

# 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;  $P < 0.0001$ ) and high density lipoprotein (HDL) cholesterol ( $P < 0.0001$ ) levels, left ventricular mass index (LVMI;  $P < 0.0001$ ), ejection fraction (LVEF) at rest ( $P = 0.001$ ) and at peak exercise ( $P < 0.0001$ ), peak ejection rate ( $P = 0.005$ ), and exercise duration ( $P < 0.0001$ ) and capacity ( $P = 0.002$ ) were lower, whereas total cholesterol ( $P = 0.02$ ), triglycerides ( $P = 0.003$ ), and fibrinogen ( $P = 0.005$ ) levels were higher in patients than in controls. After 12 months, increases in IGF-I ( $P < 0.0001$ ) and HDL

cholesterol levels ( $P = 0.04$ ), LVMI ( $P < 0.0001$ ), LVEF at peak exercise ( $P < 0.0001$ ), and exercise duration ( $P = 0.009$ ) and capacity ( $P = 0.003$ ) and decreases in total cholesterol ( $P < 0.0001$ ), low density lipoprotein cholesterol ( $P < 0.0001$ ), triglycerides ( $P < 0.0001$ ), and fibrinogen ( $P = 0.01$ ) 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. (*J Clin Endocrinol Metab* 86: 1874–1881, 2001)

RECENTLY, EVIDENCE has been provided that GH deficiency (GHD) in adults can be deleterious due to an increased risk of death from cardiovascular disease. In three different retrospective studies including 849 patients with hypopituitarism and receiving standard replacement for thyroid, adrenal, and sex steroids, the rates of mortality from cardiovascular disease were 1.9, 1.35, and 1.4 times higher than that in an age- and sex-matched control population (1–3). From these epidemiological data, long-term deficiency of GH secretion emerged as a possible major factor responsible for the increased risk of death in these patients. On the other hand, experimental evidence supported a direct role of GH and insulin-like growth factor I (IGF-I) in the heart as modulators of heart development, regulators of heart growth

and function in adults (4–6), and promoters of cardiac contractility (7, 8).

From a 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

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of patients with childhood-onset (co-) or adulthood-onset (ao-) disease (21–23).

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 change 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 series 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, 26.5 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 (11 men and 9 women; age range, 18–40 yr; median age, 31 yr). All patients and controls gave informed consent to participate in this study, and the study protocol was approved by the ethics committee of the Medical School of the University Federico II (Naples, Italy). None of the patients and controls presented with or had previously suffered from other concomitant diseases affecting cardiac function, such as diabetes mellitus, coronary artery diseases, long-standing hypertension, or hyperthyroidism. None of the 40 subjects was obese (body mass index, <30). Table 1 shows anthropometrical, endocrine, and metabolic data, and Table 2 shows cardiac data in patients and controls. All patients, except 3 with idiopathic co-GHD, had been previously operated on via the transphenoidal and/or transcranial route for PRL-secreting adeno-

mas, nonfunctioning pituitary adenoma, or craniopharyngioma, and 8 of them had been irradiated. Five patients had panhypopituitarism, 4 patients had FSH/LH and TSH deficiencies, 2 patients had FSH/LH and ACTH insufficiency, 4 patients had FSH/LH deficiencies, and 5 patients had GHD alone. Hormone replacement therapy with L-T<sub>4</sub> (50–100 µg, orally, daily), cortisone acetate (25–37.5 mg/day), and DDAVP (5–20 µg/day) was given where appropriate. Hypogonadism was treated in men with testosterone enanthate (250 mg, im, monthly) and in women with standard estrogenic association. The adequacy of hormone replacement therapy was periodically assessed by measurements of serum free thyroid hormones, testosterone, urinary free cortisol, and serum and urinary Na<sup>+</sup> and K<sup>+</sup> measurements. At study entry, these hormonal parameters were in the normal range for age in all patients. None of the ao-GHD patients had ever received GH treatment. Patients with co-GHD had received GH replacement with extractive and/or recombinant GH for 3–13 yr and withdrew from treatment at least 2 yr before entering the study. At study entry, the diagnosis of GHD was performed by insulin tolerance test (GH peak, <3 µg/L) and/or arginine plus GHRH test (GH peak, <9 µg/L) (29–31). The equivalent ratio of milliunits per L to micrograms per L is 2 (2 mU/L equals 1 µg/L) before January 1997 or 2.5/3 after that (32). The duration of GHD was calculated from the time of diagnosis of the pituitary tumor in ao-GHD patients and from the time of GH withdrawal in co-GHD patients; in this group estimated GHD duration was 8.6 ± 1.2 yr.

### Study protocol

At study entry all 40 subjects underwent electrocardiogram; systolic and diastolic blood pressure (SBP and DBP) and heart rate measurements; serum IGF-I; total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol, triglycerides, and fibrinogen level assays; echocardiography; and equilibrium radionuclide angiography. In GHD patients, IGF-I measurements were repeated after 1, 2, 3, 6, and 12 months; total, LDL, and HDL cholesterol; triglycerides; and fibrinogen measurements were repeated after 3, 6, and 12 months; and echocardiography and equilibrium radionuclide angiography were repeated after 12 months of GH replacement. Before and after 12 months of GH replacement all patients were subjected to magnetic resonance of the sellar region, which showed no evidence of intrasellar or parasellar residual tumor at study entry.

### Treatment protocol

All patients received recombinant GH at a starting dose of 10 µg/kg·day. Subsequently, the dose was adjusted on the basis of serum IGF-I concentrations up to the normal range for sex and age. The maximal dose used in this study was 15 µg/kg·day in men and 20 µg/kg·day in women.

### Assays

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

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

	Controls (n = 20)		GHD patients (n = 20)		P
	Range	Mean ± SEM	Range	Mean ± SEM	
M/F		11/9		11/9	
Mean age (yr)	18–40	31.6 ± 1.5	19–40	28.0 ± 1.6	0.3
Body mass index (kg/m <sup>2</sup> )	20–28	24.7 ± 1.3	23–30	26.6 ± 1.5	0.5
Peak GH after ARG + GHRH test (µg/L)	24–84	51.1 ± 3.7	0.1 ± 5.2	2.4 ± 0.4	<0.0001
Plasma IGF-I levels (µg/L)	170–410	293.5 ± 14.0	34–112	74.9 ± 5.6	<0.0001
Total cholesterol levels (mg/dL)	147–218	180.9 ± 4.1	159–347	208.4 ± 11.1	0.02
LDL cholesterol levels (mg/dL)	50–137	87.7 ± 4.3	80–137	106.1 ± 3.9	0.003
HDL cholesterol levels (mg/dL)	40–92	61.0 ± 2.8	35–55	44.4 ± 1.5	<0.0001
Total/HDL cholesterol ratio	2.1–5.4	3.1 ± 0.2	3.0–8.3	4.9 ± 0.3	<0.0001
Triglyceride levels (mg/dL)	54–188	97.8 ± 6.7	81–210	134.6 ± 9.6	0.003
Fibrinogen levels (mg/dL)	170–300	214.5 ± 7.8	180–400	268.3 ± 16.3	0.005

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; triglyceride, 50–200 mg/dL; fibrinogen, <400 mg/dL.

**TABLE 2.** Cardiac and hemodynamic parameters in patients with GHD and controls

	Controls (n = 20)		GHD patients (n = 20)		P
	Range	Mean ± SEM	Range	Mean ± SEM	
Interventricular septum thickness (mm)	9–11	10.0 ± 0.1	8–9.5	8.8 ± 0.1	<0.0001
Left ventricular posterior wall thickness (mm)	9–11	9.7 ± 0.1	7.7–10	8.8 ± 0.1	<0.0001
Left ventricular mass index (g/m <sup>2</sup> )	85–100	93.6 ± 1.0	80–98	87.1 ± 1.2	<0.0001
Heart rate (beats/min)					
At rest	55–96	74.9 ± 2.7	57–90	74.2 ± 2.4	0.6
Exercise	113–191	150.8 ± 3.9	95–170	138.9 ± 4.8	0.07
Systolic blood pressure (mm Hg)					
At rest	100–125	118.5 ± 1.7	90–140	111.0 ± 2.8	0.03
Exercise	130–200	160.3 ± 5.2	120–190	155.3 ± 5.0	0.5
Diastolic blood pressure (mm Hg)					
At rest	60–90	77.7 ± 1.7	60–95	72.2 ± 2.4	0.07
Exercise	80–120	96.7 ± 2.6	80–100	91.3 ± 1.7	0.1
Left ventricular ejection fraction (%)					
At rest	50–67	59.8 ± 1.1	34–70	51.6 ± 2.1	0.001
Exercise	60–95	72.3 ± 2.1	30–64	46.9 ± 1.6	<0.0001
Δ	8.9–50.7	21.2 ± 3.2	–24–14.3	–7.5 ± 2.5	<0.00001
Peak ejection rate (EDV/s)	2.6–4.6	3.5 ± 0.1	1.4–4.5	2.9 ± 0.2	0.005
Peak filling rate (EDV/s)	1.8–4.1	2.8 ± 0.1	1.2–4.2	2.6 ± 0.2	0.4
Peak filling rate/peak ejection rate	0.6–1.2	0.8 ± 0.03	0.5–1.5	1.5 ± 0.05	0.09
Exercise duration (min)	7–12	9.6 ± 0.2	6–10	7.3 ± 0.4	<0.0001
Exercise capacity (watts)	75–125	100.0 ± 4.1	50–100	82.9 ± 3.3	0.002

Normal left ventricular mass indexed; <110 g/m<sup>2</sup> in women and <135 g/m<sup>2</sup> 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 0.2 µg/L. The intra- and interassay coefficients of variation (CVs) 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). The normal range in 20- to 40-yr-old subjects is 110–450 µg/L. The sensitivity of the assay was 0.8 µg/L. 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%, 1.5%, and 3.7% for the low, medium, and high points of the standard curve. Fasting total, LDL, and HDL cholesterol, triglycerides, and fibrinogen levels were measured by standard procedures. The total/HDL cholesterol ratio, considered the index of severe cardiovascular risk (33), was also calculated.

### Echocardiography

M-mode, two-dimensional, and pulsed Doppler echocardiographies were performed with commercially available ultrasound systems (Sonos 2500, Hewlett-Packard Co., Andover, MA) using a 2.5-MHz transducer during three to five consecutive cardiac cycles. All patients were studied in the left lateral recumbent position after a 10-min resting period according to the recommendations of the American Society of Echocardiography (34). The following measurements were recorded on M-mode tracing: interventricular septum thickness (IVST) and posterior wall thickness (LVPWT), and LVM calculation by Devreux's formula according to the Penn convention with the following regression-corrected cube formula: LVM = 1.04[(IVST + LVID + PWT)<sup>3</sup> – (LVID)<sup>3</sup>] – 14 g. LV hypertrophy was considered when LVMi was 135 g/m<sup>2</sup> or more in men and 110 g/m<sup>2</sup> or more in women. The echocardiography operator was blinded to control or patient examination.

### Equilibrium radionuclide angiography

The angiography study was performed as previously reported (10, 18, 21–23). *In vivo* labeling of red blood cells was performed with 555 megabecquerels (15 mCi) <sup>99m</sup>Tc. Radionuclide angiography was performed at rest and during dynamic physical exercise in the 45° left anterior projection with a 15° cranio-caudal tilt with the patient in a supine position. A small field of view γ-camera (Starcam 300 A/M, General Electric, Milwaukee, WI) equipped with a low energy, all purpose collimator was used. Data were recorded at a rate of 30 frames/cardiac cycle for the resting study and 16 frames/cardiac cycle for the exercise study on a dedicated computer system (General Electric). At least 200,000 counts/frame were acquired. Exercise studies were per-

formed using a bicycle ergometer with a restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 watts every 2 min until angina, limiting dyspnea, or fatigue developed. No patient developed high grade ventricular arrhythmias necessitating termination of exercise. Heart rate and SBP and DBP, determined by cuff sphygmomanometer, were monitored during exercise at each stage. Radionuclide angiography studies were analyzed using a standard commercial software system (General Electric). The LV regions of interest were automatically drawn for each frame, and a background region of interest was also computer delineated on the end-systolic frame. After background correction, a time-activity curve was generated. Indexes of LV function were derived by computer analysis of the background-corrected time-activity curve. LVEF was computed on the basis of relative on end-diastolic and end-systolic counts. Peak LV ejection and filling rates were also calculated after Fourier expansion with four harmonics. Peak ejection rate (PER) was computed as the minimum negative peak before end-systole, and peak filling rate (PFR) was calculated as the maximum positive peak after end-systole on the first derivative of the LV time-activity curve. Both PER and PFR were computed in LV counts per s, normalized for the number of counts at end-diastole and expressed as end-diastolic volume per s (EDV/s). When normalized for end-diastolic volume, both PER and PFR are influenced directly by the magnitude of LVEF (35). To minimize this effect, we also analyzed PFR as the PFR to PER ratio (36), a method that is background independent.

### Statistical analysis

Data are reported as the mean ± SEM. Statistical analysis was performed by means of an SPSS, Inc. (Cary, NC), package using two-tailed ANOVA to analyze differences between controls and patients and between co- and ao-GHD patients before and after GH replacement. Student's *t* test for paired data was used to analyze the effect of GH replacement in GHD patients. The linear regression analysis was used to correlate patients' age, duration of GHD, and exercise-induced changes in LVEF with GH peak after testing; IGF-I; total, LDL, and HDL cholesterol, triglycerides, and fibrinogen levels; LVMi; LVEF at rest and at peak exercise; PFR; PER; and the percent increase in IGF-I levels and LVMi after GH replacement. Significance was set at 5%.

### Results

Age and BMI were similar in patients and controls (Table 1). Conversely, IGF-I and HDL cholesterol levels were lower,

and total cholesterol, LDL cholesterol, triglycerides, and fibrinogen levels and total/HDL 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%;  $\chi^2 = 5.2$ ;  $P = 0.02$ ), 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 ( $\chi^2 = 6.2$ ;  $P = 0.01$ ), and inadequate response of LVEF at peak exercise was found in 16 (80%) and none ( $\chi^2 = 23.4$ ;  $P < 0.0001$ ), 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 HDL cholesterol levels and a significant decrease in total and LDL cholesterol, triglycerides, and fibrinogen levels and the total to HDL 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, HDL 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  $111.0 \pm 2.9$  to  $104.0 \pm 2.1$  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

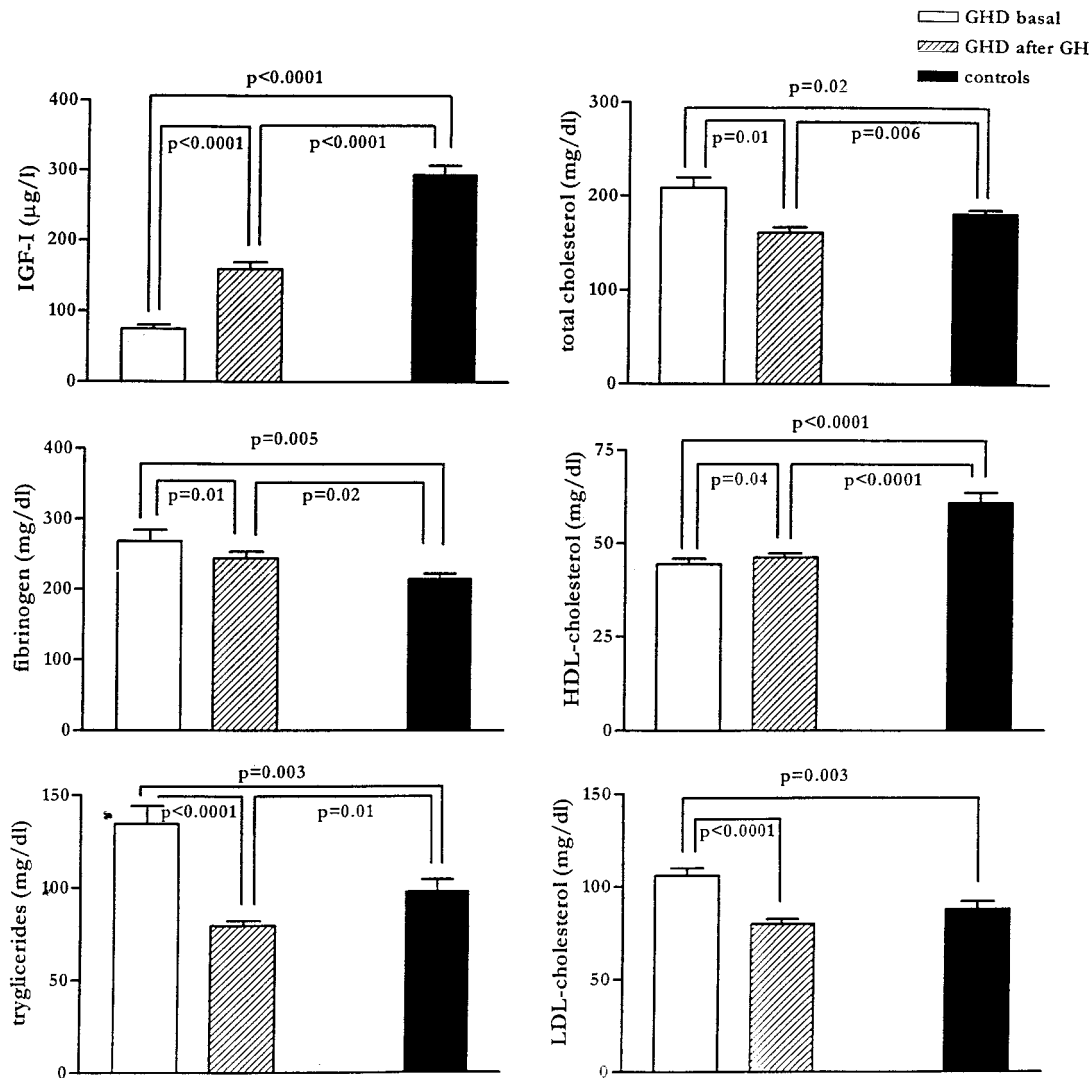


FIG. 1. Serum IGF-I (top left), fibrinogen (middle left), triglycerides (bottom left), total cholesterol (top right), HDL cholesterol (middle right), and LDL cholesterol (bottom right) before and after 12 months of GH replacement in young patients with GHD compared with sex- and age-matched controls.

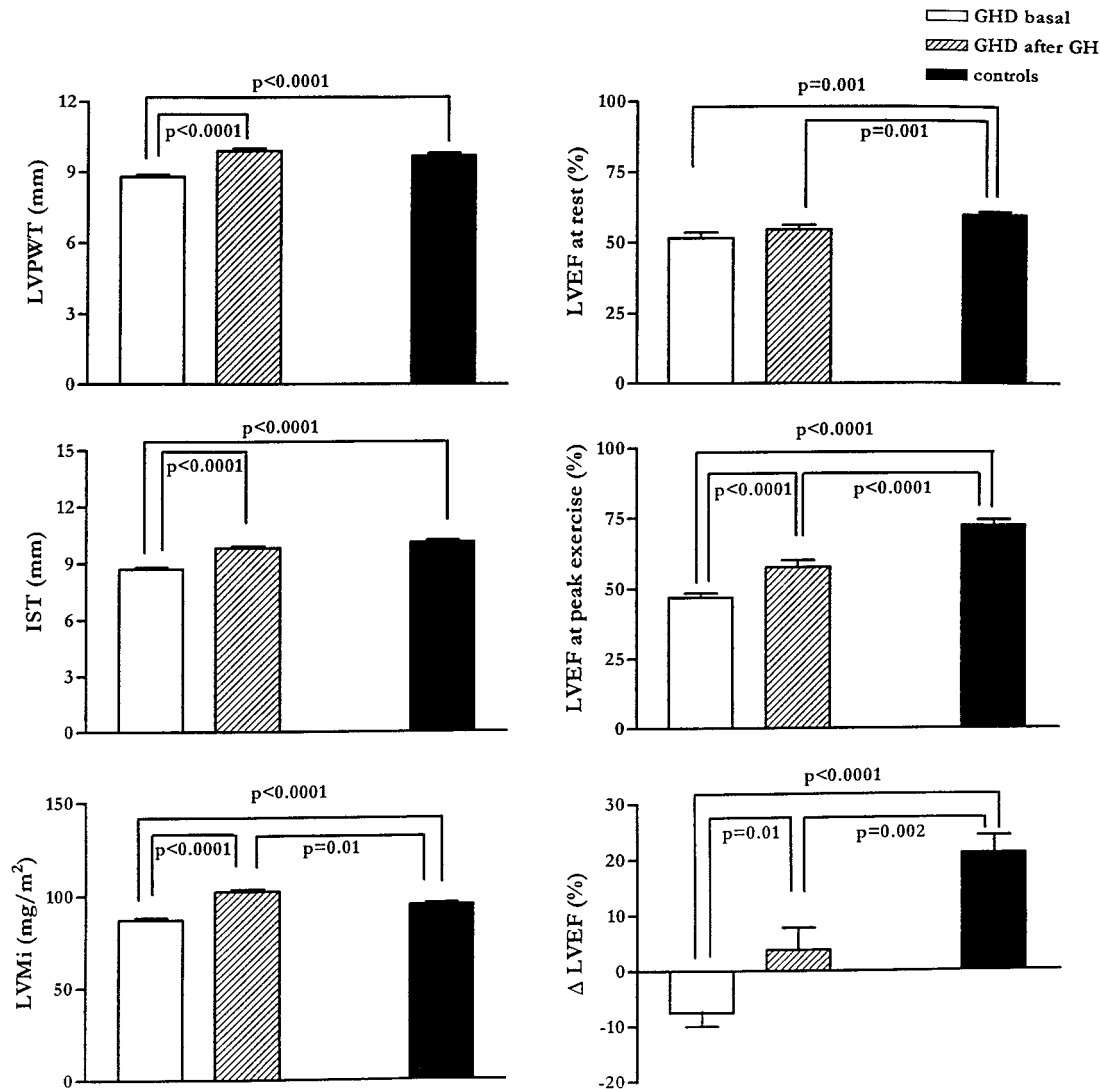


FIG. 2. LVPWT (top left), IST (middle left), and LVMi (bottom left) evaluated by echocardiography and LVEF at rest (top right) and at peak exercise (middle right) and exercise-induced changes ( $\Delta$ ) in LVEF (bottom right) before and after 12 months of GH replacement in young patients with GHD compared with sex- and age-matched controls.

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 ( $3.6 \pm 0.2$  vs.  $3.0 \pm 0.2$ ;  $P = 0.04$ ), 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 ( $32.6 \pm 1.6$  vs.  $23.4 \pm 1.7$  yr;  $P < 0.0001$ ) and disease duration ( $11.6 \pm 1.6$  vs.  $5.6 \pm 1.0$  yr;  $P = 0.01$ ) and lower PER ( $2.5 \pm 0.2$  vs.  $3.4 \pm 0.2$  EDV/s;  $P = 0.01$ ) and LVEF at rest ( $47.5 \pm 2.2\%$  vs.  $55.7 \pm 3.0\%$ ;  $P = 0.01$ ) and at peak exercise ( $42.4 \pm 1.7\%$  vs.  $51.9 \pm 1.7\%$ ;  $P < 0.0001$ ) 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 ( $r^2 = 0.4$ ;  $P = 0.001$ ), PFR/PER ( $r^2 = 0.2$ ;  $P = 0.03$ ), heart rate at rest ( $r^2 = 0.2$ ;  $P = 0.02$ ), and SBP at peak exercise ( $r^2 = 0.3$ ;  $P = 0.02$ ), whereas GHD duration was significantly correlated with the exercise-induced changes in LVEF ( $r^2 = 0.6$ ;  $P = 0.0002$ ) and SBP and DBP at peak exercise ( $r^2 = 0.4$ ;  $P = 0.004$  and  $r^2 = 0.2$ ;  $P = 0.04$ , respectively). Exercise-induced changes in LVEF were significantly correlated with LVEF at

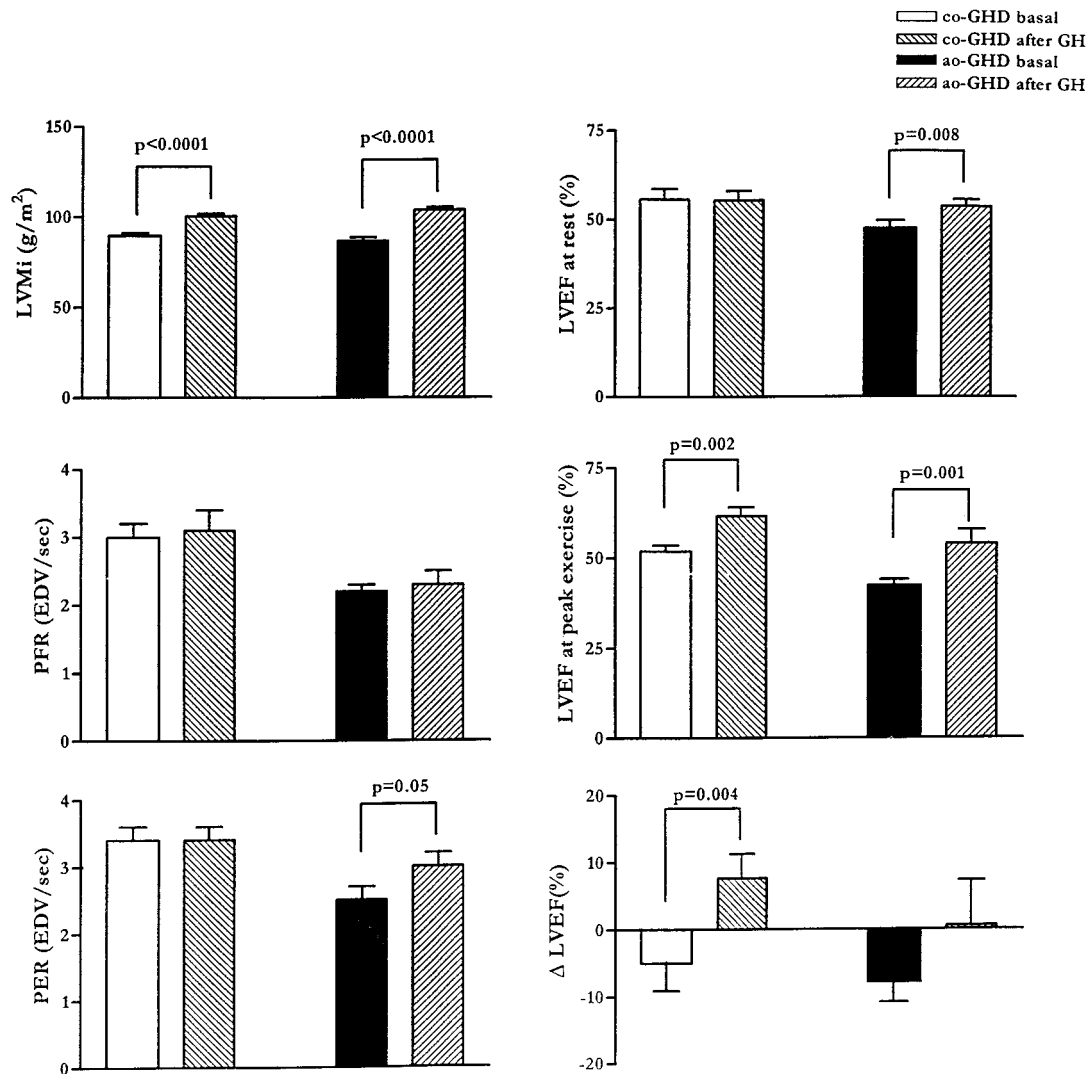


FIG. 3. LVPWT (top left), IST (middle left), and LVMi (bottom left) evaluated by echocardiography, LVEF at rest (top right) and at peak exercise (middle right), and exercise-induced changes ( $\Delta$ ) in LVEF (bottom right) before and after 12 months of GH replacement in co-GHD and ao-GHD patients.

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, peculiarly hands, knees, and feet, was reported by one patient after increasing the dose to 20  $\mu\text{g}/\text{kg}\cdot\text{day}$ ; 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

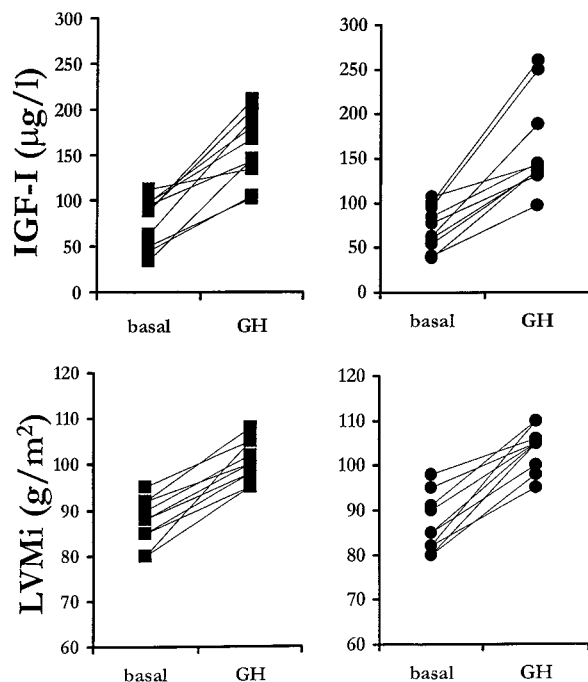


FIG. 4. Individual data for IGF-I levels (*top*) and LVMi (*bottom*) in co-GHD (■) and ao-GHD (●) patients before and after GH replacement.

ultimate clinical efficacy of GH treatment on the reversibility of the cardiovascular risk is still unknown. Furthermore, the dose of GH employed during the last decade was progressively reduced and largely varied in different studies, ranging from 6–26  $\mu\text{g}/\text{kg}$  BW. GH replacement was shown to increase 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  $\mu\text{g}/\text{kg}$  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  $17.5 \pm 1.3\%$  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 Gibney *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 angiography 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 57.1% 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.

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