Effect of Short-Term Treatment With Recombinant Human Growth Hormone on Lipids and Lipoproteins in Women and Men Without Growth Hormone Disturbances

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The effect of recombinant human growth hormone (rHGH) on cholesterol, high- and low-density lipoprotein (HDL and LDL) cholesterol, triglycerides (TG), apolipoprotein (apo) B, apo A-I, and lipoprotein(a) [Lp(a)] was studied in 40 postmenopausal women treated with 0.05, 0.1, or 0.2 IU/kg/d rHGH or placebo for 7 days. Cholesterol, LDL cholesterol, and HDL cholesterol decreased in a dose-dependent manner ($P = .001$, $P = .001$, and $P = .003$, respectively), whereas apo B decreased insignificantly ($P = .15$). Apo A-I decreased significantly only among women treated with rHGH at a dose of 0.1 IU/kg/d ($P = .03$). When all rHGH-treated women were grouped together, Lp(a) increased ($P = .001$). We also studied 20 young men treated with either 0.2 IU/kg/d rHGH or placebo. As in women, cholesterol and apo B decreased ($P = .005$ and $P = .02$, respectively), whereas Lp(a) increased ($P = .05$). There was no detectable effect of rHGH on TG concentrations in men. As in women, there was no significant effect of 0.2 IU/kg/d rHGH on apo A-I concentrations. All lipid and lipoprotein measures reached pretreatment levels during the first week after treatment was stopped, except Lp(a), which remained elevated 2 weeks after rHGH cessation.

BOTH DECREASED AND INCREASED production of growth hormone (GH) have been associated with increased frequency of atherosclerotic cardiovascular disease.[1,2] Metabolism of lipids and lipoproteins is abnormal in both hypopituitarism[3,4] and acromegaly.[1] Treatment of hypopituitary patients with GH decreases plasma cholesterol and low-density lipoprotein (LDL) cholesterol concentrations,[5-9] but increases lipoprotein(a) [Lp(a)] concentrations.[7] In contrast, Winter and Green[4] reported no effect of treatment with GH on plasma cholesterol. Treatment of acromegalic patients with octreotide (a somatostatin analog) caused a decrease in plasma triglycerides (TG) and a (nonsignificant) decrease in cholesterol.[10] However, whether disturbances of lipid and lipoprotein metabolism in hypopituitarism and acromegaly are responsible for the increased frequency of atherosclerotic cardiovascular disease in these patients remains to be documented.

The effects of GH treatment in subjects without disturbances in GH secretion have been less extensively explored. A decrease in cholesterol and increase in TG and Lp(a) has been described.[11,12] The increase in TG may in part be due to an increase in the very-low-density lipoprotein 2 ($VLDL_2$) subclass.[13]

Access to recombinant human GH (rHGH) has increased the interest in potential therapeutic uses of this hormone not only in GH deficiency but also in diseases with increased catabolic stress to the organism such as recovery after major surgery, cancer, and severe infections. Furthermore, the use of rHGH in the treatment of osteoporosis[14] and its effects on fracture healing is under investigation. Particularly in the case of long-term treatment with rHGH, it is important to understand its effects and side effects. The purpose of the present study was to investigate the effect and dose-response relationships of rHGH on plasma lipids and lipoproteins in non–GH-deficient subjects.

SUBJECTS AND METHODS

Study A

Forty women aged 52 to 73 years participated in the study. All were postmenopausal, had suffered at least one distal-forearm fracture within the last 10 years, and had low bone mineral density of the lumbal spine.[15] No dietary recommendations were given before or during the study. None of the subjects received lipid-lowering drugs. None suffered from renal diseases, and all were euthyroid at the time of study.

The study was placebo-controlled and double-blind. Participants were randomly allocated to treatment with either placebo (n = 10) or rHGH (Norditropin; Nordisk, Gentofte, Denmark) in a dosage of 0.05 (n = 10), 0.10 (n = 10), or 0.20 (n = 10) IU/kg body weight administered subcutaneously between 6 and 8 PM for 7 days. Blood samples for lipid and lipoprotein analyses were drawn in the morning after an overnight fast before drug administration (day 1) and at days 8, 12, and 21.

Study B

Twenty healthy male volunteers (aged 22 to 31 years)[16] were randomly allocated to treatment for 7 days with either placebo (n = 10) or rHGH (Norditropin) in a dosage of 0.2 IU/kg body weight per day (n = 10). No subjects received drugs or suffered from metabolic diseases with potential effects on lipid metabolism. They were instructed not to change their diet during the study period. Blood samples for lipid and lipoprotein analyses were drawn in the morning after an overnight fast on days 0, 1, 2, 3, 4, 5, 6, 7, and 8 and after 2 and 3 weeks.

Lipid and Lipoprotein Measurements

Total plasma cholesterol, high-density lipoprotein (HDL) cholesterol, and TG were determined by standard enzymatic assays (Boehringer, Mannheim, Germany). LDL cholesterol level was calculated using the Friedewald formula.[17] Apolipoprotein (apo) B and apo A-I together with Lp(a) concentrations were measured by commercial radioimmunoassays (Pharmacia, Uppsala, Sweden).

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All radioimmunoassay measurements were performed with the same batch of reagents.

During precipitation of apo B–containing lipoproteins before HDL cholesterol measurement, the supernatant developed some peculiar aggregates in plasma from some of the men. This led to an excessively large coefficient of variation in this analysis, which is why we have chosen to report only the apo A-I results for men, whereas both HDL cholesterol and apo A-I measurements are reported for women.

Lp(a) was phenotyped by sodium dodecyl sulfate-gel electrophoresis and immunoblotting as previously described.[18] Briefly, lipoproteins in whole plasma were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis, and apo(a) isoforms were identified by immunoblotting using a monoclonal antibody specific to apo(a).[19] The phenotypes were designated according to their relative mobility as compared with apo B, as proposed by Utermann et al[20]: F is faster than apo B, B has the same mobility as apo B, and S_1 to S_4 have increasingly lower mobility than apo B.

Statistical Analysis

Between-group differences in pretreatment lipids and lipoproteins were tested by the Kruskal-Wallis test for several group means. Changes in lipid and lipoprotein concentrations during treatment were expressed as a percent of pretreatment concentrations. Maximum percent change was assessed as the change from day 0 (before treatment) to day 8 (last day of treatment). The difference in maximum percent change in groups treated with different doses of rHGH was tested by the Kruskal-Wallis test. The maximum percent change from pretreatment concentration in separate treatment groups was tested by the Wilcoxon test for matched pairs. A 5% significance level was used throughout the study, although certain nonsignificant results are given if they are in the same direction or consistent with other significant results.

RESULTS

Study A

There was no significant between-group difference in pretreatment concentrations of cholesterol, HDL cholesterol, TG, LDL cholesterol, apo B, apo A-I, or Lp(a) (Table 1). However, Lp(a) concentrations were insignificantly higher in actively treated groups than in the placebo group ($P = .08$) mainly because of a relatively higher number of apo(a) protein null-phenotypes (Table 2), which are known to correlate with low concentrations of the protein,[20] in the placebo group.

rHGH decreased cholesterol ($P = .001$) and LDL cholesterol ($P = .001$) in a dose-dependent manner (Table 3). The lowest concentrations were measured in plasma samples taken immediately after the 7 days of rHGH treatment, and concentrations increased to pretreatment levels in the following 4 to 10 days.

TG increased ($P = .09$) and HDL cholesterol decreased ($P = .003$) (Table 3), with a maximum change after the 7 days of treatment, and returned toward baseline concentrations during the first 4 days after the last injection. However, when each treatment group was analyzed separately, HDL cholesterol only decreased significantly ($P = .005$) among women treated with 0.1 IU/kg/d rHGH. This is consistent with a significant apo A-I reduction ($P = .03$) only among women treated with this dose of rHGH.

Lp(a) concentrations tended to increase during treatment with rHGH in a dose-dependent manner (Table 3). When all actively treated women were grouped together, the mean increase in apo(a) concentration from pretreatment to day 8 was 24% ($P = .001$). Pretreatment levels in the 0.2- and 0.1-IU/kg/d groups were not reached by day 18. There was no difference in Lp(a) response across different apo(a) phenotype groups.

Study B

There were no significant differences in pretreatment lipid or apolipoprotein concentrations between rHGH- and placebo-treated subjects, with the exception that TG were higher at baseline in the rHGH group ($P = .05$, Table 4).

At day 8, cholesterol concentrations were decreased ($P = .005$) to the same extent as in women treated with 0.2 IU/kg/d rHGH (−14.7% *v* −13.5%, Table 5). Cholesterol decreased from the first injection and reached a new steady-state level after 5 days of treatment. Six days after the last injection, cholesterol concentrations had increased to pretreatment levels.

Apo A-I concentrations did not change significantly ($P = .17$), consistent with the nonsignificant reduction in apo A-I concentrations in women treated with 0.2 IU/kg/d rHGH.

In contrast to female subjects, there was no significant effect of rHGH on TG concentrations (Table 5).

As in women, apo B concentrations decreased ($P = .02$) and Lp(a) concentrations increased ($P = .05$) during treatment (Table 5). Apo B returned to pretreatment values 6 days after the last injection, whereas Lp(a) did not reach

Table 1. Pretreatment Lipid and Lipoprotein Concentrations in Women Grouped by rHGH Dose or Placebo

		rHGH (IU/kg/d)			
	Placebo (n = 10)	0.05 (n = 10)	0.1 (n = 10)	0.2 (n = 10)	P*
Cholesterol (mmol/L)	6.51 ± 0.81	6.85 ± 1.64	7.38 ± 1.47	7.33 ± 1.40	.52
HDL (mmol/L)	1.73 ± 0.38	1.53 ± 0.33	1.93 ± 0.74	1.51 ± 0.31	.39
TG (mmol/L)	1.20 ± 0.47	1.23 ± 0.37	1.21 ± 0.34	1.53 ± 0.57	.39
LDL (mmol/L)	4.23 ± 0.73	4.77 ± 1.68	4.91 ± 1.57	5.13 ± 1.41	.69
Apo B (g/L)	1.04 ± 0.23	1.14 ± 0.40	1.17 ± 0.36	1.22 ± 0.36	.66
Lp(a) (mg/dL)	7.0 (1.4-36.8)	20.0 (3.9-84.8)	21.3 (15.1-113.6)	21.5 (2.6-40.1)	.08
Apo A-I (g/L)	1.52 ± 0.16	1.47 ± 0.25	1.63 ± 0.39	1.43 ± 0.15	.47

NOTE. Results are the mean ± SD except for Lp(a) which are the median with 95% confidence intervals.

*Kruskall-Wallis test for several group means.

Table 2. Lp(a) Phenotype Distribution in Women and Men Grouped by Treatment (n = 10 in each group)

Lp(a) Group	Women				Men	
		rHGH (IU/kg/d)				
	Placebo	0.05	0.1	0.2	Placebo	rHGH 0.2 IU/kg/d
I					2	
II	1	5	3	1	3	1
III	3	3	6	7	4	8
IV	6	2	1	2	1	1

NOTE. Lp(a) phenotypes are grouped as previously described[18]: I, Lp(a) type F, B, and S_1; II, Lp(a) type S_2, S_2S_3, and S_2S_4; III, Lp(a) type S_3, S_4, and S_3S_4; IV, Lp(a) null-phenotype.

Table 4. Pretreatment Lipid and Lipoprotein Concentrations in Men Treated With rHGH 0.2 IU/kg/d or Placebo

	Placebo (n = 10)	rHGH 0.2 IU/kg/d (n = 10)	P*
Cholesterol (mmol/L)	5.20 ± 0.98	5.20 ± 0.42	.85
TG (mmol/L)	1.05 ± 0.27	1.47 ± 0.62	.05
Apo B (g/L)	0.72 ± 0.24	0.76 ± 0.15	.34
Lp(a) (mg/dL)	12.2 (1-71.7)	3.5 (1-8.8)	.20
Apo A-I (g/L)	1.52 ± 0.40	1.53 ± 0.31	1.00

NOTE. Results are the mean ± SD, except for Lp(a) which are the median with 95% confidence intervals.

*Kruskal-Wallis test for several group means.

pretreatment values after 2 weeks following the last injection. The number of men in each apo(a) phenotype group (except phenotype group III) was too small to warrant subgroup analysis among different apo(a) phenotypes.

Since there were too few persons in each apo(a) phenotype group to warrant statistical analysis of a phenotype-specific difference in the Lp(a) increase at different doses of rHGH, we divided the apo(a) phenotypes into two groups: group A contained phenotypes I and II and group B contained phenotypes III and IV. In analyzing all actively treated subjects together (men and women), there was no difference in the Lp(a) increase between these two groups (group A *v* group B, $P = .15$ by Kruskal-Wallis test of different group means).

DISCUSSION

There is evidence from previous studies that GH stimulates both the synthesis and catabolism of lipoproteins. In accordance with this, our data show that rHGH has profound effects on lipid metabolism.

VLDL Synthesis

rHGH increased plasma levels of TG in women. Raben and Hollenberg[21] showed that GH is lipolytic and increases the plasma concentration of nonesterified fatty acids (NEFA). NEFA are substrates for hepatic synthesis of TG-rich VLDL, and increased delivery of NEFA to hepatocytes stimulates VLDL synthesis. There is evidence, moreover, that GH directly stimulates hepatic esterification of NEFA into TG.[22,23] Sjöberg et al[24] showed that GH increases apo B mRNA editing in rat hepatocytes, which could increase the synthesis of apo B–containing lipoproteins (VLDL).

Asayama et al[8] found that GH decreased the activity of lipoprotein lipase and hepatic lipoprotein lipase, thus retarding the catabolism of VLDL to LDL. Together, these effects of GH could explain the higher plasma TG concentrations seen in acromegaly[1] and during treatment of normal subjects with GH[11,13] (and the present study).

In the present study, there was no effect of rHGH on TG concentrations in men. This could be due to gender-dependent effects of GH on lipoprotein metabolism in humans, as shown by Oscarsson et al[25] in rats. However, since plasma TG are affected by a variety of other exogenous factors, this lack of effect in a small sample of 10 men could be due to a type II error.

We also found that rHGH decreased HDL cholesterol, as well as apo A-I in women; however, this was only significant in the 0.1-IU/kg/d rHGH group. The well-known close inverse correlation between TG and HDL cholesterol concentrations, due to the intimately linked intermediate catabolism of VLDL and HDL constituents,[26] may well explain the decreased concentrations of HDL cholesterol and apo A-I by rHGH treatment in our study, since the increasing effect of rHGH on TG concentrations was most abundant in the 0.1-IU/kg/d rHGH group.

Table 3. Maximum Percent Change in Lipid and Lipoprotein Concentration (mean ± SD) in Women Treated With Different Doses of rHGH or Placebo

	rHGH (IU/kg/d)				
	0.05 (n = 10)	0.1 (n = 10)	0.2 (n = 10)	Placebo (n = 10)	P*
Cholesterol	−7.0 ± 9.0†	−11.9 ± 8.2‡	−13.5 ± 7.8§	3.5 ± 5.6	.001
HDL	−0.4 ± 18.9‖	−15.1 ± 6.8¶	−6.7 ± 19.3#	2.0 ± 8.4	.003
TG	23.0 ± 31.9**	61.2 ± 50.6††	44.7 ± 47.0‡‡	16.2 ± 33.6	.09
LDL	−13.1 ± 13.5§§	−18.3 ± 12.2‖‖	−22.5 ± 12.0¶¶	3.4 ± 8.8	.001
Apo B	0.1 ± 12.5	−3.7 ± 15.9	−7.7 ± 16.4	5.0 ± 13.3	.15
Lp(a)†††	16.9 ± 20.8	25.4 ± 42.7	30.5 ± 56.6	6.3 ± 18.8	.65
Apo A-I	−6.1 ± 8.5##	−7.0 ± 6.9***	−1.2 ± 7.7	−0.9 ± 6.5	.10

NOTE. Maximum change was achieved after 1 week of treatment.

*Kruskal-Wallis test for several group means.

Wilcoxon's test for matched pairs (% change at day 8 v day 1): †$P = .075$, ‡$P = .005$, §$P = .01$, ‖$P = .20$, ¶$P = .005$, #$P = .21$, **$P = .075$, ††$P = .01$, ‡‡$P = .02$, §§$P = .02$, ‖‖$P = .007$, ¶¶$P = .01$, ##$P = .03$, ***$P = .08$.

†††When all actively treated women were grouped together, the mean increase in Lp(a) from day 1 to day 8 was 23.8% ± 40.2% ($P = .001$).

Table 5. Maximum Percent Change (after 1 week of treatment) in Lipid and Lipoprotein Concentrations (mean ± SD) in Men Treated With rHGH 0.2 IU/kg/d or Placebo

	rHGH 0.2 IU/kg/d (n = 10)	Placebo (n = 10)	P*
Cholesterol	−14.7 ± 8.3[2]	−4.4 ± 5.3	.01
Apo B	−16.0 ± 15.7[3]	−7.6 ± 6.6	.08
Lp(a)	171.2 ± 296.1[4]	16.3 ± 70.6	.17
TG	−7.7 ± 26.5[5]	−5.6 ± 32.2	.62
Apo A-I	−7.3 ± 14.2[6]	8.6 ± 19.3	.10

*Kruskal-Wallis test for several group means.

Wilcoxon's test for matched pairs (% change at day 8 *v* day 1): †P = .005, ‡P = .02, §P = .05, ‖P = .37, ¶P = .17.

Synthesis and Catabolism of LDL and LDL Precursors

In the present study, cholesterol and LDL cholesterol decreased during treatment with rHGH. As mentioned earlier, GH inhibits lipoprotein lipase–induced conversion of VLDL to LDL. However, because the input rate of VLDL to plasma is increased, this inhibition does not necessarily affect LDL concentrations. Rudling et al[27] have demonstrated increased LDL-receptor (LDL-R) activity in hepatocytes from hypophysectomized rats treated with GH. The same researchers also showed increased LDL-R mRNA concentrations in hepatocytes isolated from liver biopsy specimens obtained from patients who underwent surgery for gallstones and were treated with rHGH preoperatively. Beher et al[28] demonstrated decreased conversion of cholesterol to bile acids in GH-deficient rats. This may lead to increased intracellular cholesterol concentrations in hepatocytes, and thus to decreased formation of hepatic LDL-R through negative-feedback control by intracellular cholesterol concentration on LDL-R synthesis. Whether GH treatment, on the other hand, increases conversion of cholesterol to bile acids, thus stimulating LDL-R synthesis, remains to be shown. Oscarsson et al[25] showed that apo E secretion is increased by GH. Apo E, like apo B, acts as a ligand for the LDL-R—mediated catabolism of lipoproteins. Since apo E is mainly found in TG-rich lipoproteins such as VLDL and VLDL remnants, this could, together with a dose-dependent upregulation of LDL-R by rHGH, explain why high doses of rHGH (0.2 IU/kg/d) induce a smaller increase in TG concentrations than a 0.1-IU/kg/d dose. Furthermore, an increased catabolism of LDL precursors (VLDL and VLDL remnants) would decrease the influx of LDL in plasma, which, together with the upregulation of LDL-R, would add to the observed reduction in LDL concentrations. The overall effect of decreased conversion of VLDL to LDL and increased catabolism of LDL and LDL precursors by hepatic LDL-R may explain the lower plasma cholesterol both in acromegaly[1] and as a result of treatment with GH[8,11,13,27] (and the present study). Further, in the anabolic state induced by GH treatment, cell proliferation is increased, and therefore, the need for cholesterol for incorporation into cell membranes is also increased. This could also decrease plasma cholesterol.

If the decrease in cholesterol is mainly caused by an increased fractional clearance rate of LDL by the LDL-R, this also explains the decrease in apo B concentrations in our study, since each LDL particle contains only one molecule of apo B, ie, the molar ratio of LDL to apo B is 1:1. However, the decrease in apo B concentrations is relatively smaller than the decrease in LDL cholesterol. This may be explained by the simultaneous increase in Lp(a) concentrations observed in our study, since each Lp(a) particle also contains one molecule of apo B.

Lp(a)

Although plasma concentrations of Lp(a) are thought to be regulated mainly by the liver synthesis rate of Lp(a),[29] little is known about the exact regulatory mechanisms. The concentration of Lp(a) is inversely correlated with the size of the apo(a) protein, which again reflects a length polymorphism in a DNA repeat region coding for the kringle IV domain of the protein.[20] In general terms, the smaller the apo(a) protein, the higher the Lp(a) concentration in plasma. Even less is known about the catabolism of this lipoprotein. Hypolipidemic drugs acting through upregulation of hepatic LDL-R have no effect[30] or may even increase Lp(a) concentrations.[31] Moreover, patients with familial hypercholesterolemia due to LDL-R mutations do not have higher Lp(a) concentrations than normal relatives.[32] The LDL-R therefore does not seem to play a significant role in the catabolism of this lipoprotein. On the other hand, the hypolipidemic drug nicotinic acid decreases both Lp(a) and VLDL concentrations.[33] Although not completely understood, part of the decreasing effect on VLDL concentrations by nicotinic acid is thought to be due to an antilipolytic effect, thus restricting the source of NEFA for hepatic lipoprotein synthesis. Since GH increases the plasma NEFA concentration and increases Lp(a) concentrations[7,12] (and this study), this could point to a stimulatory effect of increased NEFA concentrations for Lp(a) synthesis, as well as for VLDL synthesis. There was no difference in Lp(a) response to rHGH treatment among different apo(a) phenotype groups. This indicates that the regulation of Lp(a) concentrations associated with differences in the number of kringle IV repeats occurs through mechanism(s) other than the stimulatory effect of rHGH on Lp(a) concentrations.

Except for the possible gender difference in the rHGH effect on plasma TG, the effects of short-term treatment with rHGH in a daily dose of 0.2 IU/kg/d on lipid and lipoprotein concentrations are qualitatively and quantitatively similar in women and men, although the age difference between men and women in this study may confound gender comparison.

In conclusion, our study, together with others, shows that GH has important and complex effects on lipoprotein metabolism. Both increased synthesis of TG-rich lipoproteins and increased catabolism of LDL and LDL precursors seem to be induced by rHGH administration in normal human volunteers. However, it seems that the net effects of both increased synthesis and catabolism of lipoproteins in the VLDL-to-LDL cascade depend on the dose of rHGH administered.

Whether the rHGH-induced changes in lipid and lipoprotein concentrations are atherogenic or antiatherogenic is

unclear: decreased cholesterol, LDL cholesterol, and apo B concentrations could be antiatherogenic, but increased TG, decreased HDL cholesterol, and increased Lp(a) concentrations would be expected to be atherogenic. Finally, Hochberg et al[34] have demonstrated that GH increases the uptake and degradation of LDL in macrophages, mediated by insulin-like growth factor-I. This process mimics an important step in atherogenesis.[35]

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