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Risk factors of cardiovascular disease in GH-deficient adults with hypopituitarism: A preliminary report

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Background:

We estimated the influence of GH deficiency (GHD) in adults on chosen risk factors of cardiovascular disease and bone density.

Material/Methods:

Fifty-four adults (mean age: 50.4 years) with hypopituitarism were studied. We measured blood pressure, body mass index, waist-to-hip ratio, total body fat, and bone mineral density and the serum levels of lipids, glucose, insulin, pituitary hormones, estradiol, testosterone, and thyroxine, and the excretion of free cortisol in 24-h urine. GHD was confirmed with the insulin intravenous test (IIT) with a GH response to IIT of <3 µg/ml. The control group consisted of 73 healthy adults.

Results:

Increased levels of LDL-cholesterol and triglycerides and decreased levels of HDL-cholesterol in the GHD group were observed. Fasting serum glucose and insulin levels were significantly higher in the GHD group than in controls. Significant differences in the QUICKI and FIRI indexes were observed. Twenty-three percent of the hypopituitary patients were hypertensive and 65% were obese. The percentage of total body fat was significantly higher in the studied group than in controls. Thirty-seven percent of the GHD patients were osteoporotic and 23% were osteopenic.

Conclusions:

An atherogenic lipid profile, insulin resistance, obesity, and increased body and trunk fat in GHD adults may cause the higher risk of cardiovascular disease in these patients. GHD adults should receive human recombinant GH along with conventional replacement therapy. This may be a useful method in protecting against early onset of atherosclerosis, metabolic disturbances, and osteoporosis, especially in young patients.

Key words:

GH-deficient adults • risk factors • metabolic syndrome

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BACKGROUND

Recent studies have drawn attention to the negative consequences of growth hormone deficiency (GHD) in adults with hypopituitarism [1–3]. The most frequent causes of GHD in adults are pituitary tumors (mainly macroadenomas), side effects of neurosurgery or pituitary irradiation, tumor hemorrhages, inflammation, granuloma, and cancer metastases. Clinical manifestations of adults-onset GHD consist of weakness, fatigue, low mood, reduced activity, and no interest in appearance, family, and work. Hypopituitary patients with GHD demonstrate a reduction in lean body mass, increased subcutaneous and visceral fat, muscle atrophy and reduced strength, skin pallor, scalp-hair thinning, and loss of axillary and pubic hair [4,5]. Hypopituitary patients have an increased risk of mortality and cardiovascular disease. This increase in mortality has been attributed to the higher prevalence of risk factors for atherosclerosis, such as dyslipidemia, decreased plasma fibrinolytic activity, and increased prevalence of insulin resistance [1,2,4–7]. These observations have been used to support the use of GH replacement therapy with human recombinant growth hormone to decrease the risk of premature mortality and to improve quality of life. The aim of the study was to estimate the influence of GH deficiency in adults on chosen risk factors of cardiovascular disease and bone mineral density.

MATERIAL AND METHODS

Fifty-four adults with hypopituitarism and GH deficiency, aged 20–65 years (29 females and 25 males), were studied. The control group consisted of 73 healthy, age-matched persons (47 females and 26 males). The causes of hypopituitarism in studied group are presented in Table 1. Four patients were additionally irradiated after neurosurgical treatment.

Pituitary function was examined by measuring the serum levels of GH, prolactin (PRL), adrenocorticotropin (ACTH), thyrotropin (TSH), gonadotropins (LH and FSH), and hormones excreted from endocrine glands subjected to pituitary control, i.e. cortisol in a diurnal rhythm and free cortisol in 24-h urine, dehydroepiandrosterone sulfate (DHEA-S), testosterone (T), estradiol (E2), and free thyroxine (fT4). Fifty-one of the patients were gonadotropin deficient, 41 TSH deficient, and 33 ACTH deficient. All gonadotropin-insufficient females of fertile age and males received sex hormone treatment. ACTH- and TSH-deficient patients were treated with glucocorticoids (hydrocortisone acetate, 20–30 mg/day) and thyroid hormones (levothyroxine, 0.050–0.150 mg/day). Treatment with antidiuretic hormone analog (desmopressin, 0.1–0.4 mg/day, orally) was given to nine patients with diabetes insipidus. The serum hormone levels in the GHD patients are presented in Table 2. All the patients received adequate hormone replacement for hormone deficits before the testing of GH secretion.

The insulin tolerance test (ITT) was used to establish GHD. 0.1 U/kg of regular insulin (Actrapid) was administered i.v. with a target blood glucose level of less than 40 mg/dl. The levels of GH were estimated before and 10, 30, 60, 90, and 120 min after insulin bolus. GHD was defined by a peak GH response to ITT of less than 3 µg/l. In all patients, blood pressure (BP), waist-to-hip ratio (WHR), body

Table 1. The sources of hypopituitarism.

Causes of hypopituitarism and GHD	Number of patients
1. Postoperative hypopituitarism	43
– suprasellar macroadenoma without hormonal function	35 (4: craniopharyngioma)
– macroprolactinoma	3
– microprolactinoma	1
– ACTH – dependent Cushing's syndrome	4
– intracranial tumors (meningioma)	2
2. Native-GHD	3
3. Idiopathic hypopituitarism	2
4. Tuberculosis	1
5. Empty sella syndrome	1
6. Trauma	1
7. Postpartum pituitary necrosis – Sheehan syndrome	1

mass index (BMI), body mass density (BMD), and percent of total and trunk fat mass (using dual photo X-ray absorptiometry) were examined. Blood samples to measure total cholesterol (T-cho), low-density cholesterol (LDL-cho), high-density cholesterol (HDL-cho), triglycerides (TG), glucose, insulin, and electrolytes were collected after an overnight fast. We used commercial kits to measure the above parameters. The level of LDL-cho was calculated from the Friedewald formula [8]. Insulin resistance was evaluated using the fasting insulin resistance index (FIRI) and the quantitative insulin sensitivity check index (QUICKI) according to the following validated formulae: $FIRI = [G0 (mmol/l) + 10 (mU/l)/25]$ and $QUICKI = 1/[\log(I0) + \log(G0)]$, where I0 is fasting insulin in µU/ml and G0 is fasting glucose in mg/dl. Lumbar and femoral bone mineral density (BMD) was evaluated by means of dual energy x-ray absorptiometry (DEXA) method (densitometer DPX (+) Lunar, USA).

Statistical analysis

Results are expressed as mean ±SD, and statistical comparisons were made using student's t-test and Wilcoxon's rank sum test. The Pearson's and the Spearman's correlation tests were used to determine the relationship between variables. Differences were considered to be statistically significant when a *p* value of less than 0.05 was obtained.

RESULTS

In physical examination, 23% of our patients and 22% of controls were hypertensive. Mean values of systolic blood pressure were 132±18 mm Hg in men and 142±14 mm Hg in women, diastolic blood pressure values were, respectively, 85±10 mm Hg and 90±8 mm Hg. Mean blood pressure was 112.4±11.7 and was significantly higher (*p*<0.01) than in the control group, who had 105.7±13.2 mm Hg. Sixty-five percent of the GHD adults were obese (BMI >25–30 kg/m²), but the BMI was not significantly different that of healthy age-matched controls (Table 3). The results of total body

Table 2. Hormone levels in 54 GHD adults and 73 controls.

	GHD patients (n=54)		Controls (n=73)		P
	Median	Range	Median	Range	
TSH (mU/l)	0.9	0.14–5.9	1.5	0.5–3.5	≤0.0005
freeT4 (pmol/l)	12.0	6.2–24.0	13.5	10.0–19.0	0.04
PRL (µg/l)	4.3	0.1–46.0	9.0	2.0–15.0	0.0002
FSH (U/l)	1.0	0.1–12.0	12.0	3.7–50.0	0.00001
LH (U/l)	1.0	0.1–15.0	10.0	2.9–40.0	0.00001
DHEA-S (µg/dl)	35.0	30.0–284.0	190.0	80.0–260.0	0.00001

Table 3. Antropometric data (mean ±SD) in GHD adults and controls.

Characteristic	Controls (n=73)		GHD adults (n=54)		P
	Range	Mean ±SD	Range	Mean ±SD	
Age (yr)	25–65	50.4±9.5	20–65	46.3±11.9	NS
Body mass index (kg/m ²)		27.3±5.6		27.3±5.1	NS
% of fat mass		34.8 ± 8.7		38.8±8.2	0.038
% of trunk fat		32.8±6.5		37.9±7.0	0.036
Waist-to-hip ratio		0.82 ± 0.1		0.9±0.1	<0.01

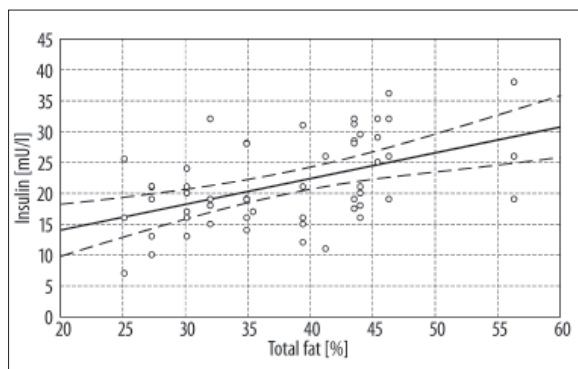


Figure 1. The correlation between plasma fasting insulin and body fat $r=0.46, p<0.001, n=53$.

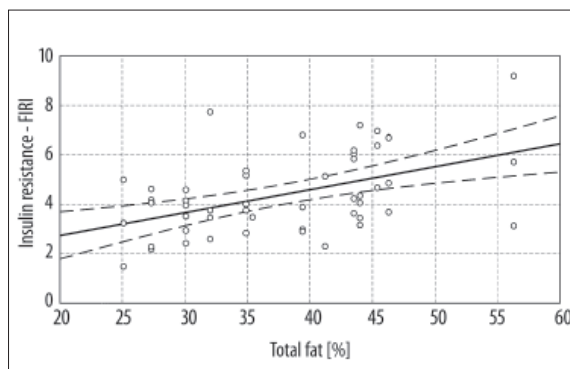


Figure 3. The correlation between total fat contribution and insulin resistance $r=0.47, p<0.001, n=53$.

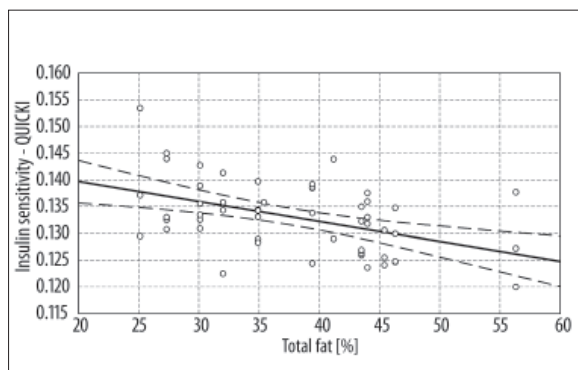


Figure 2. The correlation between total fat and insulin sensitivity $r=-0.46, p<0.001, n=53$.

dual energy x-ray absorptiometry were compared in both groups. The percentage of total and abdominal fat mass in our patients was significantly higher than in controls, regardless of sex (Table 3). We observed that the amount of trunk fat significantly positively correlated with insulin plasma concentration (Figure 1) and FIRI (Figure 3) and negatively correlated with QUICKI (Figure 2). The WHR was significantly higher in the hypopituitary patients than in the age-matched healthy controls (Table 3).

The results of lipids investigation (total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol) in the GHD adults and the controls are presented in Table 4. The serum concentrations of total cholesterol in both GHD patients and controls were not significantly different. The HDL-cholesterol

Table 4. Biochemical data (mean \pm SD) in 54 GHD adults and 73 controls.

Variable	Controls	GHD – adults	P
Total cholesterol (mg/dl)	227.3 \pm 40.0	238.8 \pm 47.8	NS
HDL-cholesterol (mg/dl)	53.5 \pm 13.5	39.2 \pm 8.7	<0.01
LDL-cholesterol (mg/dl)	143.3 \pm 38.2	164.7 \pm 48.8	<0.05
Triglycerides (mg/dl)	129.2 \pm 61.5	181.7 \pm 8.29	<0.001
Fasting glucose (mg/dl)	88.5 \pm 13.0	92.6 \pm 8.9	<0.05
Fasting insulin (μ U/ml)	10.6 \pm 6.3	21.6 \pm 7.1	<0.001
FIRI	2.5 \pm 1.3	4.4 \pm 1.6	<0.001
QUICKI	0.26 \pm 0.05	0.1 \pm 0.01	<0.001

level was lower and the TG level higher in hypopituitary patients than in controls. The differences were statistically significant. The level of LDL-cholesterol was significantly higher in GHD women, while in men the difference was not statistically significant. The mean serum fasting levels of glucose, insulin, as well as QUICKI and FIRI in the examined group and in controls are shown in Table 4. Serum glucose and insulin concentrations were significantly higher in the hypopituitary patients than in the control group. BMD measured at the lumbar spine revealed that 37% of hypopituitary patients were osteoporotic (T-score <-2.5 SD) and 23% were osteopenic (T-score -1.5 – 2.5 SD). In the control group these values were 15% and 8%, respectively.

DISCUSSION

In 1992, Cuneo et al. reviewed the consequences of growth hormone deficiency during adult life and coined the term “growth hormone deficiency (GHD) syndrome in adults” [9]. Life expectancy in hypopituitary patients under routine replacement treatment was previously assumed to be normal. Rosen and Bengtsson were the first to demonstrate decreased life expectancy in these group of patients [10]. The increased mortality in GHD adults has been attributed to a high prevalence of risk factors of atherosclerosis, such as dyslipidemia, hypertension, and increased hip-to-waist ratio. However, we must remember that the data were obtained from heterogeneous cohorts of patients with GH deficiency of varying etiology, often in a setting of panhypopituitarism requiring multiple pituitary hormone replacement, which may itself affect metabolic and cardiovascular indexes [3].

In our group of patients we observed lipid disturbances. The levels of LDL-cholesterol and triglycerides were significantly higher and that of HDL-cholesterol significantly lower than in controls. The levels of LDL-cholesterol were especially high in hypopituitary women and were significantly different from those of the healthy women in the control group. Lipid alterations were observed in both older and younger hypopituitary females with GHD by Al-Shoumer et al. [in 2] and seemed to be independent of sex hormone or glucocorticoid replacement. Our observations confirmed the results of White [11] and Ishibashi [12], who demonstrated increased serum levels of TG and normal or decreased levels of HDL-cholesterol in hypopituitary patients. Wuster et al. reported that 77% of adult hypopituitary patients had abnormal

lipid profiles [in 3], and Rosen et al. [13] showed that plasma triglyceride levels in GHD patients were higher, but that the total cholesterol levels were not statistically different from those in controls. Thus plasma lipid profile with increased LDL-cholesterol and TG and decreased HDL-cholesterol constitutes a vascular risk. In one investigation by Beshyah [3], these abnormalities were more marked in women, which is in agreement with our findings.

Studies in both rats and humans have shown an important effect of GH on hepatic cholesterol metabolism. The administration of growth hormone up-regulates hepatic LDL-cholesterol receptors, thereby increasing the clearance of LDL-cholesterol by the liver [14]. The increase in plasma cholesterol with age or hypopituitarism is at least partially secondary to the GHD-induced decrease in LDL receptor activity [15]. This effect does not seem to be mediated by IGF-1 [16]. A reduction in the number and/or activity of these receptors could have contributed to the high LDL-cholesterol levels in our patients. Thyroid hormones also influence serum lipids and lipoproteins. However, replacement therapy with different doses of levothyroxine in hypothyroid subjects did not cause a significant decrease in HDL-cholesterol levels, even if the serum free T4 levels were elevated above the normal reference range [2]. In our study, serum levels of free T4 in GHD patients were within the normal range.

Central obesity may contribute to the atherogenic lipid profile. The levels of HDL-cholesterol and TG observed in our patients were not different from the lipid profile classically associated with central obesity. The importance of obesity as an independent risk factor for vascular disease has been emphasized, although the distribution of body fat seems to be the most important aspect here. Central obesity is associated with increased vascular mortality and morbidity and with risk factors for vascular disease, such as hyperlipidemia and insulin resistance. Total fat mass and trunk fat in our study group was greater than in the age- and body-weight-matched controls. This is consistent with the findings of other authors [3,7]. Increased abdominal fat mass was evaluated in GHD adults by indirect methods such as measurement of the waist-to-hip ratio (WHR). This parameter was significantly higher in hypopituitary patients than in controls.

Mean fasting glucose and insulin plasma concentrations were significantly higher in the GHD patients. QUICKI was significantly lower and FIRI significantly higher in the patient

group than in controls. These results indicate a decrease in insulin sensitivity in GHD adults. Our data support the observations by Cuneo [in 3] and Weaver [7]. They observed that the fasting plasma immunoreactive insulin concentration was higher in hypopituitary adults in comparison with the reference ranges in their studies. Untreated hypopituitarism in men was a cause of increased insulin sensitivity in study by Besyach [3]. The cause of insulin sensitivity reduction in GHD patients is not clear, but the role of obesity may be important. It has been demonstrated that fasting plasma insulin levels correlate significantly with BMI and WHR, and with total body fat mass and central body fat mass [17,18]. We observed a positive correlation between the amount of abdominal fat mass and insulin concentration. It has been suggested that insulin resistance is responsible for the typical lipid profile observed in the obese and hypertensive population [19,20] and in patients with hypopituitarism and abdominal obesity who are receiving other pituitary hormone replacement [3].

Twenty-three percent of our patients were hypertensive, as in control group, but the mean values of blood pressure were significantly higher in the GHD patients. Some authors [3,21,22] found no significant difference between the prevalence of treated hypertension in GHD patients and in controls, but others observed an increased frequency of treated hypertension in hypopituitary patients compared with the population at large. The increased prevalence of hypertension compared with normal populations may reflect the medical attention which patients receive [3]. The findings of Barrheto-Filho et al. demonstrated that in a genetically homogenous group of GH-native adult patients with GHD due to a null GHRHR mutation, lifelong isolated GHD is associated with central obesity, lipid disturbances, and increased systolic blood pressure [16]. There is information that perturbations in the sympathetic nervous system may be anticipated in adults with hypopituitarism and untreated GH deficiency because the syndrome is associated with both peripheral and central factors known to modulate sympathetic traffic. Low levels of IGF-1 may contribute to hypertension by activating the sympathetic nervous system. The intense sympathetic discharge is suggested to be of central origin and may be an important underlying mechanism for secondary hypertension in the increased cardiovascular morbidity/mortality in GHD patients [16,22].

Reduced bone mineral density (BMD) has been reported in patients with isolated GH deficiency or with multiple pituitary hormone deficiencies (MPHD). Colao et al. showed a significant reduction in BMD associated with abnormalities in bone turnover parameters only in patients with very severe or severe GHD and normal BMD in non-GHD hypopituitary patients [23]. All of our hypopituitary patients had severe (GH in IIT <3) GHD, and 60% of them were osteopenic and/or osteoporotic in comparison with the control group, where a decrease in BMD was seen in only 23% of those examined. It is known that suboptimal GH replacement therapy during childhood is a major cause of osteopenia in young adults with childhood-onset GHD. In adolescents with GHD who normally discontinue GH therapy at completion of linear growth, BMD is substantially lower than the peak bone mass (PBM) in the young adult population [24]. These data suggest that GH treatment leads to improved bone density and that patients may require pro-

longed GH treatment beyond the time of growth to improve PBM. Cessation of GH at achievement of final height, with limiting PBM, may predispose to clinically significant osteoporosis in later life, also by a superimposed accelerated loss of BMD with advancing age similar to the situation observed in adult-onset GHD [24]. Some authors assert that the bone abnormalities result from non-optimal thyroid, gonadal, and adrenal hormone replacement therapy [25,26]. In our patients, proper replacement therapy was given when TSH, fT4, ACTH, gonadotrophins, estradiol, or testosterone were deficient. This suggests that it is GHD per se, rather than inadequate or supraphysiological replacement of deficient anterior pituitary hormones, which is the cause of the low bone mass.

CONCLUSIONS

Hypopituitary adults with GH deficiency demonstrate an atherogenic lipid profile, insulin resistance, obesity, and higher total body and trunk fat than healthy controls. GH deficiency may cause the higher risk of cardiovascular morbidity and mortality in these group of patients. This investigation suggest that GHD adults with hypopituitarism should receive human recombinant GH together with conventional replacement therapy. GH replacement therapy, especially in young patients, may be regarded as a useful method to protect against the onset of atherosclerosis, metabolic disturbances, and osteoporosis.

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