pituitary adenoma	S	T
	M	52	23.1	Pituitary adenoma	S	H + L + T
	M	55	27.4	Pituitary adenoma	S	
	M	56	26.2	Pituitary adenoma	S	L + T
	M	61	23.3	Pituitary adenoma	S	H
MD	F	41	25.6	Pituitary apoplexy	S	E + L
	F	42	18.3	Idiopathic	Neither	E + H + L
	F	44	26.4	Pituitary adenoma	Both	D + E + H + L
	F	54	33.0	Pituitary adenoma	S	E + H + L
	F	57	26.4	Pituitary adenoma	S	H + L
	F	60	30.2	Pituitary adenoma	Both	
	F	61	33.2	Pituitary adenoma	S	H
	F	64	31.9	Pituitary adenoma	S	D + H + L
	M	25	34.4	Craniopharyngeoma	Both	D + H + L + T
	M	27	26.8	Pituitary adenoma	Both	H + L + T
	M	27	19.7	Craniopharyngeoma	S	H + L + T
	M	47	27.5	Pituitary apoplexy	Neither	H + L + T
	M	56	29.9	Pituitary adenoma	S	H + L + T
LD	M	57	24.9	Pituitary adenoma	S	L + T
	M	60	19.9	Idiopathic	Neither	H + L + T
	F	22	25.3	Idiopathic	Neither	D + E + L
	F	29	40.5	Craniopharyngeoma	I	D + E + H + L
	F	41	25.5	Craniopharyngeoma	S	D + E + H + L
	F	49	25.9	Pituitary adenoma	S	E
	F	57	22.8	Pituitary adenoma	S	H + L
	F	60	27.7	Rathke Poche	S	D + E + H + L
	M	25	26.5	Pituitary apoplexy	Neither	H + L + T
	M	26	31.6	Colloid cyst	S	T
	M	31	29.5	Meningitis	Neither	D
	M	42	26.5	Hypophysitis	Neither	
	M	47	28.6	Pituitary adenoma	S	H + T
Placebo	M	48	28.1	Pituitary adenoma	S	D
	M	61	29.1	Pituitary adenoma	S	L + T
	M	62	32.0	Pituitary adenoma	S	H + L + T
	F	38	26.9	Pituitary adenoma	S	H + E
	F	49	23.1	Pituitary adenoma	Both	H + L
	F	51	33.7	Pituitary adenoma	Neither	
	F	53	19.6	Pituitary adenoma	S	H
	F	54	29.2	Pituitary adenoma	S	H + L
	M	20	27.8	Pituitary apoplexy	Neither	H + L + T
	M	21	23.8	Germinoma	I	H
	M	32	27.1	Craniopharyngeoma	S	H + L + T
	M	33	26.1	Pituitary adenoma	S	H + L + T
	M	35	28.4	Pituitary adenoma	S	H + L + T
	M	44	22.5	Pituitary adenoma	S	
	M	51	26.8	Pituitary adenoma	S	
	M	52	27.2	Pituitary adenoma	S	H
	M	52	26.2	Pituitary adenoma	S	
	M	53	26.1	Pituitary adenoma	S	

BMI, body mass index; D, desmopressin; E, oestradiol; H, hydrocortisone; L, levothyroxine; T, testosterone; S, surgery; I, irradiation.

dose–response relationship, the modifying influence of gender was then assessed by the Wald test within a multiple regression analysis with robust standard errors using sex and GH dose as predictors with adjustment

for baseline values. In a subsequent statistical reappraisal of the data, we pursued the hypothesis raised by other researchers in the field that patients with the most adverse baseline lipid values had the greatest

lipid-lowering response to GH (16, 17). Because this type of analysis may be subject to regression toward the mean, a multiple regression analysis was undertaken, in which the effect of baseline values on the dose-response relationship was assessed by introducing an interaction term. In this analysis, the effect of baseline values on outcome within the placebo-treated group is used as an estimate of regression toward the mean, and a confidence interval is then calculated for the difference in the coefficients for the influence of baseline values between placebo and active treatment. A post-hoc analysis was also performed in which treated patients were grouped by their 12-month serum IGF-I (normal or raised) as opposed to the allocated dose.

Results

Study completion and adverse events

Fifty-six patients completed the clinical trials. Two patients (3.4%) withdrew from the studies; one after 3 months due to recurrence of her pituitary adenoma (study A, placebo arm) and the other after 11 months for family reasons (study B, MD). One patient with glucose intolerance developed overt diabetes mellitus during treatment with GH at 0.5 IU/m² per day (study B, LD). Other adverse effects were limited to six patients in the 1.7 IU/m² per day group (study A, HD) who complained of arthralgias. The arthralgias, which were not observed in any of the lower dose groups or with placebo treatment, disappeared after a 25% GH dose reduction.

GH doses assigned and received

GH doses were reduced in the presence of adverse effects (both studies) or raised serum IGF-I levels (study B only) as described above. In the HD group the doses decreased in the first months and then remained largely unchanged. The whole year mean dose was 1.7 IU/m² per day (equivalent to a daily dose of 3.3 IU or approximately 14 µg/kg per day) in this group. In the MD group the doses were gradually reduced according to serum IGF-I levels, reaching a whole year mean GH dose of 1.0 IU/m² per day (1.9 IU/day or 9 µg/day). GH doses remained stable at 0.5 IU/m² per day (1.0 IU/day or 4 µg/kg per day) in the LD group.

IGF-I response

At 12 months, the mean serum IGF-I in the four groups had changed by +8%, +161%, +239% and +412% respectively. The increase in serum IGF-I was dose dependent ($P < 0.001$) across the four study groups, but no significant trend was found when the analysis was restricted to the three active treatment groups. The increase was of a similar magnitude in men and

women, when analysed using multiple regression analysis with robust standard errors controlled for sex and GH dose through the use of sex-specific dose variables (men vs women $P = 0.28$ for relative change in IGF-I and $P = 0.92$ for absolute change). Baseline IGF-I levels were similar in women (91 ± 53 mg/l) and men (107 ± 58 mg/l, $P = 0.30$). Further, there was no significant difference in absolute or relative terms in the observed change in IGF-I at 12 months. This was $257 \pm 70\%$ (133 ± 102 mg/l) in GH-treated men and $266 \pm 76\%$ (95 ± 97 mg/l) in GH-treated women. Dividing the change in IGF-I levels in each GH-treated patient by his or her GH maintenance dose revealed a 25% lower Δ IGF-I per unit GH in women compared with men; the difference was just short of statistical significance ($P = 0.10$). Raised IGF-I levels were observed in 4/14 patients in the LD group, 7/14 in the MD group and 9/13 in the HD group ($\chi^2 = 4.5$, $P = 0.11$) at the 12-month visit.

Lipoproteins at baseline

The four treatment groups did not differ in baseline lipoprotein concentrations, with the exception of a slightly higher (0.1 mmol/l) median HDL cholesterol level in the LD and MD groups. Moreover, men and women did not differ significantly in their baseline lipid levels. Fifty-seven percent of patients exhibited LDL cholesterol levels above 4.16 mmol/l, corresponding to the American Heart Association (AHA) intervention threshold of 160 mg/dl (18) for patients with no more than one cardiovascular risk factor. TG levels were significantly correlated with total (Spearman $r = 0.33$, $P < 0.05$) and, in particular, trunk fat mass ($r = 0.46$, $P < 0.001$).

Dose-response relationship for lipoproteins

GH treatment resulted in significant decreases in TC (median change 6.3%, 0.40 mmol/l, $P < 0.01$) and LDL (median 10.8%, 0.43 mmol/l, $P < 0.001$) cholesterol, with no demonstrable change in HDL cholesterol or TGs (Fig. 1A). After 12 months, the proportion of patients who exhibited LDL cholesterol levels above the AHA 160 mg/dl threshold was significantly higher in the placebo-treated group compared with the GH-treated groups (χ^2 $P < 0.05$; Table 2). The number of patients meeting the stricter AHA thresholds of 100 and 130 mg/dl was not significantly higher with active treatment. The placebo-treated group exhibited no significant changes in lipid levels. In patients allocated to active treatment, the decrease in TC and LDL cholesterol was significantly correlated with the GH dose given ($r = 0.48$, $P < 0.01$ and $r = 0.43$, $P < 0.01$). LD treatment induced no significant changes in lipid levels, whereas MD reduced LDL levels and HD GH treatment decreased both LDL cholesterol and TC. The absence of a significant reduction in

Figure 1 (A) Changes in serum lipids with 12 months of GH treatment by dose. Placebo (open bars), LD (bars with horizontal lines), MD (bars with crossed lines) and HD (hatched bars). CHOL, cholesterol. * $P < 0.05$, ** $P < 0.01$. There were no gender-dependent differences (see text). (B) Changes in serum lipids with 12 months of GH treatment by IGF-I level. Placebo (open bars), patients with physiological serum IGF-I at 12 months (bars with vertical lines) and raised IGF-I at 12 months (dotted bars). * $P < 0.05$. There were no gender-dependent differences (see text).

Table 2 Pre- and post-treatment LDL cholesterol levels. Percent of patients below the respective AHA targets of 160 mg/dl (recommended in patients with no more than one risk factor), 130 mg/dl (two or more risk factors) or 100 mg/dl (risk equivalent to diabetes or pre-existing coronary disease). Parentheses denote the corresponding baseline prevalences.

LDL cholesterol	Placebo	LD	MD	HD	χ^2 (baseline)	χ^2 (12 months)
<4.2 mmol/l (160 mg/dl)	21.4% (42.9%)	61.5% (50.0%)	71.4% (42.9%)	75.0% (38.5%)	$P = 0.95$	$P < 0.05$
<3.4 mmol/l (130 mg/dl)	14.3% (7.1%)	23.1% (28.6%)	42.9% (28.6%)	16.7% (0)	$P = 0.09$	$P = 0.29$
<2.6 mmol/l (100 mg/dl)	0 (0)	15.4% (14.3%)	7.1% (7.1%)	0 (0)	$P = 0.29$	$P = 0.29$

TC in the MD group, despite reduction in LDL cholesterol levels, was due to concomitant – but not significant – increases in the TG and HDL fractions. HD therapy was associated with a 12.6% (0.80 mmol/l) decrease in TC and a 17.0% (0.72 mmol/l) decrease in LDL cholesterol. Multiple regression analysis with robust standard errors confirmed that overall effects depended significantly on GH dose (TC $P < 0.01$, LDL $P < 0.001$, TG and HDL not significant (n.s.)). A dose–response relationship was also present when the analysis was confined to patients receiving active treatment (TC $P < 0.001$, LDL $P < 0.05$). Effects on serum cholesterol levels were independent of sex (TC $P = 0.88$, LDL $P = 0.97$).

We subsequently tested the hypothesis that patients with the highest baseline levels of TC and LDL cholesterol could show the greatest benefit of GH treatment. In this analysis, there was a modest modifying effect of baseline lipid values on dose–response relationships for both LDL cholesterol and TC, but there was no significant difference between the placebo-treated group and the GH-treated group in this respect as tested by the interaction term. When the benefit was marginally greater in patients with the highest baseline values, this was equally true in patients who did not receive active treatment. In the post-hoc analysis of IGF-I levels and changes in lipids (Fig. 1B), significant changes occurred only in patients with supraphysiological 12-month IGF-I levels, with intermediate reductions in patients who

achieved IGF-I in the physiological range. Again, significant changes were confined to TC and LDL cholesterol (both $P < 0.05$).

Body composition at baseline

The four groups had similar fat mass, LBM and percent body fat (BF%) at baseline ($P = 0.66$ – 0.82 , Kruskal–Wallis test). The median fat mass was 20.0 (inter-quartile (IQ) range 16.1–22.3) kg in men and 25.6 (21.1–30.8) kg in women, with an LBM of 66.0 (56.9–68.0) kg and 44.4 (42.2–53.3) kg respectively. Male patients had a median BMI of 27.1 kg/m² and a BF% of 23.3 (20.2–26.3), and female patients a median BMI of 26.3 kg/m² with a BF% of 34.9 (32.2–39.5).

Dose–response relationship for body composition

Fat mass Twelve months of GH replacement induced significant reductions in fat mass in both sexes, with a significant correlation between dose and reduction in fat mass in GH-treated patients (Spearman $r = 0.48$, $P < 0.001$). The median reductions in fat mass (Fig. 2A) were 0.5 kg (placebo, 2.0%, n.s), 1.5 kg (LD, 8.0%, $P < 0.05$), 1.8 kg (MD, 9.0%, $P < 0.05$) and 4.7 kg (HD, 20.9%, $P < 0.01$). Multiple regression analysis with robust standard errors confirmed that

Figure 2 (A) Changes in body composition with 12 months of GH treatment by dose. Placebo (open bars), LD (bars with horizontal lines), MD (bars with crossed lines) and HD (hatched bars). Men and women are shown separately. * $P < 0.05$, ** $P < 0.01$. For significant gender-dependent differences (see text). (B) Changes in body composition with 12 months of GH treatment by IGF-I level. Placebo (open bars), patients with physiological serum IGF-I at 12 months (bars with vertical lines) and raised IGF-I at 12 months (dotted bars). Men and women are shown separately. * $P < 0.05$, ** $P < 0.01$. For significant gender-dependent differences (see text).

changes were GH dose dependent (Table 3), both across the total study population ($P < 0.001$) and in GH-treated patients alone ($P < 0.001$). Dose/effect coefficients did not differ significantly between men and women ($P = 0.97$), and baseline values did not interact to modify GH dose effects ($P = 0.89$, see Methods section). The reduction in fat mass of the trunk was dose dependent ($P < 0.001$) but not demonstrably different between the two sexes ($P = 0.87$), and this also applied to fat mass of the extremities (dose $P < 0.05$, sex $P = 0.70$). Reductions in body fat were significantly correlated with the decreases in LDL cholesterol in the total population (Spearman $r = 0.47$, $P < 0.001$) and in the men ($r = 0.52$, $P < 0.01$), but not when women were viewed separately ($r = 0.37$, n.s.). In women, 55% (median) of the reduction in fat mass was accounted for by changes in the fat mass of the extremities whereas this was only 36% in men. The two sexes did not differ significantly in this respect, however ($P = 0.10$). Patients with both physiological and supraphysiological 12-month IGF-I levels exhibited significant reductions in fat mass (Fig. 2B).

Lean body mass Increases in LBM of the total body and of the extremities were observed in the men ($P < 0.01$ to $P < 0.05$, Fig. 1), but not in the women. For the two sexes taken together, the median increases in LBM were 0.7 kg (placebo), 3.2 kg (LD, 4.9%), 2.5 kg (MD, 5.1%) and 2.4 kg (HD, 4.1%), with a significant correlation between dose and absolute change (Spearman $r = 0.81$, $P < 0.05$). Again, the nature of the dose-response relationship was explored using multiple regression analysis (using the same model of analysis as in the preceding sections), revealing that the change in LBM did not increase with increasing GH dose ($P = 0.97$) when the analysis excluded the placebo-treated group. The magnitude of the change in LBM was sex dependent, with men achieving greater

increases in total and regional (extremities and trunk) LBM than women (median change in total LBM 4.1 kg in men and 0.6 kg in women, $P < 0.001$). Increases in LBM in men occurred both in the presence of normal and raised IGF-I levels (Fig. 2B).

Discussion

This study has shown that GH given for 1 year at a dosage between 0.5 and 1.7 IU/m² per day (approximately 4–14 µg/kg per day) increases LBM in patients with severe GHDA, and more importantly reduces body fat, TC and LDL cholesterol in a dose-dependent manner. For serum lipids, treatment leading to supra-physiological IGF-I levels was accompanied by more pronounced changes than those seen in the presence of normal IGF-I levels. In the present study, altered TG levels or adverse changes in HDL cholesterol did not accompany the reductions in TC and LDL cholesterol.

GH deficiency leads to the accumulation of a range of risk factors for cardiovascular disease, such as obesity, increased intra-abdominal fat mass, raised TC and LDL cholesterol and decreased HDL cholesterol levels (1–3). Despite replacement therapy for other accompanying pituitary endocrine deficiencies, patients with unsubstituted GHDA are at increased risk of cardiovascular disease, cerebrovascular disease and death (5). By stimulating both lipolysis and the expression of LDL receptors in the liver, while reducing endogenous cholesterol synthesis, GH replacement has the potential to improve LDL cholesterol levels while reducing fat mass (19). With respect to lipid status and body composition in GHDA, most GH replacement studies have been of short duration and the doses used comparatively large. However, within recent years the focus has moved from large doses to small, individually targeted doses tailored to normalizing serum IGF-I. At the same time, the amount of clinical experience gained within

Table 3 Multiple linear regression with robust standard errors and adjustment for baseline values in the total population, comparing response coefficients between men and women (Wald test, with *P* denoting the test probability for B_M and B_W being equal).

Absolute change	Women		Men		<i>P</i> ($B_M = B_W$)
	Coefficient B_W	<i>P</i>	Coefficient B_M	<i>P</i>	
Lean mass	−0.59	0.25	2.06	<0.001	<0.001
Trunk	−0.56	0.05	0.43	0.12	<0.01
Extremities	−0.00	0.99	1.59	<0.001	<0.001
Fat mass	−2.84	<0.001	−2.87	<0.001	0.96
Trunk	−1.73	<0.001	−1.79	<0.001	0.87
Extremities	−0.97	<0.01	−1.08	<0.001	0.70
IGF-I	87.08	<0.001	114.47	<0.001	0.28

BW, coefficient in women; BM, coefficient in men.

the field of GH replacement in adults is beginning to make placebo-controlled study designs ethically controversial. In the present study, 12 months of GH treatment reduced LDL cholesterol by a median of 0.40 mmol/l. This decrease was dose dependent and ranged from 0.16 mmol in the LD group to 0.7 mmol in the HD group. Recent low dose studies using approximately 1.1 IU/day (or 0.6 IU/m² per day), which is very similar to the dose used in the LD group in the present study, revealed a non-significant 0.17 mmol/l reduction in LDL cholesterol at 12 months (16). This reduction, which is almost exactly the same as that observed with the corresponding dose in the present study, continued over time and led to a 0.3 mmol/l reduction in LDL cholesterol at 2 years. In other words, reductions in LDL cholesterol of similar magnitude can be obtained by treatment with 0.5–0.6 IU/m² per day GH for 2 years or 1 IU/m² per day for 1 year. Another 2-year study using an IGF-I titrated average dose of 1.2 IU/day (approximately 0.63 IU/m² per day) gave rise to a more substantial reduction in LDL cholesterol of 0.4 mmol/l as early as after 6 months (17). Occasionally, studies using higher GH doses have been associated with small but undesired decreases in HDL cholesterol (20) although most have reported no change (7, 21–23) or even an increased HDL cholesterol fraction (24). Low dose treatment appears to be neutral in terms of HDL cholesterol (16) or even positive (17). While lipid fractions are clearly dependent on lifestyle factors – which may well be subject to time and cohort effects and vary between studies – the findings of no change in HDL cholesterol and a modest, dose-dependent reduction in LDL cholesterol in the present study ties in well with that observed in various previous studies, each covering a more limited range of GH doses.

It is in accordance with clinical experience to expect that patients with the most adverse lipid profiles at baseline will benefit most from treatment. After all, a greater decrease in lipids is possible if lipids are severely raised as opposed to in the high normal range, and previous work (16, 17) has established that baseline values indeed influence the dose–response relationship. This was also the case in the present study, but a subsequent interaction analysis within the multiple

regression analysis revealed that this could even be demonstrated in patients who received a placebo and, more importantly, that the coefficients were not statistically significant between the placebo-treated group and active treatment. We suggest that this relationship – at least in the current study – should be attributed to regression toward the mean.

In the present study and others (25) women were associated with smaller changes in LBM relative to GH dose compared with men. This is in accordance with studies indicating that women require higher GH doses than men to obtain the same biological response. Nevertheless – in contrast to other studies (26, 27) – the changes in total IGF-I were similar in men and women, and this dose–response relationship did not differ significantly by sex when assessed using multiple regression analysis or, in an alternative approach, by comparing Δ IGF-I per unit GH dose. This was also true for serum lipids and body fat. In other words, the observed difference between men and women with regard to changes in body composition could not be attributed to a demonstrably smaller IGF-I response in women, nor was the apparently more GH-resistant body fat associated with a poorer effect on serum lipids. In this discussion, we are only able to properly address changes in total IGF-I and not changes in free IGF-I or in IGF-I-binding proteins, which were not measured and whose response to GH may also be affected by oestrogen levels (28). Moreover, a recent placebo-controlled study found similar improvement in cardiac function in both sexes (25). It should be borne in mind that the women were slightly older than the men, and that all hypogonadic men received testosterone replacement whereas not all postmenopausal women were substituted with oestrogens (Table 1). Oestrogen deficiency in itself is associated with increased gain in fat mass after the menopause, compared with women receiving hormone replacement therapy (HRT) (29). Moreover, both opposed and unopposed HRT in postmenopausal women decrease LDL cholesterol levels, with variable effects on HDL and TGs (30–32). The apparent conflicting impact of sex on the parameters of response to GH between studies may reflect differences in the age distribution of the

study populations and the extent to which postmenopausal patients receive HRT, and even the route by which HRT is given (33). Although the number of female patients was too low to allow stratification for oestrogen replacement, sex-dependent differences in GH efficacy may be somewhat less pronounced in the present study because fewer of the women had HRT-induced relative GH resistance.

The present study has a number of limitations, which should be borne in mind. The two studies were performed consecutively. Thus secular trends may contribute to the observed dose dependency of the lipid variables and the changes in body composition, although the baseline characteristics were very well matched across the four groups. Both studies were randomized and they were designed to be pooled. Moreover, the study populations were drawn from the same geographically defined background population, and they were similar in duration and severity of GH deficiency. Both studies used the same dual energy X-ray absorptiometry (DXA) device for body composition analysis and were conducted by the same group of investigators. The two studies indicate – even if viewed separately – that significant mobilization of fat and improvements in lipid parameters takes place when patients who are already substituted for other endocrine deficiencies are given GH replacement. Higher GH doses bring about greater short-term changes, but lower doses seem to have the potential to improve lipid variables to the same extent with a proportionally longer treatment period. An additional limitation applies to the extent of dose titration by IGF-I values. While the two lower dose arms employed IGF-I as a safety measure – where patients had GH their doses were reduced in the presence of raised IGF-I levels – the studies were not strictly IGF-I titrated. Finally, thyroid hormones and corticosteroids also influence lipid variables and body composition and may, of course, affect the outcome unless substitution is stable as was the case in the present study.

Using low GH doses makes clinical sense, as raising IGF-I levels above the physiological range cannot be expected to be beneficial in terms of cardiovascular risk. In acromegaly, raised levels of GH and IGF-I in the circulation are accompanied not by reductions in cardiovascular mortality but by the opposite (34). The mechanism behind increased cardiovascular morbidity in active acromegaly involves hypertriglyceridaemia, decreased HDL cholesterol levels, hyperfibrinogenaemia, insulin resistance and cardiomyopathy with compromised left ventricular ejection fraction (35–38).

In conclusion, in patients with severe GHDA, GH treatment induces favourable, dose-dependent changes in TC and LDL cholesterol levels with no adverse changes in HDL cholesterol or TGs. At the same time, body fat is reduced in a dose-dependent fashion. LD GH treatment with normal IGF-I levels is able to induce similar but smaller changes compared with HD therapy, and may need a longer treatment time to obtain a response of

the same magnitude. Ongoing long-term studies should be able to provide further data to address whether similar reductions in cardiovascular risk factors are obtained with time.

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