

Panhypopituitarism Without GH Replacement: About Insulin Sensitivity, CRP Levels, and Metabolic Syndrome

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ABSTRACT

A complete deficiency of anterior pituitary hormones from several etiologies characterizes Panhypopituitarism (PH). Despite advances in treatment, patients with PH maintain high rates of morbidity and mortality, a reason to investigate some insulin sensitivity, metabolic and inflammatory parameters that could be related to the increase of these indicators. This was a cross-sectional study comprising 41 PH patients under hormonal replacement, except for growth hormone, and 37 individuals in a control group (CG) with similar age, gender and body mass index (BMI). We assessed clinical data as age, sex, BMI, waist circumference, waist/hip ratio (WHR), history of hypertension, diabetes mellitus and dyslipidemia as well as fasting glycaemia, insulin, HOMA-IR, HbA1c, high-sensitivity CRP (hs-CRP), and lipid profile. PH patients presents lower values of glycaemia, insulin, HOMA-IR (0.88 vs 2.1) and WHR, but higher levels of hs-CRP (0.38 vs 0.16mg/dl) when compared with the CG. Although the occurrence of dyslipidemia was higher in patients with PH, the frequency of metabolic syndrome was similar between the groups. In multivariate linear regression analysis, the PH group independently predicted lower HOMA-IR and WHR values. In conclusion, this study demonstrated that patients with PH without GH replacement have lower HOMA-IR and WHR values and higher levels of hs-CRP than a CG paired by age, gender and BMI. The diagnosis of dyslipidemia was more frequent in patients with PH, but the occurrence of MS was similar to CG. Further studies are needed to confirm our findings and to better understand the metabolic characteristics of patients with PH.

Introduction

Panhypopituitarism (PH) is characterized by a complete deficiency of anterior pituitary hormones resulting from several etiologies. These patients need replacement of thyroid hormones, glucocorticoids, sex hormones, and growth hormone (GH) [1, 2]. These heterogeneous characteristics regarding etiologies and therapeutic diversity make it difficult to interpret the results of clinical studies in patients with PH. The increase in PH prevalence due to advances in the treatment of hypothalamic-pituitary region diseases [3] justifies new studies for the better understanding of the pathophysiology of increased morbidity and mortality rates present in these patients.

The assessment of insulin sensitivity in patients with PH without GH replacement is controversial. Although some studies show decrease in insulin sensitivity [4, 5], other studies did not [6, 7].

Although some authors demonstrated increased markers of cardiovascular disease in PH under hormonal replacement, except for growth hormone [8–11], it is still debatable whether cardiovascular mortality is actually increased in these patients and the true importance of each hormonal deficiency in this outcome [12–16].

It is known that adult patients with growth hormone deficiency have cardiovascular risk factors, such as adverse lipid profiles [17–19], abnormal body composition [20, 21], and increased body weight [22, 23]; however, the increased prevalence of metabolic

syndrome (MS) in PH patients under hormonal replacement, except for growth hormone is not well established. In spite of some studies show an increase in the rates of MS [24, 25], interestingly, a study has shown an increase in the prevalence of metabolic syndrome in women, but not in men with PH [23]. Some authors verified that patients with hypopituitarism have a higher BMI than the general population [26–28], a factor that is closely related to MS.

Despite the existence of several studies evaluating the metabolic, inflammatory and insulin sensitivity characteristics in patients with PH without GH replacement, the results are still contradictory. With the hypothesis that the BMI could influence these results, it's necessary to make adjustments for BMI to investigate if PH is associated with insulin resistance independently of elevated BMI.

For this reason, we assessed insulin sensitivity as measured by HOMA-IR index in patients with PH without GH replacement and compared to a control group paired by BMI, gender, and age. Additionally, we evaluated some related factors as the inflammatory activity, the frequency of MS, and dyslipidemia diagnosis.

Patients and Methods

Study design

This was a cross-sectional study. We evaluated patients with previous diagnosis of PH, all followed in the tertiary Service of Neuroendocrinology of the clinics hospital of the University of Campinas between the years 2013 and 2015. All patients were on levothyroxine, prednisone, estrogen and progesterone or testosterone replacement and none on GH therapy. We assessed clinical and epidemiological data and fasting blood samples were drawn for glucose, insulin, HbA1c, hs-CRP, and lipid profile. HOMA-IR was calculated as an insulin resistance parameter. Clinical and laboratory characteristics of PH patients were compared with the control subjects. The control group consisted of individuals with normal pituitary function, paired by age, gender and BMI. The study was approved by the local Research Ethics Committee. Written informed consent was obtained from all the participants after full explanation of the study.

Patients

Fifty-four patients older than 18 years with deficiency of all hormone axes of anterior pituitary were included. Thirteen patients did not show up for the exams, leaving 41 patients for analysis. Data regarding age, sex, height, weight, waist and hip measures, diagnosis of hypertension, type 2 diabetes mellitus, and dyslipidemia were assessed. The diagnosis of PH was based on previous measurements of thyroid-stimulating hormone (TSH), free T4 (FT4), prolactin, adrenocorticotrophic hormone (ACTH), basal cortisol, growth hormone (GH), insulin-like growth factor (IGF-1), luteinizing hormone (LH), follicle stimulating hormone (FSH), total and free testosterone (in male patients) or estradiol (in women), and insulin tolerance test for cortisol and GH evaluation. All patients were under standard hormone replacement therapy without GH replacement, dosages were monitored and adjusted as required. Adequate substitution was assumed when medication had not been adjusted for at least six months, patients had no complaints, and basal

hormone levels were within the recommended values [29]. Lipid-lowering, antihypertensive and antidiabetic drugs were started at the discretion of the treating physicians. The diagnosis of MS was confirmed based on the IDF-AHA/NHLBI criteria 2009 [30].

Exclusion criteria were acutely infirm patients, malignant tumors, active inflammatory disease, class III/IV heart failure (NYHA classification), severe hepatic disease (low albumin or increased IRN), advanced kidney disease (stage 4 or 5), patients under hemodialysis, those with psychiatric diseases or with HIV, and/or hepatitis C infection.

Control group

Forty-one individuals without pituitary disease and with normal pituitary function, paired by age, gender and BMI, were recruited as a control group in the same period and following the same criteria for exclusion applied to patients with PH. The individuals were recruited among the relatives of patients from the outpatient neuroendocrinology clinic. Four individuals withdrew consent before exams, leaving our control group with 37 individuals for analysis. The same clinical and laboratory parameters evaluated in the group of patients with PH were assessed in the control group.

Clinical parameters

Clinical data were recorded consisting of age, sex, BMI, waist circumference, waist/hip ratio (WHR), and presence of hypertension (blood pressure > 130/80 mmHg or treatment for this condition), type 2 diabetes mellitus (fasting glycemia > 126 mg/dl on more than two occasions or treatment of the condition) and dyslipidemia diagnosis (abnormal lipid profile or treatment for this condition).

Laboratory measurements

Total cholesterol, HDL and LDL-cholesterol and triglycerides were measured by automated enzymatic method). Hs-CRP was measured by ELISA (Cusabio Biotech Co, Ltd; Wuban, Hubei, China). Sensitivity is the least amount that can be differentiated from zero, no known cross-reactivity. Relative value (RV) > 0.1 mg/dl for inflammatory conditions. Insulin was measured by immunoassay-chemiluminescence (Siemens medical solutions diagnostics, USA), RV: 2.0–28.4 μ U/ml. HbA1c was measured by high performance liquid chromatography method (RV: 4–5.6%) and fasting glycemia by the hexokinase method (RV: 70–100 mg/dl). HOMA-IR was calculated by the formula $\text{insulin} \times \text{glucose} / 22.5$, considering as insulin resistance values ≥ 2.7 .

Statistical analysis

Continuous variables are reported as median (interquartile range) and categorical variables as frequencies (percentages). As continuous variables had a non-normally distribution pattern, nonparametric tests were used. Association between two continuous variables was verified by using the Spearman's correlation coefficient, and between two categorical variables, using the Chi-square test or Fisher's exact test, when the expected counts in one or more cells were less than 5. Differences between medians from two groups were assessed using the Mann-Whitney test.

The influence of PH on MS and dyslipidemia risk was verified by multivariate logistic regression analysis. To assess the influence of

PH on HOMA-IR values we conducted multivariate linear regression models with log-transformed nonlinear variables. All multivariate models had the group (PH or control) as a dependent variable and were adjusted for age, sex, BMI, WHR, HbA1c, hs-CRP, and HOMA-IR values. The Nagelkerke's index was used as a surrogate value for R² values in logistic regression models. Group PH or control was used as a dependent variable to assess the influence of PH in the risk of MS. Analyses were considered statistically significant when p-values < 0.05.

Results

Characteristics of pituitary disease

The etiology of panhypopituitarism was shown in ► **Table 1**. The deficiencies of pituitary hormones, associated diseases and treatment of PH patients compared to control group are listed in ► **Table 2**.

► **Table 1** Etiology of panhypopituitarism.

Variable	Patients with PH (n=41)
Nonfunctioning macroadenomas (postsurgical or not)	16
Macroadenomas produced GH /ACTH (surgically cured)	9
Sheehan's Syndrome	5
Craniopharyngioma	4
Pituitary hypoplasia	3
Cystic tumors of the turcica sella	1
Pineal germinoma	1
Traumatic brain injury	1
Empty sella	1

► **Table 2** Frequency of deficiencies of the pituitary hormones vs treatment and frequency of associated diseases vs treatment in patients and control group.

Variable	Patients with PH (n=41)	Control subjects (n=37)
GH deficiency/treatment	41/0	0/0
ACTH deficiency/treatment	41/41	0/0
TSH deficiency/treatment	41/41	0/0
LH-FSH deficiency/treatment	41/32	0/0
ADH deficiency/treatment	11/11	0/0
Dyslipidemia/treatment	31/31	19/14
Hypertension/treatment	11/11	14/14
Diabetes mellitus/treatment	8/8	11/11

Baseline characteristics of patients and individuals of control group

Our study comprised 41 patients with PH (21 females and 20 males). Median age was 48 years and median BMI 27.2 kg/m². The control group comprised 37 individuals (23 females and 14 males). Median age was 45 years and median BMI was 27.9 kg/m² (► **Table 3**).

Comparative analysis between patients with panhypopituitarism and the control group

The two groups did not present significant differences in age, BMI or waist circumference. Similarly, the frequency of MS, diabetes mellitus and hypertension was not different between groups. We found a significant higher frequency of dyslipidemia and a lower WHR in patients with PH (► **Table 1**).

PH patients had lower fasting glucose and insulin levels, as well as HOMA-IR when compared with the control group. Serum levels of hs-CRP were higher in PH patients (► **Table 4**).

Regression analysis

In multivariate linear regression analysis, we found that PH group independently predicted lower HOMA-IR values (B = -0.787, 95% CI = -0.05, -1.53; p = 0.038) as did lower WHR values (B = 0.102, 95% CI = 0.06; 0.15; p < 0.001).

PH was not a risk factor for MS in the multivariate model (p = 0.3). The only significant factors in this analysis were BMI (OR = 1.345; 95% CI = 1.14–1.59; p < 0.001) and age (OR = 1.062; 95% CI = 1.02–1.11; p = 0.004). Nagelkerke R square value for the multivariate MS risk factor model was 0.4.

In the multivariate logistic regression for dyslipidemia, PH group conferred an increased risk (OR = 3.591, 95% CI = 1.28; 10.08; p = 0.015) and higher BMI values too (OR = 1.154, 95% CI = 1.03; 1.29; p = 0.013). Nagelkerke R square value for this multivariate model was 0.2.

► **Table 3** Clinical characteristics and comparative analysis of patients with PH and the control group.

Variable	Patients PH (n=41)	Control group (n=37)	p-Value
Sex (female)	21 (51.2%)	23 (62.2%)	0.330
Age (years)	48 (35-59)	45 (39.5-59)	0.596
BMI (kg/m ²)	27.2 (23.9-30.4)	27.9 (24.7-31.7)	0.571
Waist circumference (cm)	97 (88.5-103)	99 (88-108)	0.565
Waist/hip ratio (cm)	0.84 (0.8-0.9)	0.91 (0.88-0.95)	<0.001
Hypertension	11 (26.8%)	14 (37.8%)	0.298
Diabetes mellitus	8 (19.5%)	11 (29.7%)	0.294
Dyslipidemia diagnosis	31 (75.6%)	19 (51.4%)	0.026
Metabolic syndrome	27 (65.9%)	22 (59.5%)	0.560

Significance: p < 0.05; Values are shown as median (interquartile range) or number and frequency (percentage); PH: Panhypopituitarism; BMI: Body mass index.

► **Table 4** Laboratory characteristics and comparative analysis of patients with PH and Control group.

Variable	Patients with PH (n=41)	Control subjects (n=37)	p-Value
Blood glucose (mg/dl)	83 (76.5–96)	90 (94.5–101.5)	0.010
HbA1c (mmol/mol)	36.61 (33.33–39.89)	37.7 (36.06–43.71)	0.089
Total cholesterol (mg/dl)	205 (174.5–232.5)	197 (180.5–229)	0.674
HDL-c (mg/dl)	49 (38.5–61.5)	44 (39.5–57)	0.370
LDL-c (mg/dl)	121 (93–147)	115 (99–146.5)	0.944
Triglycerides (mg/dl)	127 (84.5–255.5)	134 (95.5–179.5)	0.829
hs-CRP (mg/dl)	0.38 (0.18–0.69)	0.16 (0.11–0.44)	0.011
Insulin (μU/ml)	3.9 (2–7.7)	8.8 (5.5–15.6)	<0.001
HOMA-IR	0.88 (0.42–1.55)	2.1 (1.32–3.62)	<0.001

Values are shown as median (interquartile range); PH: Panhypopituitarism; hs-CRP: High-sensitivity C-reactive protein; HOMA-IR: Homeostatic model assessment of insulin resistance.

All multivariate models were adjusted for age, sex, BMI, WHR, HbA1c, hs-CRP, and HOMA-IR values.

Discussion

This study evaluated the insulin sensitivity as measured by HOMA-IR index, the inflammatory activity as measured by CRP, the frequency of MS and dyslipidemia in patients with PH without GH replacement when compared to a control group paired by BMI, gender and age. In line with these objectives, our study demonstrated that our patients with PH presented lower HOMA-IR values, glycemia and insulin levels, as well as lower WHR. Furthermore, the inflammatory activity and the frequency of dyslipidemia diagnosis were higher in patients with PH. On the other hand, the frequency of MS was similar in PH patients and the individuals with normal pituitary function. We highlighted that PH independently predicted lower HOMA-IR, WHR values and dyslipidemia diagnosis.

When we talk about glycemic metabolism in PH, we should say it is well known that patients with PH are more prone to episodes of hypoglycemia [31]. Thus, we found a significantly lower HOMA-IR, fasting glucose and insulin values in patients with PH when comparing with our control group. This result could be a consequence of the absence of insulin counter-regulators hormones such as cortisol and GH that decreases the hepatic glucose production [32, 33]. Another explanation for these findings would be that the decrease of serum IGF-1 present in these patients would lead to increased expression of the IGF-1 receptor and binding of insulin to IGF-1 receptors would justify the lower blood insulin levels found in our patients. Additionally, as already described, the action of insulin in the signaling pathway of IGF-1 to control glucose metabolism leading to lower values of blood glucose, which would result in lower values of HOMA-IR [34]. Besides that, our patients with PH showed lower WHR than the control group, a known clinical marker indicative of IR. It is known that WHR is positively correlated with obesity and worsened insulin sensitivity as already demonstrated in twins discordant for obesity [35]. With regard to this last point, the finding of PH as an independent predictor of HOMA-IR even

after adjustment for WHR values suggests that panhypopituitarism alters the relationship between BMI with insulin sensitivity.

Few studies have evaluated insulin sensitivity in patients with PH under hormonal replacement, except for growth hormone and results are discordant. Some studies did not find differences regarding the insulin and glycemia levels in these patients [4, 36]. Although the only study with a hyperinsulinemic euglycemic clamp in patients with PH demonstrated a decrease in insulin sensitivity, baseline glycemia and insulin levels were similar to the control group [5]. On the other hand, several authors have demonstrated in humans and animals that GH deficiency is not associated with decreased insulin sensitivity, similarly to our study [37, 38]. Evidencing the importance of pairing by BMI, one study demonstrated worsening of insulin sensitivity in women with hypopituitarism compared to the control group when the groups were not matched by BMI. After BMI pairing insulin sensitivity was similar in both groups [39]. Besides that, other authors have demonstrated that the withdrawal of GH replacement in patients with PH induces an improvement in insulin sensitivity [40]. As in our study, the absence of GH replacement in patients with PH, besides decreasing insulin and glycaemia levels, increases CRP levels.

The higher inflammatory activity observed in our PH patients has already been demonstrated [36]. There is evidence that GH, which is reduced in patients with PH, can indirectly regulate CRP [41]. In the same way, a clinical study compared patients with GHD under GH replacement, in which one group was kept on GH, while the other was switched to placebo. The authors verified an increase in hs-CRP levels and deterioration of lipid profile in the placebo group, but also to concomitant improvements in HbA1c and insulin sensitivity [40], similarly to our findings of higher serum hs-CRP levels and lower HOMA-IR values. Regarding the highest values of CRP in patients with PH, it would be important to say that they could have a gender influence, since it is known that women with PH present greater inflammatory activity when compared to men with the same disease [39].

We found a significantly higher frequency of dyslipidemia diagnosis in patients with PH as has already been documented. Some

authors have demonstrated that changes in liver regulation and expression of LDL receptors are influenced by GH, which could at least partially justify our findings, since no patients were under GH replacement [42, 43]. Other pituitary hormone deficiencies can also contribute to altered lipid metabolism. For instance, it is known that thyroid and sex hormones may interfere with the dyslipidemia rates [44, 45]. In this context, it would be important to point out that all our patients with PH and control subjects who had dyslipidemia diagnosis were on lipid-lowering treatment, this treatment change the real values of cholesterol and triglycerides; for this reason, we analyzed the frequency of dyslipidemia diagnosis. Although some studies showed no differences between the effects of prednisone and hydrocortisone therapy on lipid profile [46], the influence of a non-physiological hormone replacement on our data cannot be ruled out, like in all studies in these kind of patients.

Even after correction by age, gender, hs-CRP and BMI, the PH group independently predicted lower values of HOMA-IR and an increased risk of dyslipidemia, data not found in the literature. These results suggest that the lower HOMA IR and dyslipidemia could be a characteristic of our group of patients with PH.

Previous studies report that the prevalence of MS is higher in PH patients without GH replacement compared with the general population [24, 25, 47]. Similarly, the frequency of MS in our patients with PH was higher than the prevalence in the Brazilian general population [48]. Despite the elevated frequency of MS (65%) in our patients with PH, the values were similar to those in the control group, probably because both groups had equivalent BMI and age. Likewise, it has already been shown that obesity is a strong predictor of MS in PH [49]. Our result is different from that found in a study with Sheehan's syndrome, where the authors showed that PH patients had higher prevalence of MS than the control group with similar age and BMI, however, in this study; they only used women [4]. Another study with 515 patients showed increased prevalence of metabolic syndrome only in women with PH, not in men, when compared to the control group, but this is a retrospective study and the patients with PH had BMI higher than the control group, which knowingly influences the results [23]. In addition, it is known that women with PH have higher mortality rates than men [13]. Probably the variations in the concentrations of the sex hormones are responsible for the differences between men and women [50, 51].

A limitation of this study was the relatively small sample size, resulting of a selective recruitment, due the inclusion only of patients with complete anterior pituitary hormone deficiency. Another limitation of our study is the use of HOMA-IR as method for the evaluation of insulin sensitivity. Although it is an accepted and validated method, it is not the gold standard for the evaluation of insulin sensitivity. There are few studies relating insulin sensitivity, inflammatory markers and MS with PH, the majority of them conducted in patients with isolated GH deficiency and fewer had a paired control group by BMI. The main strength of our study was the inclusion of patients with complete anterior pituitary hormone deficiency and the presence of a control group similar in age, gender and BMI, as these features exert great influence on the studied hormonal and metabolic variables [39, 49].

Conclusions

In conclusion, we have demonstrated that patients with PH without GH replacement presented lower HOMA-IR values and WHR when compared with individuals with normal pituitary function paired by BMI, gender, and age. Additionally, PH independently predicted lower HOMA-IR. On the other hand, patients with PH presented higher frequency of dyslipidemia diagnosis when compared to individuals in the control group and in addition, PH group independently predicted increased risk of dyslipidemia. The frequency of MS was similar between the groups. Further studies are needed to confirm our findings and to better understand the metabolic characteristics of patients with PH.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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