

Familial Isolated Growth Hormone Deficiency Is Associated with Increased Systolic Blood Pressure, Central Obesity, and Dyslipidemia

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To assess the metabolic and cardiovascular consequences of GH deficiency (GHD) on cardiovascular risk factors, we studied a homogeneous population with GHD due to a homozygous defect in the GHRH receptor gene. Anthropometric, metabolic, and cardiovascular measurements (at rest, during treadmill exercise, and during orthostatic stress) and echocardiographic data were obtained from 16 GH-naive, GH-deficient (GHD) adults and 31 age-, sex-, and body mass index-matched control (CO) subjects. The percentage of fat mass, waist to hip ratio, and total and low density lipoprotein cholesterol were higher in the GHD group. However, high density lipoprotein cholesterol, triglyceride, and fasting glucose levels were similar between groups, and fasting insulin and homeostasis model assessment of insulin resistance (HOMA_{IR}) were lower in the GHD group. Systolic blood pressure (SBP)

was higher in the GHD group, but no difference in diastolic blood pressure or heart rate (HR) existed. Blood pressure and HR responses to exercise did not differ between groups. During passive orthostatic stress the decrease in SBP was higher in the GHD than in the CO group, whereas an increase in diastolic blood pressure was not observed in the GHD group. Moreover, the increase in HR was blunted in the GHD compared with the CO group. Left ventricular mass and mass index were lower in the GHD group.

In conclusion, this genetically homogeneous isolated GHD population presents a syndrome characterized by central obesity, dyslipidemia, and elevated SBP but reduced cardiac dimensions compared with controls. (*J Clin Endocrinol Metab* 87: 2018–2023, 2002)

GH AND ITS effector, IGF-I, not only regulate somatic growth, but also help control a number of physiological processes linked to various cardiovascular risk factors (e.g. fat mass, fat-free mass, insulin sensitivity, and lipid metabolism). It also has been reported that GH and IGF-I directly or indirectly regulate arterial blood pressure (BP) and contribute to the variability in left ventricular (LV) mass associated with essential hypertension (1–4).

GH-deficient (GHD) adults have higher rates of cardiovascular morbidity (5–7) and mortality (8, 9) than age-matched controls. This increase in mortality has been attributed to higher prevalence of risk factors for atherosclerosis, such as dyslipidemia, decreased plasma fibrinolytic activity, increased prevalence of hypertension, increased hip/waist ratio, and insulin resistance (10). These observations have been used to support the use of GH replacement therapy in GH-deficient adults (10–12). However, such data have been obtained from heterogeneous cohorts of patients with GH deficiency (GHD) of varying etiologies, often in the setting of

panhypopituitarism requiring multiple pituitary hormone replacement, which may itself affect metabolic and cardiovascular indexes (5–7, 13). Therefore, it remains unclear whether the increased cardiovascular morbidity and mortality rates associated with panhypopituitarism reflect GHD itself or these confounding factors.

In Itabaianinha county in the northeastern Brazilian state of Sergipe, we recently identified a large extended pedigree with 105 affected individuals with autosomal recessive isolated GHD due to a homozygous donor splice site mutation in the GHRH receptor (GHRHR) gene (*GHRHR*) (14, 15). This is the largest homogeneous cohort of patients with severe GHD described to date. The adult patients are proportionate dwarfs and have never undergone GH replacement therapy. They constitute an ideal population to define precisely the metabolic and cardiovascular consequences of life-long untreated isolated GHD in adults.

Subjects and Methods

Subjects

Sixteen GH-naive adult patients with a genotype-proven homozygous mutation in the *GHRHR* gene (8 men and 8 women; GHD group) and 31 healthy volunteers [12 men and 19 women; control (CO) group] living in the same rural area as the affected group were studied. Patients and families were recruited through the local dwarfs' association after a detailed explanation of the protocol. Based on their medical history,

Abbreviations: BMI, Body mass index; BP, blood pressure; CO, control; DBP, diastolic blood pressure; FM%, percentage of fat mass; GHD, GH deficiency; GHRHR, GHRH receptor; HDL-C, high density lipoprotein cholesterol; HOMA_{IR}, homeostasis model assessment of insulin resistance; HR, heart rate; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; SBP, systolic blood pressure.

all subjects were free of cardiovascular or other systemic diseases, and none was receiving any medication. The appropriate institutional review committees approved these studies, and all subjects gave informed consent.

Study protocol

Metabolic data. All subjects were admitted to the clinical research center at approximately 0800 h after an overnight fast. Blood samples to measure total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, glucose, insulin, and IGF-I were collected. The total cholesterol level was determined by an enzymatic calorimetric method, and the LDL-C concentration was calculated indirectly (Friedwald formula) (16). HDL-C was separated using the phosphotungstic acid/magnesium chloride method (17). Glucose and triglycerides were measured by an enzymatic colorimetric test. Insulin was measured by RIA 1600 (Diagnostics Systems Laboratories, Inc., Webster, TX); IGF-I was measured by immunoradiometric assay 5600, with double extraction and an assay sensitivity of 0.8 ng/ml (Diagnostics Systems Laboratories, Inc.). Insulin resistance was estimated in each subject using the homeostasis model assessment of insulin resistance (HOMA_{IR}) with the following validated formula: fasting serum insulin (μ U/ml) \times fasting plasma glucose (mmol/liter)/22.5 (18).

Anthropometric measurements. After the blood sampling, the subjects had a light breakfast without coffee. Anthropometric and office BP measurements were subsequently obtained at the clinical investigation laboratory. Body mass index (BMI) was calculated by dividing body weight (kilograms) by the square of the height (meters), the waist to hip ratio was calculated by dividing the waist measurement by the hip measurement as described previously (19), and the percentage of fat mass (FM%) was measured using the near-infrared interactance method to quantify fat mass. The procedure involved placing a fiberoptic probe tangentially to the belly of the subject's biceps brachii and measuring the reflected energy in the near-infrared region at two different frequencies. A multiple regression equation was employed to use the interactance information in combination with other anthropometric data to predict body composition (20).

BP measurements

Office blood pressure. The office BP was the average of three measurements obtained in the left arm after 10 min of rest in the sitting position by one of two pretrained physicians (M.R.S.A. and V.B.) using a mercury sphygmomanometer with a cuff appropriate for the size of the arm of a dwarf.

Blood pressure during exercise treadmill

All participants were studied during a two-stage (3 min each) exercise treadmill test according to the Bruce protocol (21). Systolic and diastolic blood pressure (SBP and DBP, respectively) values were recorded by cuff in standing subjects immediately before testing (preexercise) and during the last half minute of each 3-min exercise stage. A three-lead electrocardiogram was used to determine heart rate (HR) and analyze the ST segment during exercise. The SBP, DBP, and HR responses to the exercise treadmill test were calculated by subtracting the preexercise values from measurements obtained during the sixth minute (peak exercise values).

BP during passive orthostatic stress

After 15 min of supine rest on a tilt table, baseline measurements for BP (mercury sphygmomanometer method) and HR (electrocardiogram) were obtained. Then, the tilt table was elevated to 80°, and SBP, DBP, and HR were measured at the end of the first and third minutes of orthostatic stress. The SBP, DBP, and HR responses to orthostatic stress were calculated by subtracting supine baseline values from measurements obtained at the end of the third minute.

Echocardiography

Echocardiographic studies were performed with a commercial machine (HP-Sonos 5500, Hewlett-Packard Co., Andover, ME) according to standard procedures. The M-mode echocardiography of the LV was performed according to American Society of Echocardiography recommendations (22). Only frames with optimal visualization of interfaces and simultaneously visible septum, LV internal diameters, and posterior wall were used for calculations. LV mass was calculated according to the method of Devereux *et al.* (23) and normalized according to body surface area and height. Relative wall thickness was calculated as $(2 \times \text{posterior wall thickness})/\text{LV internal radius}$.

Statistical analysis

Statistical analysis was performed using the statistical software SPSS/PC 10.0 (SPSS, Inc., Chicago, IL). Values for continuous variables are expressed as the mean \pm sd. Categorical variables were compared with the χ^2 test. Insulin and HOMA_{IR} data were transformed into decimal logarithm before analyses. Nonparametric Mann-Whitney test was used to compare groups. Stepwise multiple linear regression was used to examine relationships between variables. *P* value of 0.05 or less was considered statistically significant.

Results

Subject characteristics

As shown in Table 1, age, sex, and BMI did not differ between groups. As expected, height, weight (Table 1), and IGF-I levels were significantly lower in the GHD group (Table 2).

Anthropometric and biochemical data

The percentage of fat mass and the waist to hip ratio were higher in the GHD group, indicative of abdominal obesity (Table 1). Total cholesterol and LDL-C levels were also higher in the GHD group than in the CO group, but HDL-C and triglyceride levels did not differ between groups. Mean fasting glucose levels were not different between the two groups,

TABLE 1. Anthropometric data (mean \pm DP) in 16 GHD individuals and 31 controls

Characteristic	CO (n = 31)	GHD (n = 16)	<i>P</i>
Age (yr)	44 \pm 12	49 \pm 14	0.164
Sex distribution, men/women	12M/19W	8M/8W	0.463
Height (m)	1.21 \pm 0.06	1.55 \pm 0.09	0.000
Weight (kg)	33.3 \pm 5.6	59.1 \pm 11.6	0.000
BMI (kg/m ²)	24.4 \pm 3.8	22.9 \pm 4.1	0.252
% of fat mass	21 \pm 1	34 \pm 7	0.000
Waist/hip ratio	0.9 \pm 0.08	0.97 \pm 0.08	0.018

TABLE 2. Biochemical data (mean \pm DP) in 16 GHD individuals and 31 controls

Variable	CO (n = 31)	GHD (n = 16)	<i>P</i>
IGF-I (nmol/liter)	0.35 \pm 0.13	20.15 \pm 10.60	0.000
Total cholesterol (mmol/liter)	5.02 \pm 0.99	6.10 \pm 1.36	0.003
LDL cholesterol (mmol/liter)	3.43 \pm 0.82	4.26 \pm 1.22	0.005
HDL cholesterol (mmol/liter)	0.98 \pm 0.18	1.03 \pm 0.22	0.387
Triglycerides (mmol/liter)	1.30 \pm 0.70	1.77 \pm 1.31	0.4
Fasting glucose (mmol/liter)	4.8 \pm 1.16	4.7 \pm 0.6	0.813
Fasting insulin (μ U/ml)	4.6 \pm 3.4	2.94 \pm 2.35	0.038
HOMA _{IR}	1 \pm 0.9	0.62 \pm 0.52	0.039

but fasting insulin and HOMA_{IR} values were lower in the GHD group than in the CO group (Table 2 and Fig. 1).

BP and HR

Office BP. Office SBP was higher in the GHD group than in the CO group. In contrast, no difference in DBP or HR was observed between groups (Table 3 and Fig. 1).

Stepwise multiple linear regression showed that the FM% explains 20.5% of the variability in SBP in the CO group, the BMI explains 46.1% of the variability in SBP in the GHD group, and the FM% and LDL-C levels explain 28.1% of the variability in SBP in the overall population (adjusted r^2).

Exercise treadmill. The preexercise standing SBP was higher in the GHD group than in the CO group. DBP in the standing position was not significantly different in the GHD group from that in the CO group. The preexercise standing HR was similar between the groups, and the magnitude of the SBP, DBP, and HR responses to treadmill exercise did not differ between the groups. During the 6-min Bruce protocol, no symptoms or electrocardiographic changes suggestive of myocardial ischemia were observed (Table 3).

Orthostatic passive stress. Supine SBP and DBP were higher in the GHD group than in the CO group, but no difference in supine HR was observed between groups. During passive orthostatic stress, the decrease in SBP was significantly higher in the GHD group, and the increase in DBP observed in the CO group was not observed in the GHD group. More-

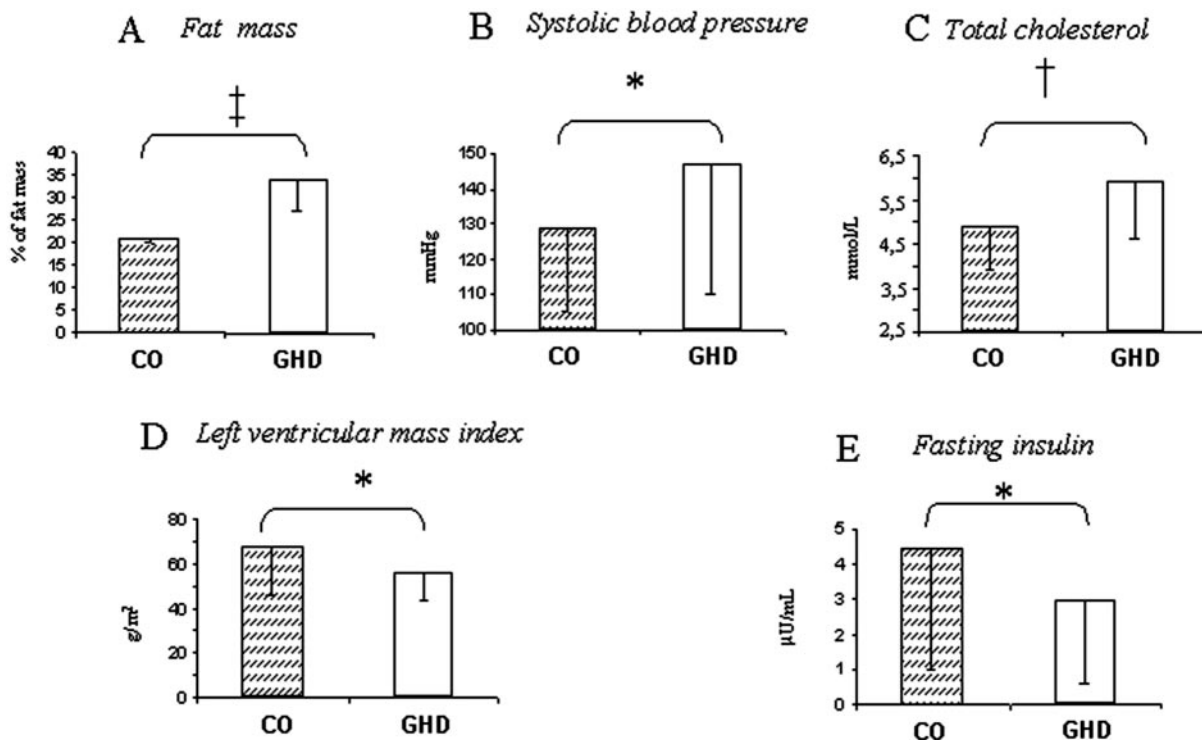
over, the HR response to orthostatic stress was significantly blunted in the GHD group compared with the CO group (Table 3).

Echocardiography

Septal wall thickness, posterior wall thickness, and end-diastolic diameter were significantly lower in the GHD group than in the CO group. The ejection fraction, fractional shortening, and E/A ratio were similar between groups, indicative of normal resting systolic and diastolic function. The LV mass, LV mass index, and LV mass/height ratio were smaller in the GHD group (Table 4 and Fig. 1). Relative wall thickness did not differ between groups. There were no correlations between the LV mass index and blood pressure, anthropometric data, and metabolic data (Table 4).

Discussion

The results of the present study indicate for the first time that in a genetically homogeneous group of GH-naïve adult patients with GHD due to a null *GHRHR* mutation, life-long isolated GHD is associated with a cluster of significant cardiovascular risk factors (*e.g.* central obesity and increased total cholesterol, LDL-C, and SBP) compared with age- and sex-matched control subjects residing in a similar rural area. Central obesity may contribute to the atherogenic lipid profile generally observed in this population. However, the pattern of elevated LDL-C and total cholesterol levels, but sim-



* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

FIG. 1. Metabolic and cardiovascular consequences in isolated GHD. The mean FM%, SBP, and total cholesterol level were higher in the GHD group than in the CO group. GHD subjects had a lower mean fasting insulin level and LV mass index.

TABLE 3. Office systolic (mean \pm DP) and diastolic BP, office heart rate (HR), BP, and HR preexercise and responses (Δ) during dynamic exercise (Bruce protocol); supine systolic and diastolic BP (0°); supine HR (0°); and the Δ during passive orthostatic stress (80°) in 16 GHD individuals and 31 controls

Variable	CO (n = 31)	GHD (n = 16)	P
Office SBP (mm Hg)	129 \pm 24	147 \pm 37	0.037
Office DBP (mm Hg)	80 \pm 16	84 \pm 16	0.375
Office HR (beats/min)	72 \pm 10	76 \pm 13	0.43
Standing SBP (preexercise, mm Hg)	123 \pm 21	143 \pm 32	0.03
Standing DBP (preexercise, mm Hg)	75 \pm 13	82 \pm 13	0.1
Standing HR (preexercise, beats/min)	76 \pm 12	78 \pm 14	0.716
Δ SBP (exercise, mm Hg)	37 \pm 20	35 \pm 17	0.76
Δ DBP (exercise, mm Hg)	0.3 \pm 11	3.5 \pm 15	0.42
Δ HR (exercise, beats/min)	53 \pm 17	51 \pm 14	0.77
Supine SBP (0°, mm Hg)	129 \pm 22	153 \pm 39	0.009
Supine DBP (0°, mm Hg)	77 \pm 15	88 \pm 15	0.03
Supine HR (0°, beats/min)	69 \pm 10	73 \pm 11	0.21
Δ SBP (80°, mm Hg)	-3 \pm 10	-13.5 \pm 19	0.000
Δ DBP (80°, mm Hg)	+5 \pm 10	-9 \pm 9	0.000
Δ HR (80°, beats/min)	+7.5 \pm 7	+3 \pm 4	0.018

ilar levels of HDL-C and triglycerides, observed in the GHD group differs from the lipid profile classically associated with central obesity (*i.e.* lower HDL-C and higher triglyceride levels) (24–26). Together, our data suggest that GHD reduces FFM, increases FM%, and is associated with an adverse lipid profile in adults. In the same population our group has shown that the effect of isolated GHD on body composition was already present in children who had a reduced fat-free mass and increased FM% (27).

Studies in both rats and humans have shown an important effect of GH on hepatic cholesterol metabolism. The administration of GH up-regulates hepatic LDL-C receptors, thereby increasing the clearance of LDL-C by the liver (28). The increase in plasma cholesterol levels with age (29) or hypothyroidism is at least partially secondary to a GHD-induced decrease in LDL receptor activity (30). This effect does not seem to be mediated by IGF-I (31). A reduction of the number and/or activity of these receptors could have contributed to the high LDL-C levels observed in our GHD patients. Accordingly, elevated total and LDL-C and decreased FFM/FM ratio were also observed in another model of dwarfism due to GH receptor deficiency (32).

The lower fasting insulin level and HOMA_{IR} in our GHD group may indicate normal or increased insulin sensitivity compared with the CO group. It has been suggested that insulin resistance is responsible for the typical lipid profile observed in obese and hypertensive populations (24–26) and in patients with long-term GHD, panhypopituitarism, and abdominal obesity who are receiving other pituitary hormone replacement (33). Other pituitary deficits or hormonal replacements could contribute to the insulin resistance in these patients, and our data in isolated severe GHD would support this. However, as we did not evaluate peripheral insulin sensitivity with direct methods, we cannot totally rule out that insulin resistance combined with lowered insulin levels could be present in our population.

Although the pathophysiological link is still unknown,

TABLE 4. Echocardiographic data (mean \pm DP) in 16 GHD individuals and 31 controls

Variable	CO (n = 31)	GHD (n = 16)	P
Septal wall thickness (cm)	0.71 \pm 0.12	0.58 \pm 0.12	0.002
Posterior wall thickness (cm)	0.64 \pm 0.12	0.53 \pm 0.09	0.001
End diastolic diameter (cm)	4.94 \pm 0.51	3.96 \pm 0.27	0.000
Ejection fraction (%)	0.78 \pm 0.07	0.78 \pm 0.08	0.6
Fraction shortening (%)	40.16 \pm 5.81	40.6 \pm 7.7	0.621
Left ventricle mass (g)	108.05 \pm 39.4	58.4 \pm 16	0.000
Left ventricle mass index (g/m ²)	68.2 \pm 21	56.6 \pm 13	0.04
Left ventricle mass/ht (g/m)	69.2 \pm 23	48.3 \pm 13	0.002
Relative wall thickness (%)	0.26 \pm 0.04	0.27 \pm 0.04	0.427
E/A ratio	1.3 \pm 0.48	1.2 \pm 0.49	0.462

low levels of IGF-I may contribute to hypertension by activating the sympathetic nervous system. Microneurography recently demonstrated an intense sympathetic discharge in adults with hypopituitarism and untreated GHD; this finding may partially explain the higher prevalence of hypertension in adults with GHD (34, 35). An increase in central norepinephrine, which correlates with sympathetic nervous activity measured by microneurography in humans, is another potential mechanism that explains this increased sympathetic discharge. Central norepinephrine participates in the hypothalamic secretion of GHRH; it is probably elevated in patients with GHD secondary to a GHRHR mutation because of the lack of negative feedback provided by GH and IGF-I (36).

Similar to the dwarfs of Sindh reported by Maheshwari *et al.* (37), the dwarfs of Itabaianinha are a genetically homogeneous populations with a null mutation in the *GHRHR*. Both mutations generate a severely truncated protein (although via different molecular mechanisms) (14, 37), severely reduce GH secretion and serum IGF-I levels, and cause a similar degree of growth retardation. Although we cannot directly compare the BP data from the two groups because the Sindh's dwarfs were significantly younger than our patients (mean age, 18.1 yr; range, 7–28 *vs.* 49 \pm 14 yr), it is interesting to note that BP in the Sindh dwarfs was low (69/33 \pm 15/5) rather than elevated. Although in the Sindh dwarfs BP was measured with an adult-size cuff, which underestimates values by 10–15 mm Hg, this is not sufficient to explain such a large difference. However, the age difference between the cohorts may offer a possible explanation for these BP differences. It has been hypothesized that the cluster of cardiovascular risk factors associated with GHD may require several decades to reduce arterial distensibility leading to the elevation of SBP, as seen in our older adults. Increased thickness of the carotid artery wall has been reported in adults with GHD (mean age, 34 yr), indicative of premature atherosclerosis (7). Moreover, the significantly abnormal SBP and DBP responses to orthostatic stress in the subjects we studied is consistent with structural abnormalities in the aorta and carotid artery that compromise the baroreflex control of BP (38, 39). A genetic cause for reduced BP cannot be ruled out in the dwarfs of Sindh, as they are all linked by common ancestry. As our patients and controls share the same genetic and environmental background, we suggest that the elevation of SBP in our GHD group is caused by GHD.

No clinical or electrocardiographic evidence of myocardial

ischemia manifestations was observed during physical exercise. These data agree with the prior observation that despite the clustering of cardiovascular risk factors, patients with GHD do not have a higher prevalence of ischemic heart disease when evaluated by stress electrocardiography (40). It is possible that the long-term consequences of GHD on coronary pathophysiology reflects the impact of the cluster of associated cardiovascular risk factors and the balance between the beneficial effects of IGF-I in coronary vasodilation and its adverse effects on vascular wall growth that accelerates atherosclerosis (2–9, 41). Anecdotally, an unusually high incidence of coronary artery disease is not reported among Itabaianinha dwarfs.

The BP response to treadmill exercise in GHD patients did not differ from that in CO subjects, indirectly indicating normal inotropic reserve (21). Consistent with this idea, adults with Laron-type dwarfism (due to the absence of GH receptors) have reduced cardiac dimensions and outputs, but normal LV ejection fractions and E/A ratios (42). In addition, dobutamine stress echocardiography has shown normal LV contractile reserve in Laron dwarfs (42), as supported by the present findings. Instead of LV hypertrophy, the obese and hypertensive population had decreased LV mass indexes, but normal systolic and diastolic LV function. One important limitation of our study is that BP was not evaluated by ambulatory BP monitoring. Ambulatory BP monitoring provides a better indicator of LV hypertrophy than office BP measurements (4, 43).

In conclusion, a highly homogeneous adult GH-naive population with severe isolated GHD due to a monogenic *GH-RHR* defect presented reduced fat-free mass, central obesity, increased total and LDL-C, and elevated SBP compared controls from the same area. Despite the increase in SBP, GHD was associated with decreased cardiac dimensions. These findings confirm that GHD plays an important role in the expression of several cardiovascular risk factors. They also raise the question of whether it is necessary to treat these patients to prevent the possible higher cardiovascular mortality associated with GHD. Long-term longitudinal studies, which compare the prevalence of coronary artery disease in GHD patients from Itabaianinha with that in controls from the same rural setting, will tell us whether these risk factors result in clinically significant changes in cardiovascular morbidity and mortality, as observed in patients with GHD associated with panhypopituitarism.

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