Cardiovascular risk factors in adult patients with growth hormone deficiency

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Patients with adult onset growth hormone deficiency have a decreased life expectancy owing to an increased mortality from cardiovascular disease. In the present study, 104 subjects (66 men and 38 women, aged 22–74 years) with growth hormone deficiency and with adequate replacement therapy with glucocorticoids, thyroid hormones and gonadal steroids were studied with respect to known risk factors for cardiovascular disease. For comparison, data from a population study, “the MONICA study”, were obtained. The patients had a significantly higher body mass index compared to controls (p<0.001). Serum triglyceride concentration was higher (p<0.001) but there was no difference in serum total cholesterol concentration. Serum high-density lipoprotein cholesterol concentration was lower (p<0.001) in the patients. There was no difference in the prevalence of diabetes mellitus. The prevalence of treated hypertension was higher (p<0.05) in the patients but the prevalence of smoking was lower (p<0.001). Even after taking the increased body mass index into consideration, the changes in the prevalence of treated hypertension (p<0.05) and in the serum concentrations of triglycerides (p<0.05) and high-density lipoprotein concentrations (p<0.001) remained. These results indicate that growth hormone deficiency alters lipoprotein metabolism and increases the risk for development of hypertension, which in turn might contribute to the increased risk for cardiovascular disease.

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Recently, we investigated the prognosis for patients with adult onset pituitary insufficiency (1). It was shown that such patients, despite adequate replacement therapy with adrenal, thyroid and gonadal hormones when appropriate but not with growth hormone (GH), had a decreased life expectancy. The increased mortality was not due to the primary disease, mainly pituitary tumors, but rather to an increased risk of premature death from cardiovascular disease. This finding suggested possibly that untreated GH deficiency results in metabolic changes that may lead to cardiovascular disease. Therefore, we have studied risk factors for cardiovascular disease in this group of patients.

Subjects and methods

Subjects

Patients with pituitary disease diagnosed between 1956 and 1990 were investigated in terms of possible GH deficiency. Each subject had been investigated as an inpatient at the Endocrine Unit at Sahlgrenska Hospital on at least one occasion between 1956 and 1990. All patients lived in the catchment area of the Endocrine Unit, which is western Sweden including the city of Göteborg.

The patients received both written and verbal information of the study and their written consent was obtained. The study was approved by the Ethical Committee of the Medical Faculty of the University of Göteborg.

Only adult subjects with a maximum age of 75 years were included. There were 162 subjects with known pituitary deficiency living in the catchment area at the time of follow-up. One hundred and forty-seven patients were invited to the study; 130 accepted and 17 declined.

Adrenal, thyroid and gonadal functions were assessed with the laboratory tests available at the time, as described previously (1).

Growth hormone deficiency was defined as either a maximal serum GH concentration of < 5 mU/l after an iv insulin or im glucagon tolerance test performed during the inpatient investigation (45 subjects) or, at the follow-up, a plasma insulin-like growth factor I (IGF-I) concentration below the normal reference concentration (see below) in combination with a GH concentration of < 1 mU/l in three consecutive blood samples obtained at 1-h intervals from 8 a.m. to 10 a.m. (59 subjects).

Out of the 130 patients, 111 (71 men and 40 women) fulfilled these criteria. Five men and two women of fertile age with untreated gonadal deficiency were excluded. Thus, 66 men (mean age 52.0 years; range 18–73 years) and 38 women (mean age 53.2 years; range 22–73 years) remained in the study. Routine replacement
therapy with cortisone acetate (25.0–37.5 mg/day), L-thyroxine (0.05–0.20 mg/day), testosterone (mean dose 250 mg im every fourth week) and estradiol (mean dose 1.8 mg/day) was given. Thus, all hypogonadal males and all hypogonadal females below the age of 50 years had proper sex hormone substitution.

The causes of pituitary deficiency are listed in Table 1. Most patients had been treated for pituitary macroadenomas (68, out of which 21 were prolactinomas). Of these patients 35 had been subject to pituitary surgery by the transcranial route and 21 via the trans-sphenoidal route, and 50 of them had received conventional pituitary irradiation. Out of the 12 non-operated patients with pituitary tumors, five had been treated with irradiation only, two with bromocriptine only, one with a combination of irradiation and bromocriptine and four had received no special treatment. Extraptuitary tumors were the cause of hypopituitarism in 24 subjects. Fifteen of them had craniopharyngioma. Ten of these patients had been operated on by the transcranial route and four by the trans-sphenoidal route and one had had no specific treatment. Five of the operated subjects had received postoperative conventional pituitary irradiation. Nine patients had pituitary deficiency caused by other tumors, out of which eight had been subject to surgery and three of these had postoperative irradiation.

In 12 patients the cause of pituitary deficiency was unknown. Of the total patients, 79 had complete pituitary deficiency and 22 partial deficiency. Another three patients had isolated GH deficiency (Table 2).

The duration from diagnosis of hypopituitarism (or pituitary disease) to follow-up for all the patients (N=104) was, on average, 13.7 years (range 0–44 years); for the male subjects it was 11.4 years (range 0–37 years) and for the female subjects it was 17.8 years (range 0–44 years). This time period also estimates the duration of replacement therapy.

Prevalence of hypertension, diabetes mellitus and smoking

Each subject was questioned on whether he/she had hypertension requiring medical treatment (yes/no) or diabetes mellitus requiring at least a diet regimen by the time of the follow-up study.

Each subject was questioned about smoking habits and was classified into one of the following categories:

(i) non-smokers if they reported that they were not current smokers and had never smoked regularly;
(ii) ex-smokers if they reported that they had smoked in the past but did not smoke currently;
(iii) regular smokers if they smoked every day:
   (a) 1–14 cigarettes per day
   (b) ≥15 cigarettes per day.

Body weight, body height and body mass index

Body weight was measured in the morning, after the subjects had voided, to the nearest 0.1 kg using a Stahmann balance. Body height was measured barefoot and to the nearest 0.5 cm.

Body mass index (BMI) was calculated from the formula: BMI = body weight/height² (kg/m²) (2).

Blood pressure

The blood pressure was measured to the nearest 5 mmHg in the patients and to the nearest 2 mmHg in controls, as the mean of two measurements on the right arm. The patient was in the supine position after having rested for 5 min. The measurements were performed by a single observer. A random zero sphygmomanometer (Hawksley & Sons, Lancing, UK) was used, with a cuff size corresponding to the size of the right arm.

Blood sampling and biochemical methods

After one night of fasting, before the intake of the routine replacement therapy, blood samples were drawn for the determination of serum free thyroxine (T₄), serum total cholesterol, serum HDL cholesterol, serum triglycerides, serum GH and EDTA–plasma IGF-1 concentrations using
the Vacutainer system (no indwelling cannula, no intravenous heparin given during the hours preceding the sampling). Another two blood samples for assessing serum GH concentration were drawn after 2 and 3 h, respectively.

Serum free T₄ was determined by a ligand–analogue radioimmunoassay (Amerlex M, Amersham International plc, Amersham, Bucks, UK). The reference limits are 9–23 pmol/l.

Serum GH (mU/l) was determined by an immunoradiometric assay according to the manufacturer’s protocol (Pharmacia, Uppsala, Sweden).

The EDTA–plasma IGF-I was determined by a non-extraction radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). This method determines “low-affinity-bound” analyte, i.e., the concentration in non-extracted plasma that is available to a known amount of antiserum against IGF-I under defined conditions. The reference limits for adults are: men, 0.34–1.9 kU/l; women, 0.45–2.2 kU/l.

The analyses of total cholesterol, HDL cholesterol and triglyceride concentrations were performed in connection to the sampling.

The total cholesterol concentration was determined according to the method described by Allain et al. (3) and the HDL cholesterol concentration was determined according to the method described by Warnick et al. (4). The triglyceride concentration was determined with a fully enzymatic method (Boehringer, Mannheim, Germany) according to Fossati and Prencipe (5).

Reference values for serum total cholesterol, HDL cholesterol and triglyceride were obtained from the Göteborg sample of the MONICA study (6).

Control population

As a control population we used the Göteborg sample of the WHO MONICA Project (MONICA = MONItoring of trends and determinants in Cardiovascular disease) (7). The MONICA study is designed to measure the trends in mortality and morbidity from coronary heart disease and stroke and its relation to changes in known risk factors. Different populations in 27 countries took part. The control population was divided into four groups according to age: 25–34 years, 35–44 years, 45–54 years and 55–64 years. In each age group 500 subjects (250 males and 250 females) were asked to participate. Finally, 1421 subjects (691 males and 730 females) completed the study, giving a participation rate of 69.1% (range 61.2–76.5) in male subjects and 73.0% (range 64.9–80.5) in female subjects.

Statistical analysis

Conventional statistical methods were used for the calculation of means, medians, standard deviations and standard errors. Differences between groups were tested with Mantel’s test, where the influence of age is eliminated (8). Values are given as means, medians and standard deviations, and two-tailed p values were used.

Results

The mean concentration of plasma IGF-I in the male subjects was 0.28 (±0.11) kU/l and in the female subjects was 0.27 (±0.08) kU/l. The mean concentration of serum free T₄ was 13.1 (±4.3) pmol/l in males and 15.4 (±4.8) pmol/l in females.

Treated hypertension was more common (p<0.05) in patients compared to controls, even when the influence of BMI was eliminated (p<0.05) (Table 3). The prevalence of diabetes mellitus was similar in patients and controls (Table 3). There were fewer smokers (p<0.001) among the patients (Table 4). Body mass index was higher (p<0.001) in patients compared to controls, but the systolic and diastolic blood pressures did not differ (Table 3).

As expected, serum total cholesterol concentrations increased with age in both the patients and the control men and women, but there was no difference between the patients and the controls (Table 5). Also, serum triglyceride concentration increased with age in the control subjects (Table 6). In the patients, triglyceride concentrations were higher in both men (p<0.01) and women (p<0.01) compared to the controls. This difference remained significant (p<0.05) also after elimination of the influence of BMI. Control women had a higher serum HDL cholesterol concentration than control men (Table 7), as did female patients compared to male patients. Patients had a lower (p<0.001) serum HDL

Table 3. Prevalence of treated hypertension and diabetes mellitus, and median values of body mass index (BMI), systolic and diastolic blood pressures in 104 patients with growth hormone deficiency compared to controls (N = 1387).

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>p</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of treated hypertension</td>
<td>6 (11.3)³</td>
<td>&lt;0.05</td>
<td>54 (8.0)</td>
<td></td>
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<tr>
<td>Prevalence of diabetes mellitus</td>
<td>1 (1.9)</td>
<td>NS</td>
<td>18 (2.7)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4</td>
<td>&lt;0.001</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130</td>
<td>NS</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80</td>
<td>NS</td>
<td>82</td>
<td></td>
</tr>
</tbody>
</table>

³ Numbers in parentheses are percentages.
Table 4. Cigarette consumption in 104 subjects with growth hormone deficiency and in a control population (N = 1397).*

<table>
<thead>
<tr>
<th>Group</th>
<th>20-44 years</th>
<th>45-64 years</th>
<th>20-44 years</th>
<th>45-64 years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Non</td>
<td>75.0</td>
<td>33.9</td>
<td>51.4</td>
<td>28.9</td>
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<tr>
<td>Ex</td>
<td>12.5</td>
<td>34.5</td>
<td>29.7</td>
<td>38.2</td>
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<tr>
<td>1-14</td>
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<td>7.7</td>
<td>13.5</td>
<td>8.2</td>
</tr>
<tr>
<td>&gt;15</td>
<td>0</td>
<td>23.9</td>
<td>5.4</td>
<td>24.7</td>
</tr>
</tbody>
</table>

* Values are percentages. The cigarette consumption was lower in both male (p < 0.001) and female subjects (p < 0.001) compared to controls. Non: non-smokers; Ex: ex-smokers; 1-14 and ≥15: number of cigarettes per day.

Table 5. Serum total cholesterol (mmol/l) in 66 male and 38 female subjects with growth hormone deficiency and in controls (N = 1342).*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>0-24</td>
<td>3</td>
<td>4.63</td>
<td>(±0.32)</td>
<td>3</td>
</tr>
<tr>
<td>25-34</td>
<td>3</td>
<td>6.23</td>
<td>(±1.07)</td>
<td>146</td>
</tr>
<tr>
<td>35-44</td>
<td>10</td>
<td>5.75</td>
<td>(±0.87)</td>
<td>145</td>
</tr>
<tr>
<td>45-54</td>
<td>18</td>
<td>6.12</td>
<td>(±1.67)</td>
<td>180</td>
</tr>
<tr>
<td>55-64</td>
<td>19</td>
<td>6.41</td>
<td>(±1.36)</td>
<td>164</td>
</tr>
<tr>
<td>65-75</td>
<td>13</td>
<td>6.08</td>
<td>(±1.39)</td>
<td>-</td>
</tr>
</tbody>
</table>

* There was no difference in serum total concentrations between patients and controls, neither among males nor females.

Table 6. Serum triglycerides (mmol/l) in 66 male and 38 female subjects with growth hormone deficiency and in controls (N = 1339).*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>0-24</td>
<td>3</td>
<td>2.40</td>
<td>(±0.95)</td>
<td>3</td>
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<tr>
<td>25-34</td>
<td>3</td>
<td>1.73</td>
<td>(±0.67)</td>
<td>146</td>
</tr>
<tr>
<td>35-44</td>
<td>10</td>
<td>2.34</td>
<td>(±1.73)</td>
<td>144</td>
</tr>
<tr>
<td>45-54</td>
<td>18</td>
<td>1.82</td>
<td>(±1.18)</td>
<td>180</td>
</tr>
<tr>
<td>55-64</td>
<td>19</td>
<td>1.49</td>
<td>(±0.86)</td>
<td>163</td>
</tr>
<tr>
<td>65-75</td>
<td>13</td>
<td>2.74</td>
<td>(±3.22)</td>
<td>-</td>
</tr>
</tbody>
</table>

* The serum triglyceride concentration is higher in both male (p < 0.01) and female (p < 0.01) patients compared to controls.

Table 7. Serum HDL cholesterol (mmol/l) in 66 male and 38 female subjects with growth hormone deficiency and in controls (N = 1332).*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>0-24</td>
<td>3</td>
<td>0.74</td>
<td>(±0.15)</td>
<td>3</td>
</tr>
<tr>
<td>25-34</td>
<td>3</td>
<td>1.19</td>
<td>(±0.36)</td>
<td>145</td>
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<tr>
<td>35-44</td>
<td>10</td>
<td>0.97</td>
<td>(±0.25)</td>
<td>143</td>
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<tr>
<td>45-54</td>
<td>18</td>
<td>0.92</td>
<td>(±0.20)</td>
<td>181</td>
</tr>
<tr>
<td>55-64</td>
<td>19</td>
<td>1.08</td>
<td>(±0.31)</td>
<td>162</td>
</tr>
<tr>
<td>65-75</td>
<td>13</td>
<td>0.99</td>
<td>(±0.31)</td>
<td>-</td>
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</tbody>
</table>

* The serum HDL cholesterol concentration is lower in both male (p < 0.001) and female (p < 0.001) patients compared to controls.
cholesterol concentration compared to the controls, and this difference remained (p < 0.001) when the influence of BMI was eliminated.

Discussion

These results show that in a large group of adult patients with GH deficiency the HDL cholesterol concentrations were lower and triglyceride concentrations were higher compared to values obtained from a normal population sample. Furthermore, the prevalence of treated hypertension was higher in the patients.

As we were able to study most patients with GH deficiency within the catchment area, we believe that the patients studied are truly representative for the population of GH-deficient adults. It is therefore likely that the changes observed are a result of GH deficiency, because great care was taken to include only patients who received adequate replacement therapy with respect to other pituitary-dependent hormones. As there were no differences compared to the controls in the prevalence of diabetes and smoking (actually lower), it is conceivable that the changes in lipoprotein metabolism and the higher prevalence of hypertension observed contribute to the increased risk for cardiovascular disease previously observed in patients with pituitary insufficiency (1).

The lower smoking habits among the patients has no obvious explanation, but it evidently does not explain the higher incidence of cardiovascular disease among the patients.

The reason for the increased prevalence of treated hypertension among the patients is not obvious. We cannot exclude that the high prevalence in part is due to the fact that the patients, compared to the controls, are under thorough and regular medical controls. Growth hormone deficiency leads to a decrease in both extracellular water volume (9) and cardiac output (10), factors that should lower the blood pressure. On the other hand, the renal function is impaired owing to a decrease in both the glomerular filtration rate and the renal plasma flow (10, 11). This could be one possible explanation for the increased prevalence of treated hypertension. Moreover, a decreased distensibility has been shown recently in the carotid artery in patients with hypopituitarism, suggesting a possible increase in the vascular tonus (12).

There are only a few reports on changes in serum lipids and lipoproteins in GH deficiency in adults. Merimee and co-workers found that GH-deficient subjects with hyperlipidaemia had greater elevation of their serum lipids compared to non-GH-deficient members of their families (13, 14). Growth hormone treatment of GH-deficient adults for 6 months resulted in a decrease in cholesterol concentrations but no change in triglyceride concentrations were noted (15). However, in that study the HDL cholesterol was not measured. In another 6-month, double-blind, crossover study of GH treatment in adults with GH deficiency, we have found that GH treatment resulted in a transient decrease in cholesterol concentrations, which could be ascribed to a decrease in LDL cholesterol (16). After prolonged treatment, LDL cholesterol concentrations were unchanged compared to pretreatment levels but HDL cholesterol concentrations were increased. These findings are in agreement with the present results and suggest that it is the lack of GH that is responsible for the low HDL cholesterol concentrations observed.

We found that the triglyceride concentrations were increased in the GH-deficient subjects, which is in agreement with the findings that hypertriglyceridaemia was more common among GH-deficient patients (13, 14). In the study by Salomon et al. (15) no effects of GH treatment to GH-deficient adults on serum triglyceride concentrations were noted; similar results were reported by Rudman et al. (17), who treated elderly men with low IGF-I levels with GH. In our study on GH-deficient adults (16), no significant effects of GH treatment on serum triglyceride concentrations were found. However, in two patients with hyperlipidaemia there was a marked decrease in the triglyceride concentrations during treatment with GH. Together with the reports by Merimee, these findings may suggest that hypertriglyceridaemia develops with GH deficiency in subjects that have a predisposition for hyperlipidaemia.

The mechanism for the effects of GH on lipid metabolism are not understood completely. Growth hormone has major effects on body composition, and GH treatment results in loss of fat and increases of muscle mass and extracellular water (15, 18). These effects are ascribed to the lipolytic, anabolic and antinatriuretic effects of GH (19–21). We found that GH-deficient subjects had an increase in BMI, which can be ascribed to increased body fat (9) and especially visceral fat (18). Growth hormone treatment of GH-deficient adults decreases body fat, and the loss of visceral fat is more pronounced than that of other fat depots (18). Because visceral adiposity in itself is associated with increased triglyceride concentrations and decreased HDL concentrations (22), the effects of GH on body composition may contribute to the present observations.

Recent experimental studies have emphasized the important role of GH in the control of lipoprotein metabolism. In animal studies, GH has been shown to increase the triglyceride production in the liver (23) and to decrease LDL cholesterol and apolipoprotein B concentrations in blood (24–26). No changes in serum VLDL concentrations have been found, indicating that GH increases both production and turnover of VLDL. Recently, it was shown that GH increases the hepatic LDL receptor activity both in rats and in humans (27), in agreement with the contention that lipoprotein turnover is increased by GH. Increased VLDL production and turnover, together with increased LDL receptor activity, will result in increases in HDL cholesterol concentrations but the LDL cholesterol concentrations may be unchanged (28).
The main conclusion from the present study is that GH is important for the regulation of lipoprotein metabolism during adult life. Lack of GH results in higher triglyceride concentrations and lower HDL concentrations, changes that may contribute to increased risk of cardiovascular death in GH deficiency. Whether long-term treatment of GH-deficient adults with GH will normalize serum lipids and ultimately change the prognosis of these patients remains to be established, but our results strengthen the indication for including replacement therapy with GH to adults with GH deficiency.

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References


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