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Effects of 5 years of growth hormone (GH) replacement therapy on cardiac parameters and physical performance in adults with GH deficiency

Maria Claudia Peixoto Cenci · Débora Vieira Soares · Luciana Diniz Carneiro Spina · Rosane Resende de Lima Oliveira Brasil · Priscila Marise Lobo · Vera Aleta Mansur · Jaime Gold · Eduardo Michmacher · Mario Vaisman · Flávia Lúcia Conceição

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Abstract The purpose of this study was to evaluate the effects of 5 years of GH substitution on cardiac structure and function, physical work capacity and blood pressure levels in adults with GH deficiency (GHD). Fourteen patients were clinically assessed every 3 months for 5 years. Transthoracic echocardiography and exercise test were performed at baseline, 24, 48 and 60 months. Blood pressure (BP) was measured by means of ambulatory monitoring of blood pressure at baseline, 6, 12, 24 and 60 months. Left ventricular mass and its index increased progressively during the 5 years of GH substitution ($P = 0.008$ and 0.007, respectively). There were no significant changes in all others cardiac parameters evaluated. It was observed a significant improve in functional capacity ($P < 0.001$) and maximal oxygen uptake ($P = 0.006$) during the treatment. Diurnal systolic BP increased by 15 mmHg ($P = 0.024$) and diurnal diastolic BP by 4.5 mmHg ($P = 0.037$). There was no change in dirnal systolic pressure load but a considerable but non-statistically significant reduction in diurnal diastolic pressure load was observed during the study. During the night diastolic BP increased by 4 mmHg ($P = 0.012$) despite a substantial but non-statistically significant reduction in diastolic pressure load. We observed an increase in the proportion of persons with a non-physiological nocturnal fall (non-dippers) throughout the study (from 36.4% at baseline to 54.6% after 60 months of therapy). We concluded that 5 years of GH replacement promoted positive effects on exercise capacity and maximum oxygen uptake in spite of a modest increase in BP levels and left ventricular mass. Continuous monitoring is mandatory to arrive at further conclusions concerning the effects of GH substitution in adults on cardiovascular parameters with respect to possible unfavorable long term effects.

Keywords Heart · Physical exercise · GH deficiency in adults · GH replacement

M. C. P. Cenci · D. V. Soares · L. D. C. Spina · R. R. de Lima Oliveira Brasil · P. M. Lobo · V. A. Mansur · J. Gold · E. Michmacher · M. Vaisman · F. L. Conceição
Service of Endocrinology, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

M. C. P. Cenci (✉)
Rua Alvin Bauer, número 655 sala 402, Balneário Camboriú, SC CEP 88330-643, Brazil
e-mail: marclaudia@uol.com.br

Introduction

Hypopituitary adults have a reduced life expectancy, with a 2-fold higher risk of death for cardiovascular disease compared with that in the control population [1], and GHD has been considered the underlying factor influencing this increased mortality. GHD is associated with hypercoagulability, abdominal obesity, insulin resistance, unfavorable lipid profile, atherosclerosis, increased blood pressure (BP), decreased exercise performance and with reduced pulmonary capacity, left ventricular (LV) mass and LV systolic performance [2–9]. These alterations may contribute to an increase in premature cardiovascular morbidity and mortality in patients with hypopituitarism receiving conventional full pituitary hormone substitution other than GH [3, 10, 11].

Several studies have shown that patients with GHD have impaired cardiac performance [1, 9, 12], manifest mainly as alteration of the LV mass, insufficiency of ejection

fraction both at rest and during effort, and abnormalities of diastolic filling. Nevertheless, although GH substitution was reported to be able to improve cardiac parameters and the exercise capacity in many studies [9, 13–16], long-term prospective data on the cardiac function in GHD adults receiving GH are scant, and its definitive beneficial effect on the reversibility of cardiovascular risk in these patients is still to be confirmed.

The purpose of this long-term prospective study was to assess the effects of 5 years of GH substitution on cardiac structure and function, physical work capacity and BP levels in Brazilian adults with GHD.

Materials and methods

Subjects

Fourteen GHD adults (4 men and 10 women, age range 33–62 years, body mass index 24.6 ± 4.3 kg/m^2; Table 1) were studied between 1998 and 2006. All patients had multiple pituitary deficiencies and were undergoing stable conventional replacement therapy for at least 6 months before and during the study period. Prednisone (mean dosage: 2.5–5 mg/day), levothyroxine (132.3 ± 26.1 μg/day), desmopressin (15–40 μg/day) and gonadal steroids were used as necessary. All had severe GHD for at least 12 months before replacement (maximum peak serum GH response to insulin-induced hypoglycaemia and glucagon test <3 ng/ml).

Exclusion criteria included the following: GH therapy in the last 12 months, any acute severe illness during the previous 6 months, pregnancy or lactation, chronic liver or renal disease, diabetes mellitus, prior acromegaly, severe hypertension, psychiatric disease, drug or alcohol abuse, history of malignancy, and use of chronic medication (except pituitary replacement therapy, contraceptives and treatment for mild hypertension). Individuals who developed clinical asymptomatic diabetes during the trial remained in the study and received dietary instructions.

The causes of hypopituitarism were: Sheehan syndrome (8 patients), nonfunctioning pituitary adenoma [2], idiopathic [2], histiocytosis X [1] and other pituitary pathologies [1] (Table 1). Three patients had family history of type 2 diabetes mellitus in first-degree relatives and four had family history of dislipidemia.

Ethical considerations

Informed written consent was obtained from each patient and the study protocol was approved by the Human Research Ethics Committee of Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Brazil.

Study protocol

This was an open prospective study. Patients were evaluated each month during the period of dose adjustment and then every 3 months for 5 years. GH (Norditropin®, Novo-Nordisk, 3 IU/mg) was administered subcutaneously at bedtime by the patient. The initial dose was 0.015 mg/kg/week. The injection site was either abdomen or the anterior thigh, according to patient's preference, but remained constant throughout the study. Although the body weight was used to define the initial dose of GH, the ideal dose was attained with a dose titration regimen, which was based on the analysis of side effects and serum IGF-1 levels. The maintenance dose

Table 1 Age, sex, BMI and cause of hypopituitarism in the 14 GHD patients at baseline

Number	Age (year)	Sex	Cause of hypopituitarism	BMI (kg/m^2)
1	39	Male	Idiopathic	18.98
2	35	Female	Sheehan syndrome	25.68
3	50	Male	Histiocytosis X	27.16
4	58	Female	Sheehan syndrome	22.68
5	46	Female	Sheehan syndrome	25.61
6	37	Male	Nonfunctioning pituitary adenoma	29.54
7	38	Male	Idiopathic	25.71
8	62	Female	Sheehan syndrome	18.16
9	54	Female	Nonfunctioning pituitary adenoma	25.92
20	45	Female	Sheehan syndrome	26.10
11	33	Female	Sheehan syndrome	30.62
12	36	Female	Sheehan syndrome	17.21
13	61	Female	Sheehan syndrome	21.97
14	48	Female	Other pituitary pathology–vascular lesion	29.46

of GH was the one that kept IGF-I levels in the upper limit of the age-related reference range (defined by the IGF-1 assay manufacturer's instructions). The mean dose at the end of the period of dose titration was 0.83 ± 0.2 mg/day. Blood samples were drawn between 8:00 and 9:00 h in the morning after 12 h overnight fast. Serum IGF-1 was assessed at baseline and at 6,12, 24, 36, 48 and 60 months during therapy. Compliance was checked by vial count and initially all patients were asked not to change their diet and level of physical activity. Transthoracic echocardiography and exercise test were performed at baseline, 24, 48 and 60 months. Blood pressure (BP) was measured by means of 24 h ambulatory monitoring of blood pressure (AMBP) at baseline, 6, 12, 24 and 60 months.

Biochemical assays

Serum IGF-I was measured by immunoradiometric assay (DSL—5600 ACTIVE™, Diagnostic System Laboratories, Inc, TX), with an intra-assay CV of 1.5% and inter-assay CV of 3.7%. The sex and age-related reference range was:

Age (years)	Male (ng/ml)	Female (ng/ml)
18–19	197–956	193–575
20–22	215–628	110–521
23–25	169–591	129–480
26–30	119–476	96.0–502
31–40	100–494	130–354
41–50	101–303	101–303
51–70	78.0–258	78.0–258

GH was determined using an immunometric chemiluminescent assay (IMMULITE-DPC, LA, CA). The intra-assay and interassay coefficients of variation (CVs) were 5.8 and 5.7% respectively at a mean GH concentration of 3.1 ng/ml; lowest detection limit 0.01 ng/ml. Blood samples were immediately centrifuged and stored at −20 °C for analysis after a 6 month maximum period. Overall, the same assay was employed at baseline and during follow-up.

Ambulatory monitoring of blood pressure

To analyze the BP it was performed 24 h AMBP using the auscultatory method Tycos Quit Track ®, which records Korotkoff sounds. The technique has already been described in detail in our previous study [17].

Transthoracic echocardiography

The evaluation was performed with an ultrasound mechanical system (Hewlett-Packard Sonos 100 CF ®, USA, 3.5 Mhz) according to a standardized protocol. All echocardiographic investigations were made by one single investigator. M-mode measurements were performed according to the recommendations by the American Society of Echocardiography [18]. These measurements were used to determine aortic and left atrial diameters, LV end-diastolic and end-systolic dimensions, as well as the interventricular septal and LV posterior wall thickness. Percentage of LV fractional shortening was calculated as the difference between LV diastolic and systolic internal dimensions divided by the LV internal diastolic dimension. Left ventricular volumes were derived from 2D echocardiography investigations. LV mass was calculated with Devereux's formula [19]: LV mass = 0.8 [1.04 (LV end-diastolic diameter + interventricular septum thickness + LV posterior wall diastolic thickness)^3—(LV end-diastolic diameter)^3] + 0.6. The LV mass was corrected for body surface area (LV mass index): LVMi = LVM/BSA.

Exercise tolerance

Exercise assessment was performed by a graded multistage treadmill test using Bruce's standard protocol [20] (7 stages, each of 3 min duration) and tests were performed by the same physician in the same setting. All studies were performed at least 2 h after a normal breakfast with patients wearing light clothes.

Subjects were questioned for symptoms every 2 min and the heart rate, BP, and a 12-lead electrocardiogram were recorded at baseline, at the end of each stage and at peak exercise. The test was stopped if patients complained of limiting breathlessness, chest discomfort, dizziness, leg weakness, or exhaustion. Other predetermined criteria for prematurely cessation were ST segment depression or elevation of >1 mm, more than three consecutive ventricular premature beats, hypotension (defined as a fall in systolic BP of ≥40 mmHg from baseline) or a systolic BP of ≥260 mmHg or diastolic BP of ≥120 mmHg.

Functional capacity was expressed in METs (*Metabolic Equivalent*, 1 MET = the oxygen consumption of an individual at rest, estimated in 3.5 ml oxygen/kg per minute). The ratio between achieved and estimated oxygen uptake (VO_{2max}) was calculated. In this protocol, estimated VO_{2max} is obtained from a predetermined formula according to age and sex: men: 60—(0.55 × age) and women: 48—(0.37 × age). Since exercise capacity declines with age and the study lasted for 5 years, we calculated the proportion of estimated VO_{2max} reached by each patient using the achieved and estimated oxygen

uptake by means of the following formula: estimated $VO_{2max} = 100\%$

Achieved VO_{2max} = x (proportion of estimated VO_{2max})

Statistical analysis

Statistical analysis was performed with Stata software (version 7.0, 2001). Data were expressed as mean ± SD. We used analysis of variance for repeated measures (ANOVA) to analyze changes over time after log transformation, with Friedman as a complementary test when there was a high degree of non-normality in the distribution. Student's paired t-test was used to compare each parameter in time. All statistical tests were conducted based on two-tailed alternatives. A *P*-value less than 0.05 was accepted as significant for all analysis in the study.

Results

Serum IGF-I concentration was significantly increased by GH-replacement throughout the study period (from 79.1 ± 67 to 187.8 ± 137 ng/ml after 60 months; $P = 0.0001$). At the 6th month mean GH dosage was 0.87 mg/day (range 0.56–1.2). The dose of GH was gradually lowered during the study to keep IGF-I within normal levels adjusted for age. At the 5th year mean GH dosage was 0.64 mg/day (range 0.35–1.0; Fig. 1). No major side effects were observed besides edema and arthralgia at the beginning of the study.

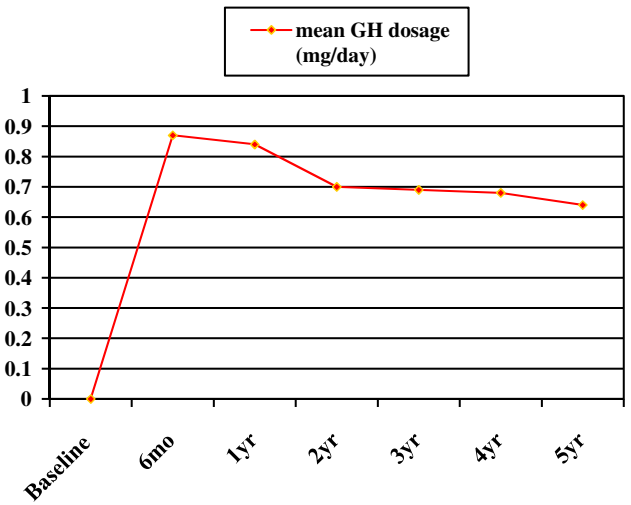

Fig. 1 The dose of GH during 5 year of GH replacement in 14 GHD adults

Echocardiographic measurements

Echocardiographic results are in Table 2. Left ventricular mass and its index increased progressively during the 5 years of GH substitution ($P = 0.008$ e 0.007, respectively). None patient presented echocardiographic criteria of LV hypertrophy during the first 2 years of GH replacement. One patient (number 13—Table 1) developed LV hypertrophy (203 g) in the third year of treatment, which remained abnormal in the 4th year (200 g) but returned to baseline values in the last year of therapy (119 g). Only another female (number 5—Table 1) whose LV mass was normal at baseline (146 g) suffered an abnormal increase in this parameter in the 5th year of the study (232 g).

There were no significant changes during the therapy in all others cardiac parameters evaluated.

Exercise test

It was observed a significant improve in functional capacity ($P < 0.001$) and maximal oxygen uptake ($P = 0.006$) during the treatment, parallel to an important increase in the proportion of estimated VO_{2max} reached by the patients during the treatment ($P = 0.013$; Table 3).

Blood pressure

AMBP was performed in 11 of the patients studied. Diurnal systolic BP increased by 15 mmHg ($P = 0.024$) and diurnal diastolic BP by 4.5 mmHg ($P = 0.037$). There was no change in diurnal systolic pressure load but a considerable but non-statistically significant reduction in diurnal diastolic pressure load was observed during the study (Table 4). During the night diastolic BP increased by 4 mmHg ($P = 0.012$) despite a substantial but non-statistically significant reduction in diastolic pressure load. There were no significant changes in nocturnal average systolic BP and its load during the therapy.

We observed an increase in the proportion of individuals with a non-physiological nocturnal fall (non-dippers) throughout the study (from 36.4% at baseline to 45.5% at 6 and 12 months and to 54.6% after 60 months of therapy).

Discussion

In this analysis, we observed that LV mass and its index increased progressively during the GH substitution. However, only two patients developed LV hypertrophy: the first one in the 3rd year of GH replacement with a return towards baseline values in the last year and the second one only in the 5th year of the study. There were no significant changes in all others cardiac parameters evaluated. An important drawback

Table 2 Echocardiographic measurements in GHD adults: baseline and after 24, 48 and 60 months of GH replacement ($n = 14$)

	Baseline	24 m	48 m	60 m	*P*-value
Aortic diameter (cm)	3.1 ± 0.3	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.4	0.64
IV septal thickness (cm)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.16
LV posterior wall thickness (cm)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.35
LV end-systolic diameter (cm)	2.7 ± 0.4	2.8 ± 0.4	2.6 ± 0.4	2.9 ± 0.6	0.61
LV end-diastolic diameter (cm)	4.4 ± 0.5	4.5 ± 0.6	4.4 ± 0.5	4.4 ± 0.6	0.95
LV fractional shortening (%)	38.9 ± 20.1	36.9 ± 6.7	4.1 ± 4.5	34.6 ± 4.8	0.2
LV mass (g)	116.4 ± 35.6	128.6 ± 41.3	153.1 ± 52	174.4 ± 49.9	**0.008**
LVMi (g/m^2)	71.5 ± 15.4	79.2 ± 19.7	94.3 ± 26.8	103 ± 23.7	**0.007**

Values are expressed by mean ± SD

GHD Growth hormone deficient; *IV* Inter ventricular; *LV* Left ventricular

P-values are based on ANOVA for repeated measurements

Bold values denote reached statistical significance

Table 3 Exercise test in GHD adults: baseline and after 24, 48 and 60 months of GH replacement ($n = 14$)

	Baseline	24 m	48 m	60 m	*P*-value
Achieved VO_{2max}	21.5 ± 5.5	24.3 ± 7.5	30 ±4.1	25.6±6.5	**0.006**
% estimated VO_{2max} reached	65.7±13.9	78.5±26.4	107.1±13.1	87.3±21.1	**0.013**
Functional capacity (METS)	5.8±1.7	6.9±2.3	8.6±1.2	7.3±1.9	**<0.001**

Values are expressed by mean ± SD

GHD Growth hormone deficient; VO_{2max}: maximum oxygen uptake

P-values are based on ANOVA for repeated measurements

Bold values denote reached statistical significance

Table 4 Ambulatoty monitoring of blood pressure in GHD adults: baseline and after, 6, 12, 24, and 60 months of GH replacement ($n = 11$)

	Baseline	6 m	12 m	24 m	60 m	*P*-value
Diurnal average SBP	119.4±11.6	115.7±11.9	115.1±11.9	118±8.5	134.1±24	**0.024**
Diurnal average DBP	78.8±10.8	73.8±11.6	76±12.3	72.6±8.1	83.2±14.3	**0.037**
Diurnal SBP^+ load (%)	15.7±14.3	10.5±17.3	9.3±13.7	7.4±7.4	13.4±19.6	0.657
Diurnal DBP^{++} load (%)	17.2±21.1	11±18.3	20.5±25.8	6.7±10	5.3±8.9	0.334
Nocturnal average SBP	101±16.7	101.5±14.5	103.6±17.2	106.7±10.9	117±17.7	0.141
Nocturnal average DBP	68.4±12.1	63.6±12.7	66.4±14.7	63.9±9.3	72.5±11.3	**0.012**
Nocturnal SBP load (%)	18.2±33.4	14.1±25.5	17.1±31.2	13.5±19.5	20.8±31.5	0.530
Nocturnal DBP load (%)	21.4±34.6	12.2±19.8	20.7±30.1	8.6±18	4.3±6.3	0.657
Total SBP load (%)	12.5±10.5	8.6±14.5	8.3±12.3	9.2±11.2	14.8±21.5	0.327
Total DBP load (%)	13.6±17.4	9.5±15.6	17.9±23.9	6.5±11.5	5.4±8.5	0.361

Values are expressed by mean ± SD

GHD Growth hormone deficient; *SBP* Systolic blood pressure; *DBP* Diastolic blood pressure

P-values are based on ANOVA for repeated measurements

Bold values denote reached statistical significance

of the present study is the lack of control subjects, but it must be emphasized that it is barely practicable to perform a placebo-controlled study throughout a 5 year period.

Left ventricular hypertrophy is a powerful predictor of morbidity and mortality in the population [21]. The possibility that prolonged GH treatment might induce LV hypertrophy has not been confirmed. It has been suggested that myocite response to GH may be dose and time-related since LV mass did not increase in adults under a GH dose substitution of 2 UI/m^2/day during 4 [22] and 6 months [23], but increased by 5% after 6 months of a GH dose of 3 UI/m^2/day [24, 25]. Two years of GH replacement was

associated with a small increase in LV mass index and improved systolic function in 13 GHD young survivors of childhood-onset acute lymphoblastic leukemia treated with prophylactic cranial radiotherapy [26]. Ter Maaten and co-workers [15] reported a significant increase in cardiac mass during the first year of a 10 year follow-up GH replacement study. However, this hypertrophic effect subsided throughout the time and in the last years of follow-up cardiac mass was similar to pretreatment values. Minczykowski and co-workers [27] observed no changes in LV mass and diameter after 12 months of GH replacement, but they described a significant increase in systolic LV posterior wall and interventricular septal thickness. On the contrary, two small long-term studies in young adults with GHD showed that GH therapy improved LV function with no concomitant change in its thickness or mass [28, 29]. Similarly, no change in cardiac size was reported after GH substitution for 2 years [30], 7 years [31] and during 10 years [13].

In accordance with Cuneo and co-workers [24], the increase in cardiac output after GH therapy may reflect increased preload due to the sodium-retaining effect of GH (Starling effect). It seems that in our study, as well as in the work of Nass et al. [23], this effect was not significant since there was no increase in LV end-diastolic diameter during GH substitution. In contrast, other studies have been shown an increase in cardiac output and in LV end-diastolic diameter, but not in end-systolic diameter [9, 14, 25, 32].

We observed a significant improve in functional capacity and estimated peak oxygen uptake reached by the patients during the study, in agreement with findings of others studies [8, 15, 22, 33–38] and a recent published meta-analysis [39]. The increase in lean body mass induced by GH substitution is an important factor for the improvement of VO_{2max} [8]. Adults with GH deficiency often complain of low energy levels resulting in a low apparent quality of life. Such significant increase in exercise capacity suggests that GHD patients under GH therapy can perform the daily tasks with more ease. Moreover, the improvement in exercise performance may indicate a reduction in risk of cardiovascular events and heart failure in sedentary individuals [40].

In the present study, diurnal systolic BP increased by 15 mmHg and diurnal diastolic BP by 4.5 mmHg. There was no change in diurnal systolic pressure load but a considerable but non-statistically significant reduction in diurnal diastolic pressure load was observed during the study. During the night diastolic BP increased by 4 mmHg despite a substantial but non-statistically significant reduction in diastolic pressure load. We also observed an increase in the proportion of individuals with a non-physiological nocturnal fall (non-dippers) throughout the study (from 36.4% at baseline to 54.6% after 60 months).

In our preceding study [17], we observed a significant decrease of the diurnal systolic BP and of the diurnal systolic and diastolic pressure loads after 2 years of GH substitution. During the night there were no changes in BP levels. Resembling this latest study, there was an increase in the percentage of patients with a non-physiological nocturnal fall (non dippers) after replacement with GH (from 30.8% at baseline to 61.5% after 24 months). A decrease in diastolic BP has previously been observed in some [25, 41, 42] but not all [13, 15, 43–45] studies in GH-treated patients.

We chose 24 h ambulatory monitoring of blood pressure (AMBP) because it is a more accurate measurement than conventional sphygmomanometry and provides a means of delineating circadian variations in BP, being particularly valuable to refine cardiovascular risk stratification in untreated subjects with isolated office hypertension, that has been found to occur in up to 32% of patients [46]. Two analyses of cohorts of patients with both untreated and treated hypertension followed for up to a decade have shown that AMBP has better predictive values for future cardiovascular events than clinical measurements of BP [47, 48]. Furthermore, AMBP can be performed during patients' routine activities. However, the analysis of 24 h AMBP was not utilized in most of the studies. Conceição et al. [49], by means of 24 h AMBP, showed an increased proportion of non-dippers in GHD adults without treatment (37%), which is very similar to the findings of the present study (36.4%). In contrast, Ahmad et al. [50] and Climent et al. [30] did not find variations in circadian rhythm with measurement of 24 h ambulatory blood pressure after 12 and 24 months of GH replacement, respectively.

We concluded that 5 years of GH replacement promoted positive effects on exercise capacity and maximum oxygen uptake in spite of a modest increase in BP levels and LV mass. Continuous monitoring is mandatory to arrive at further conclusions concerning the effects of GH substitution in adults on cardiovascular parameters with respect to possible unfavorable long term effects.

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