

The Cardiovascular Risk of Adult GH Deficiency (GHD) Improved after GH Replacement and Worsened in Untreated GHD: A 12-Month Prospective Study

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Increased cardiovascular morbidity and mortality were reported in GH deficiency (GHD), and GH replacement can ameliorate cardiac abnormalities of adult GHD patients. To test the potential progression of untreated GHD on the cardiovascular risk and cardiac function, cardiovascular risk factors, cardiac size, and performance were prospectively evaluated in 15 GHD patients (age, 18–56 yr) who were treated with recombinant GH at the dose of 0.15–1.0 mg/d, 15 GHD patients (age, 18–56 yr) who refused GH replacement, and 30 healthy subjects (age, 18–53 yr).

Electrocardiogram, systolic and diastolic blood pressure, and heart rate measurement, serum IGF-I, total cholesterol, low- and high-density lipoprotein (LDL, HDL) cholesterol, triglycerides, and fibrinogen level assay, echocardiography, and equilibrium radionuclide angiography were performed basally and after 12 months.

At study entry, low IGF-I levels, unfavorable lipid profile, and inadequate cardiac and physical performance were found in GHD patients compared with controls. After 12 months of

GH treatment, IGF-I levels normalized; HDL-cholesterol levels, left ventricular (LV) mass index (LVMI), left ventricular ejection fraction (LVEF) at peak exercise, peak filling rate, exercise duration and capacity significantly increased; total- and LDL-cholesterol levels significantly decreased. After 12 months in GH-untreated GHD patients, IGF-I levels remained stable, and HDL-cholesterol levels, LVEF both at rest and at peak exercise, and exercise capacity were further reduced; total- and LDL-cholesterol levels increased slightly. LVEF at rest and its response at peak exercise normalized in 60 and 53.3%, respectively, of GH-treated patients and in none of the GH-untreated patients.

In conclusion, 12 months of GH replacement normalized IGF-I and improved lipid profile and cardiac performance in adult GHD patients. A similar period of GH deprivation induced a further impairment of lipid profile and cardiac performance. This finding strongly supports the need of GH replacement in adult GHD patients. (*J Clin Endocrinol Metab* 87: 1088–1093, 2002)

LONG-STANDING GH DEFICIENCY (GHD) in adults is associated with unfavorable lipid profile, reduction in exercise capacity, decreased fibrinolytic activity, premature atherosclerosis, abnormalities in cardiac structure, impaired cardiac performance, and ultimately, increased cardiovascular morbidity and mortality (1–6). In young patients with either childhood-onset (co) or adulthood-onset (ao)-GHD, the impairment of cardiac performance is manifest primarily as alteration of the left ventricular mass (LVM), inadequacy of ejection fraction (LVEF) both at rest and at peak exercise, and abnormalities of diastolic filling (6). Although the administration of GH to GHD adults reverses many of the changes in body composition, bone mineral density, exercise capacity, and strength and improves lipid profile (1–6), little is still known about the ultimate efficacy of GH treatment in reversing the cardiovascular risk. In fact, in these patients the alteration of the cardiovascular system is partially reversed after GH replacement therapy (6). GH replacement was

found to increase cardiac output and LVEF and to improve other indices of LV systolic and diastolic function (6). Twelve months of GH replacement were recently demonstrated to significantly reduce total-cholesterol, LDL-cholesterol, and fibrinogen levels, increase left ventricular mass index (LVMI), and improve cardiac performance in a homogeneous cohort of young adult patients with either co- or ao-GHD (7). However, 1 yr of GH replacement was unable to normalize the systolic function that remained depressed compared with age- and sex-matched controls (7).

Little information is available on the potential progression of clinical symptoms and signs in untreated GHD, particularly concerning cardiac derangement. In two different cohorts of GHD patients, one receiving GH and another untreated, who were investigated after 10 yr, an improvement was found in energy levels, emotional reaction, and psychological well-being in GH-treated but not in GH-untreated GHD patients, whereas no difference was found in systolic and diastolic blood pressure (SBP, DBP) and cardiac parameters evaluated by echocardiography between the two groups (8).

To investigate the potential progression of cardiac derangement in untreated GHD, cardiovascular risk parameters, heart morphology, and function were evaluated in 30

Abbreviations: ao, Adulthood onset; co, childhood onset; CV, coefficient(s) of variation; DBP, diastolic blood pressure; EDV, end-diastolic volume; GHD, GH deficiency; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; LVEF, LV ejection fraction; LVMI, LV mass index; PER, peak ejection rate; PFR, peak filling rate; SBP, systolic blood pressure.

adult GHD patients, 15 receiving GH replacement and 15 refusing this treatment, compared with an appropriate sex- and age-matched healthy control group.

Patients and Methods

Patients

Thirty patients (14 men, 16 women, aged 18–56 yr) with diagnosis of GHD and 30 healthy subjects who were sex- and age-matched with the patients (15 men, 15 women, age range 18–53 yr) entered this open prospective study. All patients and controls gave their informed consent to participate in this study, and the study protocol was approved by the ethical committee of the Medical School of the University “Federico II” of Naples. No patient or control presented with or previously suffered from other concomitant diseases affecting cardiac function, such as diabetes mellitus, coronary artery diseases, long-standing hypertension, or hyperthyroidism. All patients had been operated on previously *via* transsphenoidal and/or transcranial route for PRL-secreting adenomas, nonfunctioning pituitary adenoma, or craniopharyngioma, and six of them had been irradiated. Thirteen patients had panhypopituitarism, three patients had FSH/LH and TSH deficiency, three had FSH/LH and ACTH insufficiency, four patients had FSH-LH deficiency, four patients had ACTH and TSH deficiency, three patients had TSH deficiency alone, and nine patients had diabetes insipidus. Hormone replacement therapy with L-thyroxin (50–100 μg orally each day), cortisone acetate (25–37.5 mg/d), and DDAVP (5–20 μg /d) was given where appropriate. Hypogonadism was treated in men with T enanthate (250 mg im monthly), in women with standard oral estrogen/progestin association. Adequacy of hormone replacement therapy was periodically assessed by serum-free thyroid hormones, T, urinary free cortisol plus serum and urinary Na^+ and K^+ measurements and normal blood pressure. At study entry, these hormonal parameters were in the normal range for age in all patients. None of the patients had ever received GH treatment. At study entry, the diagnosis of GHD was performed by arginine + GHRH test (GH peak, <9 $\mu\text{g}/\text{liter}$) (9, 10). Of the 30 patients, 15 were treated with GH for 12 months (group A), whereas the other 15 refused GH replacement for personal reasons, although it was strongly recommended by the physicians (group B). The 15 GHD patients treated with GH were recruited among over 100 patients with GHD followed at the Department of Molecular and Clinical Endocrinology and Oncology on the basis of sex, age, body mass index, disease history, and presence of other pituitary deficiency matching with the 15 untreated patients.

Study protocol

At study entry, all 60 subjects underwent electrocardiograms; SBP, DBP, and heart rate measurement; serum IGF-I; total-, LDL-, and HDL-cholesterol; triglycerides; and fibrinogen level assay; echocardiography; and equilibrium radionuclide angiography. Subsequently, both in GH-treated and GH-untreated patients, IGF-I, total-, LDL-, and HDL-cholesterol, triglycerides, and fibrinogen levels were measured after 1, 2, 3, 6, and 12 months; echocardiography and equilibrium radionuclide angiography were performed before and after 12 months. In controls, IGF-I, cardiovascular risk parameters, echocardiography, but not radionuclide angiography due to ethical reasons, were repeated after 12 months. A magnetic resonance imaging of the sellar region was performed in all patients at study entry. In this study, only data obtained before and after 12 months are presented.

Treatment protocol

According to previous studies (7, 11), all patients received recombinant GH at the starting dose of 4–5 $\mu\text{g}/\text{kg}\cdot\text{d}$. Subsequently, the dose was adjusted to reach the 50th percentile of normal serum IGF-I concentrations for sex and age. At the end of the study, the median GH dose was 5 $\mu\text{g}/\text{kg}\cdot\text{d}$ in men and 5.3 $\mu\text{g}/\text{kg}\cdot\text{d}$ in women; the maximal dose was 5.5 $\mu\text{g}/\text{kg}\cdot\text{d}$ in men and 10.9 $\mu\text{g}/\text{kg}\cdot\text{d}$ in women.

Assays

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

The sensitivity of the assay was 0.2 $\mu\text{g}/\text{liter}$. The intra- and interassay coefficients of variation (CV) were 4.5 and 7.9%, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction using DSL kits (Webster, TX). In our laboratory, the normal IGF-I range was 110–500 $\mu\text{g}/\text{liter}$ in ages 20–30 yr; 100–450 $\mu\text{g}/\text{liter}$ in ages 31–40; 100–300 $\mu\text{g}/\text{liter}$ in ages 41–50; 90–270 $\mu\text{g}/\text{liter}$ in ages 51–60; and 75–250 $\mu\text{g}/\text{liter}$ in subjects 60 yr or older. The sensitivity of the assay was 0.8 $\mu\text{g}/\text{liter}$. The intra-assay CV were 3.4, 3.0, and 1.5% for the low, medium, and high points of the standard curve, respectively. The interassay CV 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. Hypertriglyceridemia was diagnosed when triglyceride levels were greater than 250 mg/dl (12), whereas hypercholesterolemia was diagnosed when total cholesterol levels were greater than 240 mg/dl (13). The total/HDL-cholesterol ratio, considered the index of cardiovascular risk (14), was also calculated.

Equilibrium radionuclide angiography

The angiography study was performed as already reported (7, 15–17). Exercise studies were performed using a bicycle ergometer with a restraining harness to minimize patient motion under the camera. Exercise loads were increased by 25 W every 2 min until angina, limiting dyspnea, or fatigue developed. No patient developed high-grade ventricular arrhythmias necessitating termination of exercise. Heart rate, SBP, and DBP were monitored by cuff sphygmomanometer during exercise at each stage. Radionuclide angiography studies were analyzed using a standard commercial software system (General Electric, Milwaukee, WI). 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 end-diastolic and end-systolic counts. Peak LV ejection and filling rates were also calculated after a 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 computed 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 second, normalized for the number of counts at end-diastole, and expressed as end-diastolic volume (EDV)/sec. When normalized for EDV, both PER and PFR are influenced directly by the magnitude of LVEF (18). To minimize this effect, we also analyzed PFR as ratio of PFR to PER (19), a method that is background-independent. LV diastolic filling was considered abnormal when the peak filling rate was less than 2.5 EDV/sec; the LVEF was considered insufficient if it was less than 50% at rest and/or it increased less than 5% at peak exercise compared with resting condition (20).

Echocardiography

M-mode, two-dimensional, and pulsed Doppler echocardiography 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, as previously reported (7). 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 (21). The LVM was calculated by the Devereux's formula according to the Penn convention with the following regression-corrected cube formula: $\text{LVM} = 1.04 [(\text{IVST} + \text{LVID} + \text{PWT})^3 - (\text{LVID})^3] - 14$ g. LV hypertrophy was considered when LVMi was at least 135 g/m² in men and at least 110 g/m² in women. Exams were performed by a physician (L.S.) who was blind in respect to control or patient examination and to GH treatment.

Statistical analysis

Data are reported as mean \pm SEM. The statistical analysis was carried out using SPSS, Inc. (Chicago, IL) software. ANOVA followed by the Newman-Keuls test was used for the intergroup comparison, whereas the paired *t* test was used to compare variables at study entry and after 12 months. The significance was set at 5%.

Results

At study entry, IGF-I levels were significantly lower in GHD patients (as a whole) than in controls, whereas no difference was found between patients of group A and group B (Table 1). HDL-cholesterol levels were lower and total-cholesterol, LDL-cholesterol, total/HDL-cholesterol ratio, triglycerides, and fibrinogen levels were higher in patients than in controls (Table 1). LVMi ($P = 0.02$), exercise capacity ($P = 0.001$), and duration ($P = 0.001$), PFR ($P = 0.04$), PER ($P = 0.03$), LVEF at rest ($P = 0.01$) and at peak exercise ($P = 0.001$), and LVEF response at peak exercise (Δ LVEF; $P = 0.001$) were lower in GHD patients than in controls (Table 1). High total-cholesterol levels were found in 18 patients (60%) and 3 controls (20%; $\chi^2 = 14.2$; $P < 0.0001$); low HDL-cholesterol levels in 4 patients (13.4%) and no controls ($\chi^2 = 2.4$; $P = 0.1$); high triglycerides levels in 7 patients (23.3%) and no controls ($\chi^2 = 5.8$; $P = 0.012$); and mild hypertension in 3 patients (10%) and no controls ($\chi^2 = 1.8$; $P = 0.2$). Furthermore, 11 patients (36.6%) and none of the controls ($\chi^2 = 11.1$; $P < 0.0001$) had an impaired LVEF at rest, whereas 23 patients (76.7%) and 2 controls (6.7%; $\chi^2 = 27.4$; $P < 0.0001$) had an inadequate Δ LVEF.

After 12 months, all patients of group A had IGF-I levels within the normal limits. In this group, a significant increase of HDL-cholesterol levels, LVMi, LVEF at peak exercise,

Δ LVEF, PFR, PFR/PER, exercise duration, and capacity was observed, whereas total-cholesterol levels and the total-cholesterol/HDL-cholesterol ratio significantly decreased (Table 2). In addition, LVEF at rest was normalized in 3 of 5 patients (60%), and Δ LVEF was normalized in 9 of 13 patients (69.2%) (Fig. 1). In patients of group B, IGF-I levels remained stably below the normal limits, whereas HDL-cholesterol levels, LVEF both at rest and at peak exercise, and exercise capacity were significantly reduced. Total-cholesterol, LDL-cholesterol, and triglyceride levels, as well as the total-cholesterol/HDL-cholesterol ratio significantly increased (Table 2). In this group, cardiac mass was unchanged (Fig. 1).

No change of lipid profile, cardiac and hemodynamic parameters was found in controls (data not shown).

No relevant adverse reactions were noted in the 15 GHD patients treated with GH during the 12 months of the study period.

Discussion

The most relevant finding of this study is that adult GHD patients, both young and middle-aged, who were treated with GH for 12 months reduced their cardiovascular risk, whereas GHD patients left untreated for the same period further impaired their lipid profile and cardiac performance.

Besides its established role in the impairment of body

TABLE 1. Anthropometric, endocrine, metabolic, and cardiac parameters in adult patients with GHD and controls at study entry

	Whole GHD group	Healthy subjects	P	GHD		P
				Group A	Group B	
No.	30	30		15	15	
No. male/female	15/15	15/15		7/8	8/7	
Age (yr)	43.5 ± 2.8	42.3 ± 3.8	0.9	43.9 ± 4.3	43.1 ± 3.6	0.888
GH peak (μ g/liter)	3.4 ± 0.5	42.9 ± 3.1	0.001	3.3 ± 0.6	3.4 ± 0.9	0.927
IGF-I (μ g/liter)	75.1 ± 4.9	273.5 ± 21.4	0.001	79.4 ± 6.0	70.7 ± 7.9	0.388
BMI (kg/m^2)	29.1 ± 1.0	30.0 ± 1.0	0.7	28.8 ± 0.9	30.1 ± 1.9	0.541
Total cholesterol (mg/dl)	222.9 ± 8.8	188.9 ± 9.1	0.02	234.0 ± 13.4	217.6 ± 10.3	0.144
LDL cholesterol (mg/dl)	131.8 ± 8.2	88.8 ± 4.9	0.003	139.6 ± 13.8	124.0 ± 9.13	0.392
HDL cholesterol (mg/dl)	45.9 ± 2.2	59.4 ± 3.3	0.006	45.5 ± 3.5	46.4 ± 2.8	0.842
Total/HDL-cholesterol ratio	5.2 ± 0.4	3.4 ± 0.3	0.003	5.6 ± 0.6	4.7 ± 0.3	0.190
Triglycerides (mg/dl)	170.8 ± 18.2	82.3 ± 4.6	0.001	199.7 ± 30.6	142.0 ± 18.1	0.116
Fibrinogen (mg/dl)	331.5 ± 18.4	200.9 ± 9.13	<0.001	332.5 ± 27.2	330.7 ± 25.8	0.962
LVMi (g/m^2)	86.2 ± 2.8	100.1 ± 1.6	0.02	85.4 ± 4.5	87.0 ± 3.5	0.871
Heart rate (beats/min)						
At rest	70.1 ± 1.6	72.7 ± 2.9	0.297	67.8 ± 2.2	72.4 ± 2.2	0.150
Exercise	111.9 ± 3.7	136.8 ± 4.7	0.001	115.7 ± 6.3	108.1 ± 4.1	0.321
SBP (mm Hg)						
At rest	117.6 ± 3.1	120.7 ± 2.3	0.463	120.6 ± 4.8	114.7 ± 4.1	0.358
Exercise	150.2 ± 4.9	158.0 ± 4.7	0.538	148.0 ± 6.1	152.3 ± 7.8	0.667
DBP (mm Hg)						
At rest	80.0 ± 2.4	80.7 ± 1.8	0.179	84.6 ± 3.4	75.3 ± 3.2	0.06
Exercise	98.4 ± 2.4	100 ± 3.8	0.906	97.7 ± 2.7	99.0 ± 4.3	0.800
LVEF (%)						
At rest	54.5 ± 1.9	62.4 ± 1.6	0.02	56.6 ± 2.4	52.5 ± 3.0	0.295
Exercise	51.0 ± 2.2	73.5 ± 1.6	0.001	52.0 ± 3.6	49.9 ± 2.7	0.644
Δ	-6.6 ± 2.6	18.1 ± 3.4	0.001	-9.4 ± 3.7	-3.7 ± 3.7	0.285
PER (EDV/sec)	2.9 ± 0.1	3.4 ± 0.2	0.03	2.9 ± 0.2	2.8 ± 0.2	0.726
PFR (EDV/sec)	2.4 ± 0.1	2.8 ± 0.16	0.04	2.4 ± 0.11	2.3 ± 0.16	0.611
PFR/PER	0.85 ± 4.8	0.83 ± 0.05	0.610	0.82 ± 0.05	0.9 ± 0.08	0.404
Exercise duration (min)	6.1 ± 0.2	9.9 ± 0.26	0.001	5.6 ± 0.4	6.5 ± 0.2	0.06
Exercise capacity (W)	67.0 ± 4.1	100 ± 4.9	0.001	62.3 ± 6.8	73.3 ± 5.1	0.206

Data are expressed as mean ± SEM.

Normal ranges: IGF-I, 110–500 μ g/liter in 20–30, 100–450 μ g/liter in 31–40, 100–300 μ g/liter in 41–50, 90–270 μ g/liter in 51–60, and 75–250 μ g/liter in \geq 60-yr-old subjects; total-cholesterol, 120–200 mg/dl; HDL-cholesterol, 35–110 mg/dl; triglycerides, 50–200 mg/dl; fibrinogen, <400 mg/dl; LVMi, \leq 110 g/m^2 in women and \leq 135 g/m^2 in men; peak filling rate, \geq 2.5 EDV/sec; LVEF at rest, \geq 50%; and normal response of the ejection fraction at peak exercise, \geq 5% compared to resting values.

TABLE 2. Effect of 12 months of GH replacement or GH deficiency on endocrine, metabolic and cardiac parameters in patients with GHD

	GH-treated GHD patients		P	GH-untreated GHD patients		P
	Baseline	12 months		Baseline	12 months	
IGF-I ($\mu\text{g/liter}$)	79.4 \pm 6.0	239.6 \pm 18.1	<0.001	70.7 \pm 7.9	69.8 \pm 7.4	0.614
BMI (kg/m^2)	28.8 \pm 0.9	28.4 \pm 0.9	<0.001	30.1 \pm 1.9	30.1 \pm 1.9	0.9
Total cholesterol (mg/dl)	234.0 \pm 13.4	200.1 \pm 9.9	0.004	217.6 \pm 10.3	239.1 \pm 4.5	0.04
LDL cholesterol (mg/dl)	139.6 \pm 13.8	119.3 \pm 10.8	0.03	124.0 \pm 9.13	133.9 \pm 9.1	0.03
HDL cholesterol (mg/dl)	45.5 \pm 3.5	49.0 \pm 3.2	<0.0001	46.4 \pm 2.8	44.4 \pm 2.9	0.001
Total/HDL-cholesterol ratio	5.6 \pm 0.6	4.3 \pm 0.4	<0.001	4.7 \pm 0.3	5.1 \pm 0.3	0.002
Triglycerides (mg/dl)	199.7 \pm 30.6	160.2 \pm 13.8	0.01	142.0 \pm 18.1	148.9 \pm 17.8	0.002
Fibrinogen (mg/dl)	332.5 \pm 27.2	337.5 \pm 18.5	0.776	330.7 \pm 25.8	326.9 \pm 19.5	0.760
LVMi (g/m^2)	85.4 \pm 4.5	97.6 \pm 5.4	0.002	87.0 \pm 3.5	86.6 \pm 3.5	0.936
Heart rate (beats/min)						
At rest	67.8 \pm 2.2	71.0 \pm 1.9	0.085	72.4 \pm 2.2	71.8 \pm 2.1	0.454
Exercise	115.7 \pm 6.3	108.8 \pm 4.5	0.160	108.1 \pm 4.1	108.5 \pm 4.1	0.797
SBP (mm Hg)						
At rest	120.6 \pm 4.8	116.0 \pm 4.4	0.324	114.7 \pm 4.1	116.3 \pm 4.2	0.465
Exercise	148.0 \pm 6.1	136.0 \pm 3.2	0.031	152.3 \pm 7.8	149.3 \pm 6.7	0.308
DBP (mm Hg)						
At rest	84.6 \pm 3.4	78.3 \pm 2.3	0.022	75.3 \pm 3.2	74.7 \pm 2.6	0.792
Exercise	97.7 \pm 2.7	104.6 \pm 4.4	0.106	99.0 \pm 4.3	100.6 \pm 4.0	0.313
LVEF (%)						
At rest	56.6 \pm 2.4	57.1 \pm 2.5	0.582	52.5 \pm 3.0	50.9 \pm 2.6	0.046
Exercise	52.0 \pm 3.6	62.5 \pm 2.7	<0.0001	49.9 \pm 2.7	48.6 \pm 2.6	0.002
Δ	-9.4 \pm 3.7	11.1 \pm 2.0	<0.0001	-3.7 \pm 3.7	-4.3 \pm 3.6	0.420
PER (EDV/sec)	2.9 \pm 0.2	3.0 \pm 0.1	0.058	2.8 \pm 0.2	2.8 \pm 0.19	0.958
PFR (EDV/sec)	2.4 \pm 0.11	2.9 \pm 0.1	0.001	2.3 \pm 0.16	2.3 \pm 0.14	0.480
PFR/PER	0.82 \pm 0.05	0.99 \pm 0.04	<0.0001	0.9 \pm 0.08	0.86 \pm 0.08	0.434
Exercise duration (min)	5.6 \pm 0.4	7.1 \pm 0.4	0.001	6.5 \pm 0.2	6.1 \pm 0.2	0.168
Exercise capacity (W)	62.3 \pm 6.8	78.3 \pm 4.8	0.004	73.3 \pm 5.1	71.7 \pm 4.8	<0.0001

Data are expressed as mean \pm SEM.

Normal ranges: IGF-I, 110–500 $\mu\text{g/liter}$ in 20–30, 100–450 $\mu\text{g/liter}$ in 31–40, 100–300 $\mu\text{g/liter}$ in 41–50, 90–270 $\mu\text{g/liter}$ in 51–60, and 75–250 $\mu\text{g/liter}$ in ≥ 60 -yr-old subjects; total-cholesterol, 120–200 mg/dl; HDL cholesterol, 35–110 mg/dl; triglycerides, 50–200 mg/dl; fibrinogen, <400 mg/dl; LVMi, $\leq 110 \text{ g/m}^2$ in women and $\leq 135 \text{ g/m}^2$ in men; PFR, $\geq 2.5 \text{ EDV/sec}$; ejection fraction at rest, $\geq 50\%$; and normal response of the ejection fraction at peak exercise, $\geq 5\%$ compared to resting values.

composition, bone mass, lipid profile, and muscle strength (1–5), GHD is capable of impairing the cardiovascular function (6) and has been considered one of the main factors responsible for the increased risk of mortality for cardiovascular disease in hypopituitary patients (22–24). GH replacement induces beneficial effects on body composition, glycolipid metabolism, bone mass and turnover, quality of life (1–5), and even on the cardiovascular function (6, 25). However, its definitive efficacy in reversing the cardiovascular risk is still questioned. Several studies demonstrated that GH replacement induces an increase of the cardiac output and LVEF and improves other indices both of LV systolic and diastolic function (6, 25). Long-term prospective data on the cardiovascular risk and cardiac performance in GHD adults replaced with GH are scant. Improvement of lipid profile and cardiac performance was recently reported in a cohort of young adult patients with either co- or ao-GHD, replaced with GH for 12 months (7). However, 12 months of GH treatment were able to improve but not completely reverse the cardiac abnormalities in another cohort of young GHD patients (7).

Although a wide literature has demonstrated the beneficial effects of GH replacement in GHD patients, only fragments of information are available on the potential progression of clinical symptoms and signs, in particular of cardiac derangement, in untreated GHD patients. Gibney *et al.* (8) compared two different cohorts of patients after 10 yr, one

treated with GH and another untreated, showing improvement in energy levels, emotional reaction, psychological well-being, and lipid profile only in GH-treated patients. In addition, GH-untreated GHD patients also had a significant increase in the intima-media thickness compared with treated patients, whereas no difference was found both in the hemodynamic parameters and in the cardiac parameters, evaluated by echocardiography, between the two groups of patients (8). This finding provided strong evidence that 10-yr GH replacement is able to reduce atherogenesis, supporting the hypothesis that it could also reduce the cardiac death rate in GHD patients.

To date, our study is the only prospective comparison of the effects of GH replacement or deprivation in adult GHD patients. In agreement with previous studies (7, 8), both GHD subgroups showed at diagnosis a similar impairment of LVEF, both at rest and at peak exercise, and of the indices of diastolic function. Alteration of lipid profile was not statistically different in the two cohorts, even if a trend for a more severe profile seems to exist in GH-treated patients. Confirming previous findings (26–31), a reevaluation of these patients after 12 months showed an improvement of cardiovascular risk parameters, cardiac mass, and function parameters only in those patients who had received GH replacement. Strikingly, a further impairment of cardiovascular risk parameters, LV performance both at rest and at peak exercise, and exercise duration was observed in GHD

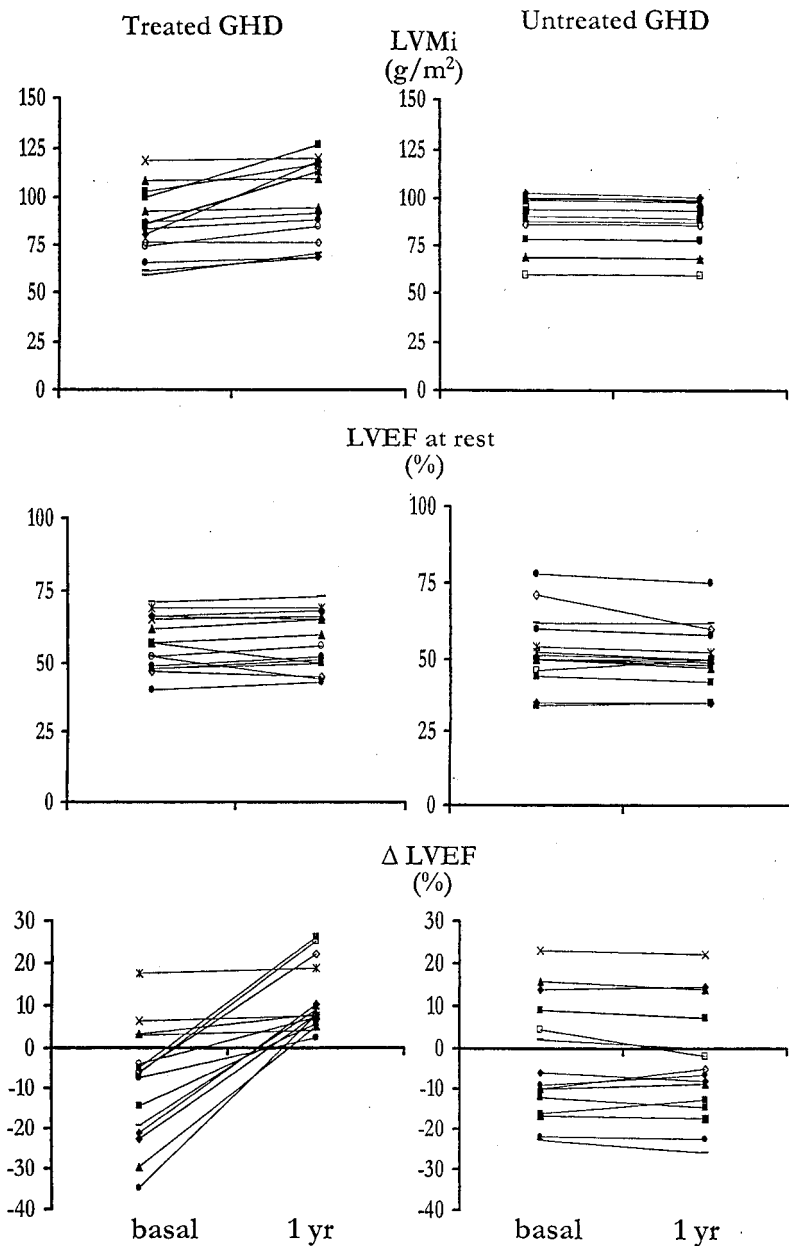


FIG. 1. LVMi (top), LVEF at rest (middle), and LVEF changes at peak exercise (Δ LVEF; bottom) in 15 GHD patients before and 12 months after hormone replacement including GH (left) and in 15 GHD patients before and 12 months after hormone replacement without GH (right).

patients who received complete hormone replacement (where required) except for GH. These findings suggest that 12 months of GH deprivation can aggravate the cardiovascular risk and likely increase the risk of cardiac accidents. It should be emphasized, however, that GH replacement for 12 months was unable to completely normalize cardiac performance, according to previous data (7), thus indicating that cardiac performance should be monitored in long-term studies.

In conclusion, 12 months of GH replacement normalized IGF-I and improved lipid profile and cardiac performance, even if LVEF remained significantly lower compared with controls. A similar period of GH deprivation induced a further impairment of lipid abnormalities and cardiac performance besides stable IGF-I levels. This finding strongly sup-

ports the need of GH replacement in adult GHD patients to reduce the cardiovascular risk of these patients.

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