The Effect of Growth Hormone on Low-Density Lipoprotein Cholesterol and Lipoprotein(a) Levels in Familial Hypercholesterolemia

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Severe elevations of low-density lipoprotein (LDL) cholesterol are not always normalized with conventional drugs. Growth hormone decreases LDL cholesterol levels, in part by augmenting liver LDL receptor activity. This increase may be on the order of magnitude of the increase induced by statins. We investigated the effect of growth hormone in familial hypercholesterolemia (FH) in a randomized, double-blind, placebo-controlled study. Thirty-one men with FH aged 20 to 48 years, of whom 81% had a known LDL receptor gene mutation, discontinued all lipid-lowering drugs 6 weeks before the study. Dietary stabilization continued for 5 more weeks, followed by single-blind placebo injections for 1 week. Thereafter, 16 subjects were allocated to recombinant growth hormone 0.05 IU/kg/d and 15 to placebo injected subcutaneously for 12 weeks. Baseline lipid levels were similar in both groups. One subject in the growth hormone group withdrew after 8 weeks due to shoulder pain. Mean compliance among the rest of the subjects was 98%. The mean change in LDL cholesterol was −0.46 mmol/L (95% confidence interval [CI], −1.00 to 0.09 mmol/L) in the growth hormone group versus 0.08 mmol/L (95% CI, −0.55 to 0.71 mmol/L) in the placebo group (difference not significant). No changes occurred in the levels of other lipids, lipoprotein particles, or apolipoproteins, with the exception of lipoprotein(a) [Lp(a)]. The median changes in Lp(a) were 33% (interquartile range, 2% to 53%) and −15% (interquartile range, −22% to 18%) in the growth hormone and placebo groups, respectively ($P = .02$). We conclude that the effect of growth hormone on LDL cholesterol levels in FH is less than expected, based on its LDL-catabolic effects, and is counteracted by profound increases in Lp(a) levels, resulting in unchanged levels of apolipoprotein B. Thus, growth hormone is probably not useful as adjunctive therapy in FH.

SEVERE ELEVATIONS of low-density lipoprotein (LDL) cholesterol may occur in familial hypercholesterolemia (FH), an autosomal dominant defect in the LDL receptor gene.[1] Cholesterol-lowering drugs are almost always indicated, usually 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), that reduce LDL cholesterol levels by 35% to 45%. Treatment with a combination of a statin and a bile acid sequestrant is particularly efficacious, decreasing LDL cholesterol levels by 50% to 60%, but may not always normalize LDL cholesterol levels.[2] The combination of other drugs such as fibrates or niacin with conventional treatment increases the risk of side effects.[3] Some individuals with FH do not respond to the standard drugs. Thus, new approaches to therapy are needed.

Several reports have focused on the improvement in cardiovascular risk factors induced by replacing growth hormone in hypopituitary patients. Growth hormone augments muscle mass,[4] decreases fat mass,[4] and reverses dyslipidemia by decreasing total and LDL cholesterol[4-7] and increasing high-density lipoprotein (HDL) cholesterol.[5,8] Whether the net cardiovascular outcome is improved is not settled, since growth hormone replacement may affect carbohydrate tolerance adversely[8,9] and increase levels of lipoprotein(a) [Lp(a)],[5] a lipoprotein independently associated with cardiovascular disease.

Recently, the effects of growth hormone in subjects with normal pituitary function have been studied, since growth hormone may be useful in treating diseases not primarily caused by growth hormone deficiency, including osteoporosis. In short-term studies of 5 to 21 days' duration, growth hormone decreased total and LDL cholesterol,[10-14] but in some cases, it decreased HDL cholesterol[12] and increased triglyceride.[13] A decrease in apolipoprotein B has been reported in a single study.[12] As in growth hormone–deficient patients, levels of Lp(a) have been reported to increase.[11-13]

Current evidence indicates that the LDL cholesterol–lowering effect of growth hormone appears to be at least partly mediated by an increase in liver LDL receptor activity.[15] Although growth hormone apparently stimulates LDL receptors as effectively as stains, blood levels of LDL cholesterol in normolipidemic or nearly normolipidemic subjects are reduced only modestly, on the order of 10% to 15%,[4-14] possibly due to growth hormone's other effects on lipid metabolism.[12,15] To our knowledge, the effect of growth hormone on LDL cholesterol levels in FH has not been reported previously. In this 12-week double-blind randomized trial, we compared low-dose recombinant growth hormone with placebo in men with FH to clarify its efficacy, tolerability, and safety in modulating elevated levels of LDL cholesterol and apolipoprotein B. In addition, since growth hormone may increase myocardial contractility,[16] we examined the effects of growth hormone on proatrial natriuretic factor levels.

SUBJECTS AND METHODS

Men between the ages of 20 and 48 years with prior off-therapy total cholesterol levels of at least 7.0 mmol/L and triglyceride levels not higher than 3.0 mmol/L were recruited. Diagnosis of FH was based on the detection of a specific LDL receptor mutation by

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DNA analysis or, alternatively, on the presence of an autosomally dominant pattern of total cholesterol levels of at least 7.0 mmol/L and triglyceride levels not higher than 3.0 mmol/L in first- and second-degree relatives, and either tendon xanthoma or a child aged 18 years or younger with total cholesterol levels of at least 7.0 mmol/L and triglyceride levels less than 2.0 mmol/L.[1] None had familial defective apolipoprotein B-3500.[17] Pituitary function was normal based on clinical and laboratory investigation.

Lipid-lowering drugs were discontinued at least 6 weeks before the start of the study. The use of corticosteroids, androgen, oral anticoagulants, or drugs and dietary supplements that affect lipid levels was not allowed. Other exclusion criteria were a history of cardiac infarction or cerebral stroke, unstable angina pectoris, pancreatitis, malignancy, diabetes mellitus, hypothyroidism or serum thyrotropin levels greater than 4 mU/L, renal, neuromuscular, infectious, respiratory, or liver disease, or baseline aspartate aminotransferase and alanine aminotransferase levels greater than twice the upper limit of the reference range. Nightshift workers were excluded. The study was approved by the regional medical ethics committee, and informed written consent was obtained from all participants.

Thirty-two men were recruited. All had received instruction on the American Heart Association step 1 diet previously (< 30% of dietary energy from total fat, < 10% from saturated fat, and < 200 mg cholesterol daily). Following a 4-week dietary stabilization phase, two lipid profiles were made 1 week apart. The mean of these two levels was the baseline LDL cholesterol level. If this level was greater than 5.0 mmol/L, subjects entered a 1-week single-blind placebo phase to assess adherence to the injections. Subjects able to comply were then allocated randomly to recombinant growth hormone (Saizen; Ares-Serono, Geneva, Switzerland) 0.05 IU/kg/d or placebo injected subcutaneously every evening for 12 weeks. Daily doses of growth hormone were 3.2 to 4.9 IU. Follow-up visits were scheduled 2, 4, 8, and 12 weeks after randomization. At the end of the study, two follow-up visits were scheduled after 3 and 6 weeks. Vital signs and side effects were recorded at each visit. Compliance was assessed by examining diaries of the time and amount of injections and by measuring leftover drug or placebo. The diet was assessed by a 4-day weighed record of all food and drink, including 3 weekdays and a Saturday or Sunday. The records were analyzed with the assistance of FIBER (©T.A. Ydersbond), a computer program based on Norwegian food tables.

Laboratory Analysis

At each visit, a blood sample was drawn following a 12-hour fast. Serum cholesterol and triglycerides were determined enzymatically with commercial kits. HDL cholesterol level was measured after precipitation of apolipoprotein B–containing lipoproteins with a standard heparin-manganese solution. LDL cholesterol content was calculated by the Freidewald formula, which was used in all cases, since triglyceride levels were not greater than 4.5 mmol/L. Apolipoproteins B, A-I, and A-II were assayed by immunoturbidimetric methods. Lp(a) level was measured by a two-site immunoradiometric assay (Pharmacia Diagnostics, Uppsala, Sweden). Apolipoprotein E genotyping was performed using a modification of the method of Hixon and Vernier as described previously.[18]

Serum for analysis of lipoprotein particles was sent within 48 hours of sampling at randomization and week 12 to Institut Pasteur (Lille, France) and analyzed upon arrival. HDL particles containing apolipoprotein A-I but not apolipoprotein A-II (Lp A-I) were quantified by differential electroimmunoassay on ready-to-use plates.[19] HDL particles containing apolipoprotein A-II and A-I (Lp A-II:A-I) and lipoprotein particles containing apolipoprotein B and E (Lp E:B) and apolipoprotein B and C-III (Lp C-III:B) were measured by two-site immunoenzymatic assays.[20] Lp(a) levels were also measured at Lille using an immunonephelometric assay on the Array Protein System (Beckman Instruments, Irvine, CA) in 12 subjects in the growth hormone group and 12 in the placebo group at randomization and after 12 weeks of treatment. Lp(a) levels obtained in the study laboratory were highly correlated with levels obtained in the Lille laboratory (r = .978 to .995, P = .0001).

Serum glucose levels were measured in the fasting state at each visit, and 2 hours after a 50-g glucose drink at randomization and week 12. Serum insulin and insulin-like growth factor-I (IGF-I) levels were measured by radioimmunoassay. The reference range for IGF-I in men aged 25 to 39 years was 15 to 64 nmol/L. IGF-binding protein-3 level in serum was measured by radioimmunoassay using materials provided by Diagnostic Systems Laboratory (Webster, TX). The reference range for men was 47 to 111 nmol/L. Growth hormone level in serum was measured by an immunoradiometric assay with two monoclonal antibodies. Intraassay and interassay coefficients of variation were 4% and 9%, respectively.

EDTA samples for analysis of total homocysteine were immediately placed on ice, and the plasma was separated within 30 minutes. Plasma total homocysteine level was measured using a modification of a fully automated assay.[21] The precision (between-day coefficient of variation) of the assay is approximately 2%. Plasma levels of proatrial natriuretic factor were determined by radioimmunoassay.[22] Intraassay and interassay coefficients of variation were 5% and 7%, respectively. Standard laboratory methods were used to determine other biochemical parameters.

Statistical Analysis

Based on an expected 1-mmol/L reduction in LDL cholesterol (~13%) and an expected standard deviation of 1 mmol/L, 16 subjects were required in each group to attain a power of 0.80 with a two-sided α at .05.

Subjects who completed the study were included in the calculations. Changes in continuous variables between the groups from baseline to the end of the randomized phase were compared by unpaired t tests if normally distributed or by the Mann-Whitney test if nonparametric. Changes in lipid and lipoprotein levels were also tested by a two-group repeated-measures ANOVA, taking into account all lipid and lipoprotein levels between randomization and the final visit. Univariate regression coefficients were calculated for the relation between lipid and other laboratory parameters. Calculations were performed using Statview (Abacus Concepts, Berkeley, CA) and SPSS (Chicago, IL) software.

RESULTS

Of 32 screened subjects, one was withdrawn from the study due to low LDL cholesterol levels. Thus, 31 were randomized, 16 to growth hormone and 15 to placebo. Baseline characteristics were similar in both groups (Table 1), as was compliance with the diet during the days of registration. Total fat intake (mean ± SD) as a percent of total energy was 27% ± 6% in the growth hormone group and 26% ± 6% in the placebo group, with 9% ± 3% and 7% ± 2%, of energy from saturated fat, respectively, and protein was 17% ± 2% and 17% ± 3% and carbohydrate 54% ± 8% and 55% ± 5%, respectively. Dietary cholesterol was 174 ± 76 mg/d in the growth hormone group and 153 ± 66 mg/d in the placebo group.

The most common LDL receptor mutation present was $FH_{Elverum}$, found in nine subjects in the growth hormone group and seven in the placebo group, which is also the

Table 1. Baseline Characteristics of the Study Subjects

Characteristic	Growth Hormone	Placebo
No. of subjects	16	15
Known LDL receptor mutation (n)	13	12
Age (yr)*	32.4 ± 8.3	34.8 ± 8.5
Smokers (n)	7	7
Body mass index (kg/m²)*	24.1 ± 3.3	25.6 ± 2.1
Systolic blood pressure (mm Hg)*	129 ± 19	124 ± 13
Diastolic blood pressure (mm Hg)*	77 ± 10	78 ± 8
Total cholesterol (mmol/L)*	10.4 ± 2.4	10.2 ± 2.3
HDL cholesterol (mmol/L)*	1.1 ± 0.3	1.0 ± 0.3
Triglycerides (mmol/L)*	1.7 ± 0.7	1.5 ± 0.9
Apolipoprotein E genotype 3-3 (n)	12	11
Apolipoprotein E genotype 3-4 (n)	3	3
Lp(a) (mg/L)†		
Q_{25}	64	136
Q_{50}	313	273
Q_{75}	640	362

*Mean ± SD.
†Median interquartile level.

most common mutation found in the general Norwegian FH population.[23] The rest of the mutations detected included several that have been reported previously in Norway ($FH_{Svartor}$, FH_{Q345R}, $FH_{Gujerat}$, $FH_{Cincinnati-2}$, and $FH_{Cincinnati-5}$).[23,24]

There was one withdrawal from the growth hormone group after 8 weeks, due to painful shoulders and upper-extremity edema. All other subjects completed the study. Six subjects in the growth hormone group and one in the placebo group complained of muscle pain, stiffness, or edema during the study, including two in the growth hormone group who complained of "feeling like an old man." Four in the growth hormone group and three in the placebo group complained of headache.

Levels of LDL cholesterol increased gradually in both groups up to randomization, decreased in the growth hormone group during treatment, and then decreased somewhat in both groups after the end of the randomized phase (Fig 1). The difference between groups was not statistically significant. The mean change at week 12 compared with baseline in the growth hormone group was −0.46 mmol/L (95% confidence interval [CI], −1.00 to 0.09 mmol/L) versus 0.08 mmol/L (95% CI, −0.55 to 0.71) in the placebo group. Changes in other lipids or apolipoproteins (Table 2) did not differ between treatments, nor did changes in lipoprotein particles, including Lp A-I, Lp A-II:A-I, Lp E:B, or Lp C-III:B (Table 3).

The median change in Lp(a) levels was 46 mg/L (interquartile range, 2 to 288 mg/L) and −19 mg/L (interquartile range, −55 to 54 mg/L) in the growth hormone and placebo groups, respectively ($P = .02$). Expressed as percentages, the changes were 33% (interquartile range, 2% to 53%) and −15% (interquartile range, −22% to 18%) in the growth hormone and placebo groups, respectively. Individual changes are shown in Fig 2. Subjects in the growth hormone group whose initial Lp(a) level was not higher than the median level of 287 mg/L had a smaller increase in Lp(a) compared with subjects whose initial Lp(a) level was above the median ($P = .049$; Fig 3).

Fasting and 2-hour glucose levels and insulin levels increased in the growth hormone group, but not significantly (data not shown). Mean body weight increased from 77.3 ± 10.1 kg to 79.7 ± 10.8 kg in the growth hormone group, versus 82.9 ± 6.1 kg to 83.7 ± 6.4 kg in the placebo group (not significant). Plasma total homocysteine levels decreased from 9.4 ± 3.2 μmol/L at baseline to 8.8 ± 2.2 μmol/L at week 12 in the growth hormone group, versus a decrease from 10.5 ± 5.8 μmol/L to 10.4 ± 4.2 μmol/L, respectively, in the placebo group (not significant). Changes

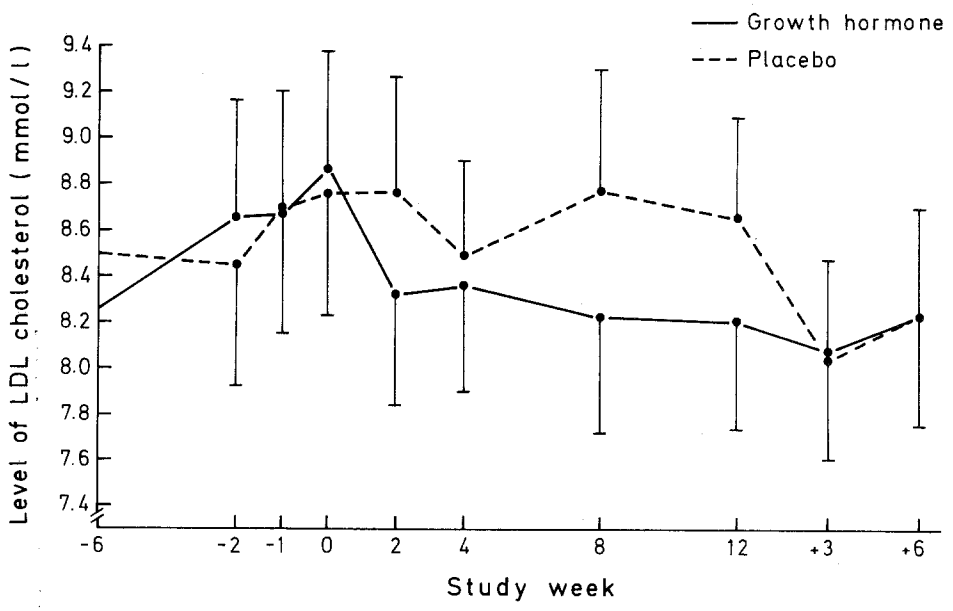

Fig 1. Mean changes in LDL cholesterol levels in the growth hormone and placebo groups.

Table 2. Lipid and Lipoprotein Levels in the Growth Hormone and Placebo Groups (mean ± SD)

Parameter	Week 0	Week 4	Week 8	Week 12	Poststudy Week + 6
Total cholesterol (mmol/L)					
Growth hormone	10.6 ± 2.0	10.3 ± 1.8	10.2 ± 2.0	10.3 ± 2.0	10.1 ± 2.0
Placebo	10.6 ± 2.3	10.4 ± 1.6	10.7 ± 2.2	10.6 ± 1.9	10.0 ± 1.9
Triglycerides (mmol/L)					
Growth hormone	1.5 ± 0.7	1.7 ± 0.7	1.7 ± 0.8	1.9 ± 0.9	1.8 ± 0.7
Placebo	1.7 ± 0.9	1.6 ± 0.8	1.8 ± 1.1	1.8 ± 0.9	1.6 ± 0.7
HDL cholesterol (mmol/L)					
Growth hormone	1.0 ± 0.2	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
Placebo	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.2
Apolipoprotein B (g/L)					
Growth hormone	1.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.5	1.8 ± 0.4	1.9 ± 0.4
Placebo	1.8 ± 0.5	1.9 ± 0.5	1.9 ± 0.5	1.9 ± 0.4	1.8 ± 0.3
Apolipoprotein A-I (g/L)					
Growth hormone	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
Placebo	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
Apolipoprotein A-II (g/L)					
Growth hormone	0.26 ± 0.05	0.27 ± 0.06	0.24 ± 0.05	0.25 ± 0.05	0.25 ± 0.05
Placebo	0.28 ± 0.06	0.27 ± 0.04	0.25 ± 0.05	0.27 ± 0.06	0.24 ± 0.06

in proatrial natriuretic factor did not differ between the groups (353 ± 149 pmol/L at baseline and 280 ± 91 pmol/L at week 12 in the growth hormone group *v* 405 ± 129 and 327 ± 94 pmol/L, respectively, in the placebo group), nor did levels of systolic and diastolic blood pressure or levels of standard safety laboratory variables (data not shown).

Mean compliance with the injections was 98% in both groups. Compliance in the growth hormone group was confirmed by changes in IGF-I and IGF-binding protein-3 levels, which increased in all subjects taking growth hormone. Mean IGF-I levels increased from 28.8 ± 8.9 nmol/L to 68.1 ± 18.3 nmol/L in the growth hormone group and returned to 29.5 ± 7.8 nmol/L at 6 weeks after the study, versus values of 30.9 ± 13.2, 27.3 ± 8.4, and 28.4 ± 7.6 nmol/L at randomization, the end of the study, and 6 weeks later, respectively, in the placebo group ($P = .0001$). Levels of IGF-binding protein-3 were 71.2 ± 9.1, 90.9 ± 13.3, and 69.1 ± 11.2 nmol/L, respectively, at the same visits in the growth hormone group, versus 76.0 ± 10.8, 72.2 ± 9.3, and 71.1 ± 8.0 nmol/L, respectively, in the placebo group ($P = .0001$). Levels of growth hormone were below the laboratory detection limit of 0.4 mIE/L in all but six participants at baseline, and increased in 12 subjects taking growth hormone versus one taking placebo during treatment.

Table 3. Levels of Lipoprotein Particles at Randomization and After 12 Weeks

Lipoprotein Particle	Week 0	Week 12
Lp A-I (g/L)		
Growth hormone	0.41 ± 0.14	0.47 ± 0.19
Placebo	0.37 ± 0.17	0.41 ± 0.13
Lp A-II:A-I (g/L)		
Growth hormone	0.80 ± 0.14	0.72 ± 0.11
Placebo	0.77 ± 0.14	0.74 ± 0.10
Lp E:B (g/L)		
Growth hormone	0.26 ± 0.10	0.41 ± 0.23
Placebo	0.34 ± 0.18	0.47 ± 0.24
Lp C-III:B (g/L)		
Growth hormone	0.06 ± 0.03	0.06 ± 0.04
Placebo	0.07 ± 0.05	0.05 ± 0.04

Changes in LDL cholesterol were not related to changes in IGF-I or IGF-binding protein-3 ($r < .2, P > .05$). When expressed as a percent of the baseline level, the change in Lp(a) was marginally correlated with the percent change in IGF-I ($r = .47, P = .08$) in the growth hormone group and significantly correlated in the entire group ($r = .57, P = .001$). In the entire group, the percent change in Lp(a) was correlated with the percent change in IGF-binding protein-3 ($r = .53, P = .003$).

Lp(a) levels were not related to IGF-I levels ($r = .02$ to $.06, P > .05$), except for a marginally significant association at poststudy week 3 ($r = -.34, P = .06$).

DISCUSSION

The main finding of this study is that in men with FH, levels of LDL cholesterol decreased modestly, only 5% (not significant), in response to treatment with low-dose growth hormone for 12 weeks. The most prominent change in lipoproteins was the increase in Lp(a), whereas the level of apolipoprotein B was unchanged.

Our point estimate of the change in the level of LDL cholesterol is valid, due to the placebo-controlled design, successful randomization on baseline characteristics in the treatment groups, and good compliance. Although greater reductions in LDL cholesterol than those observed in the present study have been reported, on the order of 10% to 15%,[5-7,11-14,25] other controlled studies have found no changes in lipid levels, even in subjects receiving growth hormone replacement.[8,26] Changes in the level of LDL cholesterol in response to growth hormone may be greater in the presence of growth hormone deficiency,[6,7] are probably dose-dependent[12] and time-dependent,[5] and may be modulated by estrogen,[10,27] gender,[12] or other factors, perhaps including basal levels of LDL receptor activity. However, there is little evidence that patients with FH differ in the magnitude of response to lipid-modifying modalities, including diet or

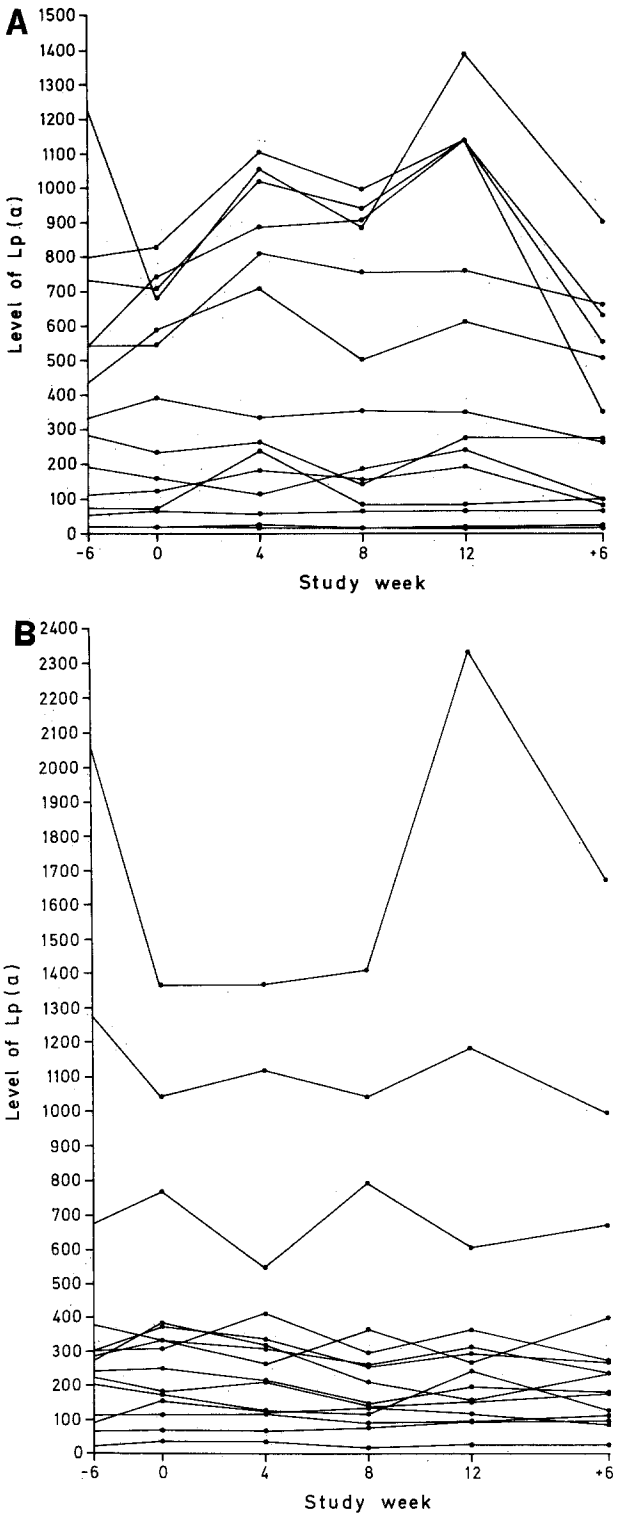

Fig 2. Changes in Lp(a) levels (mg/L) in the growth hormone (A) and placebo (B) groups.

drugs, compared with individuals without FH.[1,2,28] The increase in LDL cholesterol in both the growth hormone and placebo groups from baseline to the start of the injections and the decrease in LDL cholesterol after the end of the study compared with baseline levels suggest that the study period may have represented a stress for the subjects, and underscores the importance of controls.

Friedman et al[29,30] first attempted to decrease cholesterol levels in hypercholesterolemic, non–growth hormone–deficient men, using relatively high doses of human growth hormone. Soon after, another report,[31] which did not replicate the 20% to 25% reduction in cholesterol obtained by Friedman et al, concluded that even if cholesterol were decreased, poor tolerability would limit growth hormone's therapeutic usefulness. However, this conclusion was based on a very small number of subjects, who were mostly postmenopausal women. To avoid the well-known side effects of fluid retention and musculoskeletal pain, low-dose growth hormone was chosen. However, the dose was similar to that used in growth hormone–deficient patients, and mean IGF-I levels increased to above the normal range, indicating that the dose was not too low. Side effects were relatively common and bothersome, limiting the use of higher doses in future studies lasting more than a few days or in clinical practice.

In rats and in limited human studies, growth hormone stimulates liver LDL receptors by twofold to threefold and, as a result, would be expected to decrease LDL cholesterol levels by 20% or more, on the order of magnitude achieved by statins (reviewed in Angelin and Rudling[15]). Studies in rats have shown that growth hormone increases very–low-density lipoprotein secretion from the liver; however, very–low-density lipoprotein catabolism is also increased, via an increase in muscle lipoprotein lipase activity.[32] These effects should at least partly correct the abnormalities in lipid metabolism in FH.[1] Why the resulting decrease in LDL cholesterol is small is unclear,[15] although it remains possible that LDL production balances LDL clearance in

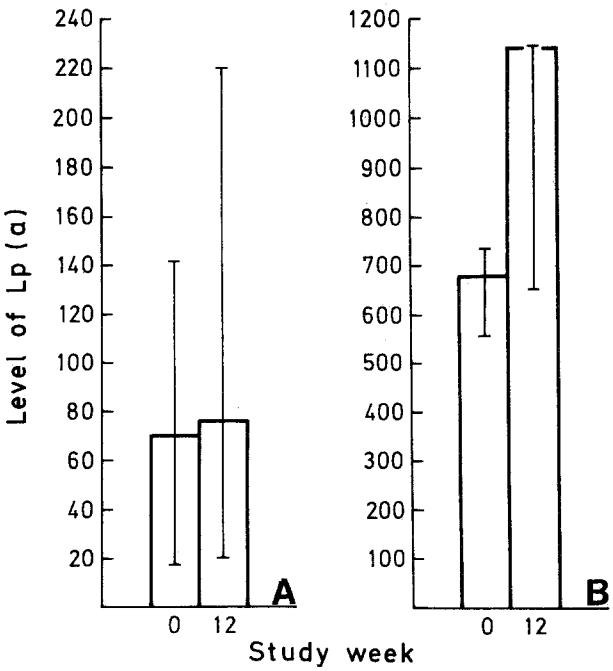

Fig 3. Median and interquartile range for Lp(a) levels (mg/L) in the growth hormone group whose initial level was ≤ the median (A) or > the median (B).

growth hormone–treated subjects who are deficient in LDL receptors. A dose-response study may have revealed greater reductions in LDL cholesterol with higher-dose growth hormone than used in the present study. In growth hormone–deficient rats, conversion of cholesterol to bile acids is decreased[33]; however, growth hormone does not alter biliary lipid metabolism in healthy adults, and thus a new steady state may be reached, without a change in the absolute mass of LDL cholesterol that is removed.[14] It is possible that LDL receptor activity may not respond to pharmacologic doses of growth hormone in the presence of normal basal levels, as in relatively young, healthy individuals. The change in LDL cholesterol levels was not significantly related to age in the present study (data not shown), but a greater age range should be examined to test this hypothesis.

In contrast to its minor effects on cholesterol levels, low-dose growth hormone increased Lp(a) levels profoundly, confirming findings in normolipidemic and growth hormone–deficient subjects.[5,11-13] Although subjects with FH may have increased levels of Lp(a), catabolism of Lp(a) is independent of the LDL receptor.[34] Lp(a) level is an independent risk factor for cardiovascular disease in FH, and thus treatment with growth hormone may be detrimental in FH.[35] Growth hormone is thought to increase Lp(a) by increasing its synthesis rather than by blocking its catabolism, through an increase in the flux of free fatty acids to the liver.[13] This action is probably not mediated by IGF-I, as indicated in two recent reports showing that administration of IGF-I to men reduced rather than increased Lp(a) levels.[13,36] Although increases in Lp(a) in the present study correlated with increases in IGF-I and IGF-binding protein-3, a cause-and-effect relationship is not implied. The effects of growth hormone on Lp(a) may be compared with estrogen's effects. When postmenopausal women were given estrogen, Lp(a) and IGF-I levels decreased concomitantly and the two variables were strongly correlated.[37] In contrast to the positive correlation between Lp(a) and IGF-I in the postmenopausal women before treatment with estrogen,[37] we found no relationship or only a very weak relationship between the two variables. The present data raise the possibility that growth hormone increases Lp(a) only in genetically susceptible individuals who carry apolipoprotein(a) genotypes causing high Lp(a) levels, since we found that Lp(a) levels did not increase in several subjects with low baseline levels. Interestingly, susceptibility to the Lp(a)-increasing effects of saturated fatty acids may be greatest among subjects with high baseline levels.[38]

Several studies have reported decreases in apolipoprotein B levels during growth hormone replacement,[6,7,9,39] but a decrease in apolipoprotein B in non–growth hormone-deficient subjects has only been reported once, to our knowledge, in a study that used a relatively high dose of growth hormone.[12] The lack of change in apolipoprotein B in the present study may reflect the opposing effects of both an increase, due to increased Lp(a), and a decrease, due to decreased LDL. A decrease in LDL cholesterol with no change in the level of apolipoprotein B may indicate an increase in small, dense LDL, which has been associated with an increased risk of coronary heart disease[40]; however, we did not measure small, dense LDL levels. Growth hormone increases the synthesis and catabolism of very–low-density lipoprotein–containing particles,[15,32] usually resulting in minor effects on triglyceride levels[4-14] (and the present study).

We found that levels of HDL cholesterol and apolipoproteins A-I and A-II were unchanged. The effects of growth hormone on some of these levels have been conflicting.[5-8,12,27] To our knowledge, the effect of growth hormone on lipoprotein particles has not been reported previously. It has been suggested that lipoproteins involving apolipoprotein A-I but not apolipoprotein A-II participate in cholesterol efflux, in contrast to lipoproteins involving both apolipoproteins A-I and A-II.[41] Levels of lipoprotein E:B and lipoprotein C-III:B vary according to the presence of premature coronary artery disease in some populations.[42] These levels were unchanged in the current study.

Safety parameters, including plasma total homocysteine level, were unchanged during treatment with growth hormone. However, failure to detect a significant difference in insulin and glucose levels between the groups is probably due to small sample size, since previous evidence has shown that these levels are increased by growth hormone.[8,9,43] We found no change in proatrial natriuretic factor levels, indicating that growth hormone does not decrease this factor, at least in the absence of cardiac failure.

We conclude that the LDL cholesterol–lowering effect of growth hormone in men with FH during 12 weeks of treatment is limited, and that any beneficial changes may be counteracted by its effect on Lp(a). Studies that elucidate how growth hormone increases Lp(a) will be helpful in the search for modulators of Lp(a).

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