Growth Hormone Treatment of Growth Hormone-Deficient Adults Results in a Marked Increase in Lp(a) and HDL Cholesterol Concentrations

Staffan Edén, Olov Wiklund, Jan Oscarsson, Thord Rosén, and Bengt-Ake Bengtsson

The effects of growth hormone treatment of adults with adult-onset pituitary insufficiency on lipoproteins and apolipoproteins were investigated. Nine patients, one women and eight men (age range, 34–58 years), who had been treated for pituitary tumors were studied. They had complete pituitary insufficiency with a duration of at least 1 year. All patients received replacement therapy with thyroid hormones, glucocorticoids, and gonadal steroids. The study had a double-blind, placebo-controlled, crossover design for active treatment with recombinant human growth hormone (0.25–0.5 units/kg per week s.c. given each evening) for 6 months. Fasting serum levels of cholesterol; triglycerides; high density lipoprotein and low density lipoprotein cholesterol; apolipoproteins A-I, B, and E; and lipoprotein (a) were measured before and after 6 and 26 weeks of treatment. Lipoprotein (a) concentrations increased markedly during treatment and were about twice as high compared with pretreatment levels. Serum cholesterol and low density lipoprotein cholesterol concentrations were decreased after 6 weeks of treatment, but levels had returned to pretreatment levels after 26 weeks. High density lipoprotein cholesterol concentrations increased during treatment and were significantly higher than pretreatment levels after 26 weeks of treatment. Serum triglyceride concentrations did not change significantly, but in two patients with marked hypertriglyceridemia, growth hormone treatment resulted in a marked decrease. Serum concentrations of apolipoproteins A-I, B, and E did not change significantly, but changes in apolipoprotein A-I and B concentrations were in parallel to those observed for high density lipoprotein cholesterol and low density lipoprotein cholesterol, respectively. These results suggest that growth hormone is a major regulator of lipoprotein metabolism and also demonstrate that lipoprotein (a) concentrations are regulated by growth hormone. (Arteriosclerosis and Thrombosis 1993;13:296–301)

KEY WORDS • lipoproteins • growth hormone • hypopituitarism

Few human studies have been performed on the effects of growth hormone (GH) on the different lipoprotein fractions and apolipoprotein levels. Moreover, studies on the effects of GH on the regulation of serum lipid levels have given conflicting results. However, both GH excess, as in acromegaly, and deficiency result in an increased risk of death due to cardiovascular disorders, which might indicate a role for GH in the control of lipoprotein metabolism in humans.

Several recent publications have reviewed the genetics, biochemistry, and possible role in arteriosclerosis and thrombogenesis of lipoprotein (a) (Lp[a]). The plasma concentration of Lp(a) is mainly genetically determined and is related to the isoform of apolipoprotein (a) (apo[a]), which also explains the markedly skewed frequency distribution of serum Lp(a) concentrations. The association of Lp(a) with cardiovascular disease has been attributed to the structural similarities between apo(a) and plasminogen. It has been shown that apo(a) may interfere with plasminogen activation and thrombolysis.

Little is known about the physiological role of Lp(a), which is found only in primates and the hedgehog. Furthermore, the synthesis and breakdown of Lp(a) are poorly understood. Messenger RNA for apo(a) has been detected not only in the liver but also in the testes and brain of the rhesus monkey; however, the liver is the sole site of Lp(a) synthesis. The degradation of Lp(a) is not completely understood. Lp(a) has been shown to bind to the low density lipoprotein (LDL) receptor, and Lp(a) degradation is increased in transgenic mice that express the LDL receptor. However, nonspecific receptor pathways have also been suggested.

Recent studies have indicated that although Lp(a) concentrations are mainly genetically determined, they are also hormonally regulated. The concentration does not seem to be influenced by age or sex, but a role for gonadal steroids has been suggested, since Lp(a) con-
centrations in early pregnancy and decrease after administration of norethisterone or anabolic steroids. A role for gonadal steroids in the regulation of Lp(a) has recently been emphasized by the marked increase in early pregnancy and decrease after administration of norethisterone or anabolic steroids. The gonadal steroids are also of major importance in the regulation of the secretion of GH. The gonadal steroids are also of major importance in the regulation of the secretion of GH. In the rat, hypophysectomy results in increased LDL and apo B concentrations, which are normalized by GH treatment. GH also affects high density lipoprotein (HDL) and apo E metabolism in this species, but this effect is dependent on the sexually differentiated pattern of secretion of GH and thus indirectly dependent on gonadal steroids.

In the present study, the effects of 6-month GH-replacement therapy on adults with adult-onset complete pituitary insufficiency were evaluated in a double-blind crossover study. All patients received appropriate replacement therapy with thyroid hormones, glucocorticoids, and gonadal steroids. The subjects were thoroughly investigated with respect to changes in body composition. The results reported here will focus on the changes in serum lipoproteins, apolipoproteins, and especially Lp(a) concentration.

Methods

Patients

Ten patients (one woman and nine men 34–58 years of age) who regularly visited the outpatient clinic of the Division of Endocrinology because of adult-onset pituitary insufficiency were asked to participate in the study. All patients had been treated for pituitary tumors (five prolactinomas, four "nonsecreting" adenomas, and one meningioma). All had complete pituitary insufficiency that had been present for at least 1 year before the study. All patients were taking adequate replacement doses of thyroid hormone (L-thyroxine, 0.1–0.15 mg/day), glucocorticoids (cortisone acetate, 25–50 mg/day), and gonadal steroids. GH deficiency was confirmed by measuring GH concentrations after insulin-induced hypoglycemia (serum GH concentration <2.5 milliunits/L) and by the absence of GH concentrations >2.5 milliunits/L determined in plasma samples obtained at 30-minute intervals over a 24-hour period. None of the patients had previously been treated with GH.

Study Design

The design was a double-blind, crossover, placebo-controlled study using recombinant human GH (rhGH; Humatrope, Eli Lilly & Co., Indianapolis, Ind.). The patients were studied for a period of 12 months and were randomized to one of two treatment groups: 1) 6-month treatment with rhGH followed by a 6-month treatment with placebo and 2) 6-month treatment with placebo followed by 6-month treatment with rhGH. The patients received both written and verbal information about the study, which was approved by the local ethics committee and the Swedish Board of Health, Stockholm.

Study Protocol

The dosage of rhGH was 0.5 units/kg per week s.c. given daily before bedtime. In four patients (No. 2, 3, 6, and 9) the dose was reduced by 50% after 2–6 weeks of treatment because of fluid retention and edema.

The patients were hospitalized for 1 week before initiation of active treatment or placebo and then after 6, 26, 32, and 52 weeks. A 24-hour diet recall was performed 1 month before entrance to the study, and dietary instructions were given to keep food intake and composition constant. During the inpatient period, food intake was standardized. Body weight was measured (to the nearest 0.1 kg using a Statmos balance) in the morning of the first day of each period with the patient wearing underwear but no shoes and after voiding. Body height was measured to the nearest 0.01 m.

Blood Sampling

Blood samples were drawn in the morning after an overnight fast. Serum was separated and stored at −20°C in sealed glass ampules until assay.

Biochemical Assays

In this study, frozen serum samples were used and the assays were performed after all patients had completed the study. For each assay, all samples were analyzed in one assay run. Serum cholesterol and triglyceride concentrations were determined with fully enzymatic methods (Boehringer, Mannheim, FRG) using a Cobas Fara autoanalyzer (Hoffman LaRoche, Basel, Switzerland). HDL cholesterol concentrations were determined after precipitation with MgCl₂ and heparin. LDL cholesterol concentrations were calculated according to Friedewald et al. Apo A-I and B levels were determined with immunoturbidimetric methods (UniKit Roche, catalog No. 07 2995 7 and 07 2994 9, Hoffman LaRoche) in a Cobas Fara autoanalyzer. Between-assay variation was 4.4% and 3.4% for apo A-I and apo B, respectively. Apo E was determined by electroimmunoassay. The within-assay variation for this analysis was 4.8%. For determination of Lp(a) concentrations, a radioimmunoassay was used (catalog No. 10-6497-01, Pharmacia Diagnostics AB, Uppsala, Sweden) as previously described. The effect of freezing the serum was tested by freezing several samples overnight before analysis and comparing the obtained results with those from samples that had been stored at 4°C. No effect of freezing could be observed, which agrees with the results of Jauhiainen et al. Reference values for serum cholesterol, triglycerides, and apo A-I and B were obtained from the Göteborg sample of the MONICA study.

Statistical Analysis

One patient was withdrawn from the study (No. 1) and was excluded from the analysis. Analysis of variance with the completely randomized block design was used. Since the patients were treated according to two different protocols (rhGH/placebo or placebo/rhGH), the effect of active treatment was evaluated using values obtained the week before initiation of rhGH treatment as control values. This approach was justified by the marked carryover effects on body composition that were noted. In four patients who started on placebo treat-
TABLE 1. Before-Treatment Concentrations of Lipoproteins and Apolipoproteins in 10 Patients With Growth Hormone Deficiency

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Chol (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>HDL chol (mmol/L)</th>
<th>LDL chol (mmol/L)</th>
<th>Apo A-I (g/L)</th>
<th>Apo B (g/L)</th>
<th>Apo E (mg/L)</th>
<th>Lp(a) (mg/L)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>7.2</td>
<td>1.4</td>
<td>1.13</td>
<td>5.47</td>
<td>1.7</td>
<td>1.74</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>58</td>
<td>8.0</td>
<td>3.3</td>
<td>0.58</td>
<td>5.72</td>
<td>1.1</td>
<td>2.07</td>
<td>66</td>
<td>238</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>54</td>
<td>3.7</td>
<td>2.2</td>
<td>0.53</td>
<td>2.13</td>
<td>1.0</td>
<td>0.94</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>34</td>
<td>4.9</td>
<td>1.6</td>
<td>0.67</td>
<td>3.45</td>
<td>1.0</td>
<td>1.22</td>
<td>33</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>34</td>
<td>5.3</td>
<td>1.7</td>
<td>0.96</td>
<td>3.57</td>
<td>1.4</td>
<td>1.36</td>
<td>35</td>
<td>168</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>36</td>
<td>5.1</td>
<td>0.8</td>
<td>1.28</td>
<td>3.49</td>
<td>1.3</td>
<td>1.13</td>
<td>32</td>
<td>381</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>46</td>
<td>6.3</td>
<td>1.0</td>
<td>1.45</td>
<td>4.40</td>
<td>1.7</td>
<td>1.27</td>
<td>57</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>52</td>
<td>4.1</td>
<td>1.9</td>
<td>0.65</td>
<td>2.59</td>
<td>1.1</td>
<td>1.17</td>
<td>59</td>
<td>109</td>
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<tr>
<td>9</td>
<td>M</td>
<td>51</td>
<td>3.9</td>
<td>0.7</td>
<td>0.95</td>
<td>2.67</td>
<td>1.2</td>
<td>0.99</td>
<td>21</td>
<td>123</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>43</td>
<td>5.3</td>
<td>4.1</td>
<td>0.63</td>
<td>2.81</td>
<td>1.1</td>
<td>1.27</td>
<td>46</td>
<td>25</td>
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</tbody>
</table>

Chol, cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; apo, apolipoprotein; Lp(a), lipoprotein (a).

ment, no significant fluctuations in any of the variables studied were noted during the placebo period. A probability value less than 0.05 was considered significant.

Results

Serum concentrations of cholesterol, triglycerides, HDL and LDL cholesterol, apo A-I, apo B, apo E, and Lp(a) before treatment are shown in Table 1. One patient (No. 2) had serum cholesterol, LDL cholesterol, and apo B concentrations above the 90th percentile of those of a control population. Serum triglyceride concentrations were above the 90th percentile in this patient and also in patient No. 10. Serum HDL cholesterol concentrations were below the 10th percentile (0.94 mmol/L for men 34-60 years old) of a control population. Serum triglyceride concentrations above the 90th percentile of those of a control population in five of nine patients. Similar observations were made with respect to apo A-I concentrations (the concentration value less than 0.05 was considered significant). Lp(a) concentrations varied markedly between subjects, as expected from the reported skewed distribution in normal populations.³-⁶

The effects of GH treatment on blood lipids and lipoproteins are shown in Table 2. GH treatment resulted in a decrease in serum concentrations of cholesterol and LDL cholesterol after 6 weeks of treatment, but after 26 weeks no significant differences compared with pretreatment concentrations were observed. HDL cholesterol concentrations were significantly increased after 26 weeks of treatment, and the HDL/LDL ratio was higher during treatment. Serum concentrations of apo A-I and apo B changed in parallel to changes in HDL and LDL cholesterol concentrations, respectively, but these changes did not reach statistical significance. There were no significant changes in serum apo E concentrations. Serum triglyceride concentrations did not change significantly during treatment, but in the two patients with marked hypertriglyceridemia, such concentrations decreased markedly during treatment (Figure 1).

Serum Lp(a) concentrations increased in all patients after only 6 weeks of treatment (205±13% of pretreatment values, mean±SEM) and remained increased after 26 weeks of treatment (196±16% of pretreatment values). In the four patients who started on active treatment, Lp(a) concentrations decreased to pretreatment concentrations 6 weeks after rhGH withdrawal (Figure 2).

Discussion

Treatment of adults with complete GH deficiency resulted in changes in cholesterol, LDL cholesterol, HDL cholesterol, and most markedly in Lp(a) concen-

TABLE 2. Effects of Recombinant Human Growth Hormone Treatment on Blood Lipids and Lipoproteins in Nine Patients With Adult-Onset Growth Hormone Deficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weeks after initiation of active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.16±1.34</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.92±1.14</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.86±0.33</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.43±1.09</td>
</tr>
<tr>
<td>Apo A-I (g/L)</td>
<td>1.21±0.22</td>
</tr>
<tr>
<td>Apo B (g/L)</td>
<td>1.26±0.34</td>
</tr>
<tr>
<td>Apo E (mg/L)</td>
<td>43±15</td>
</tr>
<tr>
<td>Lp(a) (mg/L)</td>
<td>137±113</td>
</tr>
<tr>
<td>HDL/LDL</td>
<td>0.26±0.08</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; LDL, low density lipoprotein; apo, apolipoprotein; Lp(a), lipoprotein (a). Values are mean±SD.

*p<0.05 compared with pretreatment values.

†p<0.01 compared with pretreatment values.
GH Treatment Increases Lp(a) Levels

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GH Treatment Increases Lp(a) Levels

FIGURE 1. Line plot of concentrations of serum triglycerides in nine patients during the study. Week 0 indicates concentrations before initiation of active treatment. Five patients were initially treated with placebo (weeks -26 to 0), and four patients were initially treated with growth hormone (GH) and then placebo (weeks 26 to 52).

trations, thereby demonstrating that GH has important effects on the regulation of lipoprotein metabolism in adult life. Such a role has previously been suggested by Merimee and coworkers, who found that hypertriglyceridemia was more common among GH-deficient patients and that GH-deficient subjects with hyperlipidemia had a greater elevation of their serum lipids than non–GH-deficient members of their families. There are also reports suggesting that serum cholesterol is increased in GH-deficient children, results that are in line with the present findings and that indicate that a prolonged lack of GH results in aberrations in lipoprotein metabolism.

Some of the discrepant results previously reported on the changes in total cholesterol with GH status may reflect a redistribution of serum cholesterol rather than a lack of effect of GH. Moreover, the dose and the frequency of GH injections may be important. Studies in the rat have indicated that both dose and mode of administration of GH result in different effects on lipoproteins, especially the apolipoproteins associated with HDL. In the present study, GH was given as a daily subcutaneous injection in a dose that was considered to be within the physiological range and in a manner aimed at increasing circulating GH concentrations during the night. In many of the previous studies on the effects of GH on lipoproteins in GH deficiency, GH has been given as an intramuscular injection two to three times per week.

GH induces profound changes in body composition, resulting in an increase in body cell mass, an increase in extracellular water volume, and a decrease in body fat. Using three independent methods for determination of body composition (electrical impedance, computed tomography, and determinations of total body potassium and total body water), the subjects in the present study group lost, on the average, 6 kg of body fat. No significant change in body weight was observed due to increases in muscle mass, extracellular fluid, and visceral organs. The changes observed are in line with the known anabolic and lipolytic effects of GH. Several other effects of GH treatment were also noted, effects that may be important for those observed. For example, insulin-like growth factor–1 concentrations increased severalfold and T3 concentrations were increased, probably as a reflection of increased conversion of T4 to T3 in peripheral tissues. These effects, as well as the possible effects of GH on insulin secretion and insulin sensitivity, may be important for the effect of GH on lipid metabolism, e.g., in acromegaly.

We found no significant effect of GH treatment on serum triglyceride concentrations, in accordance with previous findings in GH-deficient adults, elderly men with low serum insulin-like growth factor–1 concentrations, and children. Moreover, we found that in two patients with hypertriglyceridemia, the serum triglyceride concentration decreased markedly during GH treatment. These results are in part contradictory to those previously reported. In GH-deficient children and in normal adults, GH treatment has been reported to increase serum triglyceride levels, and acromegaly has also been associated with increased triglyceride concentrations. Studies in patients with acromegaly have indicated that a GH excess results in increased triglyceride production. Studies in rats have indicated that very low density lipoprotein (VLDL) secretion is decreased after hypophysectomy and increased after GH treatment. In favor of the possibility that GH stimulates VLDL production is the known lipolytic effect of GH that results in increased availability of free fatty acids, which in turn has been shown to increase hepatic VLDL secretion. Since GH treatment of GH-deficient adults resulted in no change in serum triglyceride concentration and in selected patients even a decrease in serum triglyceride concentration, it seems plausible
that GH treatment in these patients also resulted in increased degradation of VLDL.

We found a transient decrease in LDL cholesterol concentrations and an increase in HDL cholesterol levels after 6 months of treatment. Although the changes were significant only at the 5% level and the number of subjects studied was limited, the findings are supported by the observation that HDL concentrations were low in GH-deficient adults. Moreover, it has recently been reported that GH treatment of normal adults before elective surgery resulted in an increase in serum LDL concentrations in the liver, concomitant with a decrease in serum LDL concentrations. The transient nature of the decrease in LDL cholesterol concentrations observed in our study may be explained by increased secretion and turnover of VLDL, as discussed above. Furthermore, an increased turnover of VLDL may explain the observed increase in HDL cholesterol concentration with prolonged treatment.

The most pronounced effect of GH treatment on lipoprotein metabolism was an increase in serum Lp(a) concentration. If LDL receptor expression were increased in these GH-deficient subjects during GH treatment, one would expect Lp(a) concentrations to decrease. In this context, it is interesting to compare the effects of GH observed here to those of gonadal steroids. Estrogen treatment of men with prostatic carcinoma has been shown to decrease LDL cholesterol concentrations due to increased catabolism of LDL. These effects are similar to those of GH reported here and by others. However, Lp(a) concentrations decreased markedly after estrogen treatment of men with prostatic carcinoma. Irrespective of the mechanisms involved, our data suggest that GH affects Lp(a) in a different manner compared with the gonadal steroids. Since the serum concentration of Lp(a) is presumed to mainly reflect its synthesis, it seems likely that the effect of GH is on the synthesis of apo(a) to apo B in the liver. Another possibility is that GH treatment resulted in a shift of apo(a) between density classes rather than a true change in concentration, although we find this possibility less likely in view of the marked changes in measured Lp(a) concentrations compared with the less-pronounced changes in HDL and LDL cholesterol and triglyceride concentrations.

Although it is too early to speculate about the importance of GH in the regulation of lipoprotein metabolism in relation to “risk factors” for cardiovascular disease, the present data suggest that the lack of GH results in a decrease in HDL, an effect that may be important for the increased risk of cardiovascular disease observed in GH deficiency. The increase in Lp(a) concentrations induced by GH may be one factor that contributes to the increased risk of cardiovascular mortality observed in acromegaly. Only long-term studies with GH replacement therapy in GH deficiency can resolve these questions.

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