Improved Cardiovascular Risk Factors and Cardiac Performance after 12 Months of Growth Hormone (GH) Replacement in Young Adult Patients with GH Deficiency*

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ABSTRACT

Adult GH deficiency (GHD) is associated with increased cardiovascular morbidity and mortality due to unfavorable lipid profile, hyperfibrinogenemia, and impairment of cardiac performance. This prospective controlled cohort study evaluated the effects of 12-month GH replacement on lipid profile, fibrinogen levels, cardiac mass by echocardiography, and performance by equilibrium radionuclide angiography. To this end we studied 20 patients (11 men and 9 women, aged 19–40 yr), 10 with childhood-onset (co-) and 10 with adult-onset (ao-) disease, and 20 sex- and age-matched healthy subjects. At study entry, insulin-like growth factor I (IGF-I; \( P < 0.001 \)), and high density lipoprotein cholesterol (HDL cholesterol; \( P < 0.001 \)), triglycerides (TG; \( P < 0.001 \)), and fibrinogen (F; \( P < 0.001 \)) levels, left ventricular mass index (LVMI; \( P < 0.001 \)), systolic function, and exercise duration (\( P < 0.001 \)) at peak exercise were lower in patients than in controls. After 12 months, increases in IGF-I (\( P < 0.001 \)) and HDL cholesterol levels (\( P < 0.04 \)), LVMI (\( P < 0.001 \)), LVEF at peak exercise (\( P < 0.001 \)), and exercise duration (\( P < 0.001 \)) and capacity (\( P < 0.001 \)) and decreases in total cholesterol (\( P < 0.0001 \)), low density lipoprotein cholesterol (LDL cholesterol; \( P < 0.0001 \)), triglycerides (TG; \( P < 0.001 \)), and fibrinogen (F; \( P < 0.0001 \)) levels were found in all patients, without any difference between co- and ao-GHD. At the end of treatment, however, total cholesterol, triglycerides, and fibrinogen levels were still higher, and HDL cholesterol levels, IGF-I levels, and LVEF at rest and at peak exercise were lower in patients than in controls.

In conclusion, GH replacement for 12 months significantly improved lipid profile, decreased fibrinogen levels, and increased LVMI and LVEF in young adults with co- or ao-GHD. However, lipid profile, fibrinogen levels, and systolic function remained abnormal compared with those in age- and sex-matched controls, suggesting that a longer period of GH replacement is necessary to normalize cardiovascular parameters and reverse the cardiovascular risk of these patients.

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From clinical perspective, clear-cut evidence for the existence of specific acromegalic cardiomyopathy is now recognized (9–11), whereas in patients with GHD a decrease in left ventricular posterior wall and interventricular septum thickness leading to decreased left ventricular (LV) mass (LVM) was described by some researchers (12–14), although this was not a constant finding (15–17). Besides alterations of cardiac geometry, GHD patients present varying degrees of diastolic dysfunction, whereas systolic function at rest is reported to be normal (12–17). However, using equilibrium radionuclide angiography, a technique more sensitive than echocardiography to evaluate systolic function, we recently demonstrated that the prevalence of impaired response of the LV ejection fraction (EF) during exercise was relevant, occurring in 65.4–81.8% of adult (18) and elderly (19) GHD patients. However, the described hypokinetic syndrome of GHD patients (20) was evident only in young subjects who had heart rate and LVEF, both at rest and at peak exercise, significantly lower than age-matched controls (18). These findings confirmed previous data collected in a smaller series.
CARDIOVASCULAR RISK IN GHD AFTER GH REPLACEMENT

A large number of short-term studies have reported beneficial effects of GH replacement on lipid profile, body composition and metabolism, physical performance, cognitive function, and general well-being (24–26). Cardiac function did not improve after 6 months of treatment in one study (15), whereas in another study a 26% increase in the LVM index (LVMi) and a 12% increase in systolic function were observed (14). In a small group of adult co-GHD patients we reported an increase in cardiac performance (21, 22) after 6 months of GH replacement. However, data concerning long-term GH replacement on the reversibility of cardiovascular risk in these patients are still lacking.

The aim of this prospective controlled cohort study was to investigate the effect of GH replacement for 12 months on cardiovascular risk factors, such as lipid profile and fibrinogen levels (27) and cardiac mass and performance in adult patients with GHD. As GHD is likely to display different effects in young, adult, and elderly patients, and patients with disease onset during childhood were shown to present more severe symptoms than those with adult onset of disease (28), only young patients were enrolled in the current study.

The results were analyzed both in the entire population and separately in co- and ao-GHD patients and were compared with those from an appropriate sex- and age-matched control group.

Subjects and Methods

Patients

Twenty patients (11 men and 9 women; age range, 19–40 yr; median age, 31 yr) with diagnosis of GHD (see below) during childhood (in 10) or as adults (in 10) entered this open prospective study. As a control group we studied 20 healthy volunteers sex- and age-matched with the patients and controls presented with or had previously suffered from GHD replacement. However, data concerning long-term GH replacement on the reversibility of cardiovascular risk in these patients are still lacking.

Assays

Serum GH levels were measured by immunoradiometric assay using commercially available kits (HGH-CTK-BMS, Sorin, Saluggia, Italy).

TABLE 1. Anthropometric, endocrine, and metabolic parameters in patients with GHD and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n = 20)</th>
<th>GHD patients (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFP (mIU/L)</td>
<td>11.9±3.2</td>
<td>11.9±3.2</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>18–40</td>
<td>19–40</td>
<td>0.3</td>
</tr>
<tr>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.28</td>
<td>24.7±1.3</td>
<td>25.30</td>
</tr>
<tr>
<td>Plasma IGF-I levels (µg/L)</td>
<td>31.4±1.5</td>
<td>34.112</td>
<td>74.9±5.6</td>
</tr>
<tr>
<td>Total cholesterol levels (mg/dL)</td>
<td>180.9±4.1</td>
<td>158.0±47</td>
<td>204.4±11.1</td>
</tr>
<tr>
<td>LDL cholesterol levels (mg/dL)</td>
<td>87.7±4.3</td>
<td>80.1±137</td>
<td>106.1±3.9</td>
</tr>
<tr>
<td>HDL cholesterol levels (mg/dL)</td>
<td>61.0±2.8</td>
<td>35.55</td>
<td>44.4±1.5</td>
</tr>
<tr>
<td>Total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, and fibrinogen</td>
<td>31.9±0.2</td>
<td>30.8–33</td>
<td>4.9±0.3</td>
</tr>
</tbody>
</table>
| Normal ranges: IGF-I levels in 20 to 40-yr-old subjects, 110–450 µg/L; total cholesterol, 120–200 mg/dL; HDL cholesterol, 35–110 mg/dL; triglycerides, 50–200 mg/dL; fibrinogen, <400 mg/dL.
TABLE 2. Cardiac and hemodynamic parameters in patients with GHD and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control n = 20</th>
<th>GHD patients n = 20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>Mean ± SEM</td>
<td>Range</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td>9–11</td>
<td>10.0 ± 0.1</td>
<td>8–9.5</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>9–11</td>
<td>9.7 ± 0.1</td>
<td>7.7–10</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>55–100</td>
<td>93.6 ± 1.0</td>
<td>80–98</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>55–96</td>
<td>74.9 ± 2.7</td>
<td>57–90</td>
</tr>
<tr>
<td>Exercise</td>
<td>113–191</td>
<td>150.8 ± 3.9</td>
<td>95–170</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>100–125</td>
<td>118.5 ± 1.7</td>
<td>90–140</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>130–200</td>
<td>160.5 ± 5.2</td>
<td>120–150</td>
</tr>
<tr>
<td>Left ventricular fraction (%)</td>
<td>55–60</td>
<td>77.7 ± 1.7</td>
<td>60–85</td>
</tr>
<tr>
<td>All test</td>
<td>68–90</td>
<td>96.7 ± 2.6</td>
<td>80–100</td>
</tr>
<tr>
<td>Peak ejection fraction (%)</td>
<td>50–60</td>
<td>59.8 ± 1.1</td>
<td>34–70</td>
</tr>
<tr>
<td>Exercise</td>
<td>60–95</td>
<td>72.3 ± 2.1</td>
<td>30–64</td>
</tr>
<tr>
<td>Exercise</td>
<td>8.9–50.7</td>
<td>21.2 ± 3.2</td>
<td>24–144</td>
</tr>
<tr>
<td>Peak filling rate (EDV/s) (mm)</td>
<td>2.6–4.6</td>
<td>3.5 ± 0.1</td>
<td>1.4–4.5</td>
</tr>
<tr>
<td>Peak filling rate/EV (mm)</td>
<td>1.6–4.1</td>
<td>2.8 ± 0.1</td>
<td>1.2–4.2</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>7–12</td>
<td>9.6 ± 0.2</td>
<td>6–10</td>
</tr>
<tr>
<td>Exercise capacity (watts)</td>
<td>75–125</td>
<td>100.0 ± 4.1</td>
<td>80–100</td>
</tr>
</tbody>
</table>

Normal left ventricular mass indexed; <110 g/m² in women and <135 g/m² in men. Normal peak filling rate, 2.5 EDV/s. Normal ejection fraction at rest, 50% normal response of the ejection fraction at peak exercise, 5% of resting values.

The sensitivity of the assay was 0.9 µL. The intra- and interassay coefficients of variation (CVs) were 3.5% and 7.9%, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction using kits from Diagnostic Systems Laboratories, Inc. (Webster, TX). The intraassay coefficients of variation were 3.4%, 3.0%, and 1.5% for the low, medium, and high points of the standard curve, respectively. The interassay coefficients of variation were 8.2%, 3.5%, and 3.7% for the low, medium, and high points of the standard curve. Sensitivity of the assay was 0.2 µg/L. The intra- and interassay coefficients of variation were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction using kits from Diagnostic Systems Laboratories, Inc. (Webster, TX).

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and total cholesterol, LDL cholesterol, triglycerides, and fibrinogen levels and total/HDLC cholesterol ratio were higher in patients than in controls (Table 1). IST, LVPWT, LVMi, and exercise capacity and duration were lower in GHD patients than in controls (Table 2). Similarly, GHD patients had decreased SBP at rest ($P = 0.03$), PER ($P = 0.005$), and LVEF at rest ($P = 0.001$) and at peak exercise ($P < 0.0001$). Among the 20 patients and 20 controls, high total cholesterol levels were found in 8 (40%) and 1 (0.5%); $x^2 = 5.2, P = 0.02$; low HDL cholesterol levels were found in 3 (15%) and none, high triglycerides levels were found in 2 (10%) and none, mild hypertension was found in 2 (10%) and none, impaired LVEF at rest was found in 7 (35%) and none ($x^2 = 6.2, P = 0.01$), and inadequate response of LVEF at peak exercise was found in 16 (80%) and none ($x^2 = 23.4, P < 0.0001$), respectively. One patient could not perform the physical effort due to deep muscular asthenia. The LV diastolic filling, measured either as PFR or as the PFR/PER ratio, was similar in patients and controls (Table 2).

Effect of 12-month GH replacement

After 12 months, a significant increase in IGF-I and HDLC cholesterol levels and a significant decrease in total and LDL cholesterol, triglycerides, and fibrinogen levels and the total to HDLC cholesterol ratio (from $4.9 \pm 0.3$ to $3.6 \pm 0.2, P < 0.0001$) was observed in GHD patients (Fig. 1). Total cholesterol levels normalized in 6 of 8 patients (75%), whereas IGF-I, HDLC cholesterol, and triglycerides levels normalized in all patients. Significant increases in IST, LVPWT, and LVMi; LVEF at peak exercise; and exercise-induced changes in LVEF (Fig. 2), exercise capacity (from $82.9 \pm 3.3$ to $100.0 \pm 4.2$ watts, $P = 0.0009$), and duration (from $7.3 \pm 0.4$ to $8.9 \pm 0.4$ min; $P = 0.003$) were also obtained after GH replacement. LVEF at rest normalized in 4 of 7 patients (57.1%), whereas its response at peak exercise normalized in 6 of 16 (37.5%). Resting SBP decreased (from 111.0 ± 2.9 to 104.0 ± 2.1 mm Hg; $P = 0.01$), whereas no change in heart rate and DBP either at rest or at peak exercise, PFR or PER was found. None of

![Graphs showing changes in serum IGF-I, fibrinogen, triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol before and after 12 months of GH replacement.](image-url)
the patients developed hypertension during GH treatment, and the 2 patients with mild hypertension regained a normal DBP. However, at the end of treatment, total cholesterol levels, the ratio between total and HDL cholesterol levels (3.6 ± 0.2 vs. 3.0 ± 0.2; P = 0.04), fibrinogen levels, and LVMi were higher, whereas IGF-I levels, HDL cholesterol levels, triglycerides levels, and LVEF both at rest and at peak exercise were lower than control values (Figs. 1 and 2).

Comparison between co- and ao-GHD patients

At baseline, co- and ao-GHD patients had similar IGF-I levels, hemodynamic parameters, and exercise capacity and duration (data not shown). Conversely, ao-GHD patients had greater age (32.6 ± 1.6 vs. 23.4 ± 1.7 yr; P < 0.0001) and disease duration (11.6 ± 1.6 vs. 5.6 ± 1.0 yr, P = 0.01) and lower FFR (2.5 ± 0.2 vs. 3.4 ± 0.2 EDW/s; P = 0.01) and LVEF at rest (47.5 ± 2.2% vs. 55.7 ± 3.0%, P = 0.01) and at peak exercise (42.4 ± 1.7% vs. 51.9 ± 1.7%, P < 0.0001) than co-GHD patients. After GH replacement, IGF-I levels, LVPWT, IST, LVMi, LVEF at peak exercise, and exercise-induced changes in LVEF increased similarly in both groups (Figs. 3 and 4).

Correlation analysis

Neither age nor disease duration was correlated with baseline IGF-I, LVPWT, IST, and LVMi or with the percent increase in IGF-I levels and LVMi after GH replacement. The age of the patients was significantly correlated with PFR (r² = 0.4, P = 0.001), PFR/PER (r² = 0.2, P = 0.03), heart rate at rest (r² = 0.2; P = 0.02), and SBP at peak exercise (r² = 0.3; P = 0.0042) and SBP and DBP at peak exercise (r² = 0.4; P = 0.0002 and r² = 0.2; P = 0.04, respectively). Exercise-induced changes in LVEF were significantly correlated with LVEF at
rest ($r^2 = 0.3; P = 0.02$) and the total/HDL cholesterol ratio ($r^2 = 0.2; P = 0.0002$).

**Side-effects**

Mild arthralgia was reported during the first week of treatment by three patients (15%), whereas two other patients experienced mild fluid retention that resolved at the end of the second month of therapy without changing the GH dose. Pain at the joint sites, particularly hands, knees, and feet, was reported by one patient after increasing the dose to 20 mg/kg/day; dose reduction induced the disappearance of symptoms. No patient withdrew from treatment because of side-effects, and magnetic resonance imaging did not show any tumor recurrence after 12 months.

**Discussion**

The results of this prospective controlled cohort study demonstrated that 12 months of GH replacement normalized IGF-I, HDL cholesterol, and triglycerides levels, reduced total cholesterol and fibrinogen levels, and significantly increased LVMi and cardiac and exercise performance in young adult patients with either co- or ao- GHD. However, at the end of the treatment period, lipid profile, fibrinogen levels, and systolic function remained abnormal compared with those in age- and sex-matched controls, whereas LVMi was higher than that in controls.

The main cause of death in patients with long-standing GHD is cardiovascular disease (1–3). In our cohort, GHD was significantly associated with increased total cholesterol levels and impaired LVEF at rest and at peak exercise, confirming previous data (21–26, 29). A large number of clinical studies have reported beneficial effects of GH replacement in adult GHD patients (24–26). However, although long-term GH replacement to GHD adults was reported to be able to improve body composition, bone mineral density, exercise capacity, strength, lipid profile, and coagulation (24–26), the...
Gibney (41). Similarly, no change in cardiac size was reported by others. Follow-up cardiac mass was similar to pretreatment values throughout the study, and after the 2–10 yr of the follow-up GH replacement study at our center. A notable increase in exercise capacity and duration increased LVMi, and improved cardiac performance in our patients treated with low GH doses. Although after GH replacement, LVMi was significantly higher in GHD patients than in controls, none of the patients developed clear-cut LV hypertrophy. Interestingly, a significant increase in cardiac mass in some studies of short duration (14, 16, 37, 38), but not in others (15, 39, 40). In particular, Amato et al. (14) reported a sustained increase in LVMi up to about 26% of the baseline together with an improvement in resting LVEF after GH replacement patients at a dose of 10 μg/kg BW for 6 months; these effects were reversed by 6 months of GH discontinuation. A significant increase in cardiac mass was found during sustained (41) and low doses (16) of GH. A similar increase in LVMi by 17.3 ± 3% was observed in our patients treated with low GH doses. Although after GH replacement, LVMi was significantly higher in GHD patients than in controls, none of the patients developed clear-cut LV hypertrophy. Interestingly, a significant increase in cardiac mass was also reported by Ter Maaten et al. (41) during the first year of a 10-yr follow-up GH replacement study at elevated doses. However, the hypertrophic effect of GH replacement subsided during treatment, and after the 2–10 yr of follow-up cardiac mass was similar to pretreatment values (41). Similarly, no change in cardiac size was reported by Cibney et al. (42) in another 10-yr follow-up study.

By echocardiography, no change in cardiac performance at rest was reported by some researches (15, 38), an increase in stroke volume was reported by others (16, 37, 39, 43, 44), but improvement of cardiac performance with exercise has been investigated in only a few studies. It should be considered that the evaluation of cardiac function by echocardiography is affected by two major limitations: the intra- and interobserver variabilities and the poor sensitivity because of the assumptions necessary to calculate the LVEF (34). In fact, in a large cohort of 55 patients with ao-GHD, an impaired LVEF response at peak exercise was found by radionuclide angiocardiography in as many as 65.4% of patients regardless of age of onset of the disease, whereas LVEF at rest was impaired in only 23.6% of them (18). As the diastolic filling reduces with aging (35), to minimize the variability in the negative effect of GHD during the life span only young patients were investigated in the current study. A second end point was to disclose potential differences of the beneficial effect of GH replacement on cardiac performance between co- and ao-GHD, who were shown to bear different clinical and laboratory characteristics (28).

In the entire series of patients, LVEF at peak exercise as well as the exercise-induced changes in LVEF and exercise duration and capacity increased significantly. In particular, normalization of LVEF at rest and at peak exercise was obtained in 57.3% and 37.5% of patients, respectively. It should be noted that ao-GHD had lower LVEF both at rest and at peak exercise, PER, and PFR and higher SBP at peak exercise than co-GHD patients at study entry. These results were probably due to a longer exposure to GHD of ao-GHD patients than co-GHD patients, who were treated with GH during part of their developmental period before entering the study. In fact, the 2 patients who withdrew from GH replacement for 2 yr still had normal cardiac performance even in the presence of low IGF-I levels, whereas all ao-GHD patients had inadequate LVEF responses at peak exercise. Therefore, 57.1% of co-GHD patients regained a normal LVEF response at peak exercise compared with 22.2% of ao-GHD patients. Hemodynamic parameters are also known to be modified during GH replacement, contributing to the improvement in cardiac performance. In particular, heart rate has been reported to increase after GH replacement (16, 17, 22, 41), although in the current series heart rate at rest or at peak exercise was not significantly modified by GH treatment. In contrast, a significant decrease in SBP was found in the GHD population as a whole, probably via the endothelial action of IGF-I (45). However, the improved cardiac performance was sustained by a remarkable increase in exercise performance. In line with previous reports (24–26), we found a notable increase in exercise capacity and duration.

In conclusion, 12 months of GH replacement significantly reduced total and LDL cholesterol and fibrinogen levels, increased LVMi, and improved cardiac performance in young adult patients with co- or ao-GHD to a similar extent. However, systolic function remained depressed compared with that in age- and sex-matched controls. In particular, 42.8% and 62.5% of GHD patients had inadequate LVEF at rest and during exercise, respectively. These findings indicate that in young patients with long GHD duration, a more than 12-month period of GH replacement may be necessary to restore a normal lipid and coagulation profile and normal cardiac performance, probably reversing the poor prognosis for cardiovascular accidents.

References

Cardiovascular Risk in GHD After GH Replacement