Diabetes mellitus in a cohort of patients with acromegaly

Diabetes melito em uma coorte de pacientes com acromegalia

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ABSTRACT

Objectives: To evaluate the presence of *diabetes mellitus* (DM) in a cohort of patients with acromegaly. **Methods:** This was a cross sectional study. **Results:** Fifty-eight acromegalic patients were assessed. Only 29% met the criteria for cure, and 27% had the disease controlled. Twenty-two had DM; HbA1c was equal to 7.34 ± 2.2%. Most of the diabetic patients (18 out of 22, 82%) did not meet criteria for cure. They were more often hypertensive [16/22 (73%) *vs.* 17/36 (46%), p = 0.04], and used statins more frequently [14/22 (64%) *vs.* 8/36 (21%), p = 0.004]. After regression analysis, hypertension was associated with diabetes [odds ratio (OR): 9.28 (95% CI: 1.59 – 54.00), p = 0.01], and cured/controlled acromegaly was associated with protection against the presence of diabetes [OR: 0.17 (95% CI: 0.03 – 0.78), p = 0.02]. **Conclusions:** The presence of DM was associated with active acromegaly and presence of hypertension. However, absolute levels of GH and IGF-1 did not differ between patients with and without diabetes. Arq Bras Endocrinol Metab. 2011;55(9):714-9

Keywords
Acromegaly; *diabetes mellitus*; growth hormone

RESUMO

Objetivos: Avaliar a presença de diabetes melito (DM) em uma coorte de acromegálicos. **Métodos:** Este é um estudo transversal. **Resultados:** Cinquenta e oito pacientes acromegálicos foram analisados. Apenas 29% preencheram critérios de cura e 27% estavam com a doença controlada. Vinte e dois pacientes (38%) apresentaram DM, HbA1c 7,34 ± 2,2%. Destes, 18 não preencheram critérios de cura. Pacientes com DM foram mais frequentemente hipertensos [16/22 (73%) *vs.* 17/36 (46%), p = 0,04] e usavam mais estatina [14/22 (64%) *vs.* 8/36 (21%), p = 0,004]. Após regressão múltipla, hipertensão foi associada a DM [razão de chances (RC): 9,28 (95% CI: 1,59 – 54,00), p = 0,01], e acromegalia curada/controlada foi fator protetor para presença de diabetes [OR: 0,17 (95% CI: 0,03-0,78), p = 0,02]. **Conclusões:** A presença de DM esteve associada com acromegalia ativa e com a presença de hipertensão. No entanto, os níveis absolutos de GH e IGF-1 não diferiram entre aqueles com e sem diabetes. Arq Bras Endocrinol Metab. 2011;55(9):714-9

Descritores
Acromegalia; diabetes melito; hormônio do crescimento

INTRODUCTION

Impaired glucose tolerance (IGT) or overt *diabetes mellitus* (DM) are well-recognized comorbidities in patients with acromegaly (1,2), and found in up to 50% of cases at diagnosis (1,3). The abnormality responsible for the presence of diabetes and IGT include hepatic and peripheral insulin resistance, as well as increased hepatic glucose production (1,2,4).

One of the main metabolic functions of growth hormone (GH) is lipolysis, with consequent increase in circulating free fatty acids (FFAs), which compete for the glucose binding sites in muscle, inhibiting the uptake of serum glucose, and producing insulin resistance in muscles (5). In addition, GH stimulates gluconeogenesis, and inhibits the activity of muscle glycogen synthase (6).

Insulin resistance is a generally accepted risk factor for cardiovascular disease, and thus, hyperinsulinemia, IGT and DM may contribute to the observed increase in cardiovascular morbidity and mortality in acromegaly (1,7,8). Additionally, it is well documented that control of the disease improves glucose homeostasis (9-13) and reduces cardiovascular morbidity risk (12,13).

The prevalence of glucose intolerance in acromegaly has been shown to correlate with GH levels, age, disease duration, and family history for diabetes (3). Therefore, all these are confounding factors, should be taken into account when patients with acromegaly and diabetes are evaluated. Furthermore, somatostatin analogues (SSAs), which are largely used for medical treatment of acromegaly, may exert a negative effect on glucose homeostasis. They alter beta-cell function by inhibiting insulin secretion (14).

The objective of this article was to describe the frequency and factors associated to the DM in a cohort of acromegalic patients followed up at Hospital de Clínicas de Porto Alegre (HCPA).

PATIENTS AND METHODS

A cross-sectional study was conducted to evaluate the presence of DM and the metabolic profile of a cohort of patients with acromegaly, in the Neuroendocrinology outpatient practice of the Endocrinology Division at the HCPA. All patients included in this sample were seen, at least once a year, between 2009 and 2010. This study was approved by the Ethics Committee of the HCPA. All patients provided written informed consent.

The criteria used to define that the disease was cured were those suggested by the 2000 consensus (15): IGF-1 lower than the upper limit for age and sex, and GH nadir lower than 1 ng/dL, during the oral tolerance test with an overload of 75 g of glucose, in the absence of medication to control acromegaly. The disease was considered controlled when patients using medication to control acromegaly showed normal IGF-1 for age and sex.

The patients were examined and followed up according to the usual routine at the Neuroendocrinology outpatient practice. Blood pressure (BP) was measured twice using an aneroid sphygmomanometer, with appropriate cuff size in Korotkoff phases I and V, recording readings closest to the mark in a 2-mm range. The two measurements were performed in a 1-minute interval, with the patient in a sitting position, and after a 5-minute rest. Patients were considered hypertensive if systolic blood pressure was higher than 140 mmHg, or diastolic blood pressure was higher than 90 mmHg in two consecutive measurements at the office, confirmed by measurements at home or preview history of antihypertensive medication.

Patients wore light clothes and no shoes for weight and height measurements. An anthropometric scale was used, and body mass index (BMI) was calculated as weight (kg)/height (m) squared. Waist circumference was measured with a flexible tape measure placed on a horizontal plane, at the level of the iliac crest.

The defining criterion for the presence of microalbuminuria was urinary albumin excretion (UAE) greater than 17 mg/L in two samples of urine, or greater than 30 mg in two 24-hour urine collections at intervals of up to 6 months, in the absence of interfering factors. Albuminuria was measured by immunoturbidimetric assay using a commercial kit (Microalb; Ames-Bayer, Tarrytown, NY, USA), with urine samples with concentrations between 30 and 100 mg/L. Intra and inter-assay coefficient of variation (CV) was less than 6% for both tests (16).

Diabetes mellitus diagnosis was based on the criteria by the American Diabetes Association (17). HbA_{1c} was measured by high performance liquid chromatography, on a Merck-Hitachi 9100 chromatographer using a cation-exchange column. Reference value (RV) was lower than 6.0%. Glucose was measured by the UV kinetic method with hexokinase, in a Dimension RXL Dade Behring analyzer. Sensitivity of the method was 0.80 mg/dL, with inter and intra-assay CV were equal to 1.4% and 2.82%, respectively; and RV was 70-99 mg/dL.

Serum creatinine was measured using the Jaffe method, and the lipid profile was determined by an enzymatic colorimetric method. LDL cholesterol was calculated using the Friedewald equation.

IGF-1 dosage was performed by an immunoradiometric assay (commercial kit of Diagnostic Systems Laboratories, Inc, Webster, TX). The sensitivity of the method was 0.80 ng/dL. The inter-assay CV ranged from 1.5 to 8.2%, and the intra-assay CV ranged from 1.5 to 3.4%. RV for IGF1 for men, in ng/mL, were: 18 to 20 years old, 197-956; 20 to 23 years old, 215-628; 23 to 25 years old, 169-591; 25 to 30 years old, 119-476; 30 to 40 years old, 100-494. RV for IGF1 for women were: 18 to 20 years

old, 193-575; 20 to 23 years old, 110-521; 23 to 25 years old, 129-480; 25 to 30 years old, 96-502; 30 to 40 years old, 130-354. After the age of 40, the same RV were used for both sexes: 40 to 50 years old, 101-303; and 50-70 years old, 78-258.

GH was determined by chemiluminescence (commercial kit of Diagnostic Products Corporation (DPC), Los Angeles, CA, with IMMULITE® analyzer 1000). The sensitivity of the method was 0.01 ng/mL, inter and intra-assay CV were, respectively, 6.2% and 6.5%.

Insulin measurement was done by chemiluminescence (commercial kit of DPC, with IMMULITE® analyzer 2000). Sensitivity of this method was 2 mcUI/mL with inter and intra-assay CV of 4.9% and 3.9%, respectively, and RV of 6-27 mcUI/mL.

Insulin resistance was estimated by the Homeostasis Model Assessment, determined by the formula: HOMA-IR = [fasting insulin (pmol/l) x fasting plasma glucose (mmol/l)]/22.5.

STATISTICAL ANALYSIS

Data were presented as means ± standard deviations, absolute values, percentages and medians with percentiles ranging from 25 to 75. Chi-square test, Student's t test, and Mann-Whitney test were used. Two models of multiple logistic regression were performed, considering the presence of diabetes as the dependent variable. The independent variables were chosen based on their biological relevance and statistical significance from univariate analysis: age, status of acromegaly (cured *vs.* active disease), hypertension, and SSAs use, for model 1; and age, status of acromegaly (cured + controlled *vs.* active disease), hypertension, and SSAs use, for model 2. The analyses were performed using the Statistical Package for Social Sciences (SPSS 16.0 for Windows, Chicago, IL).

RESULTS

Fifty-eight patients with acromegaly were analyzed. Mean age was 55 ± 12 years, and 31 patients (54%) were women. Fifty-four (91%) patients underwent at least one transsphenoidal tumor resection, one underwent transcranial resection, and 11 (19%) were submitted to radiotherapy (RT). Seventeen patients (29%) met the criteria for cure, while 16 (27%) had the disease controlled with pharmacological therapy for acromegaly; 25 presented IGF-1 levels that showed that the disease was not controlled. Eight patients (12%) were using cabergoline, 38 (64%) were using long-acting release octreotide (LAR), and three (5%) were under treatment with pegvisomant.

Twenty-two patients (38%) had DM: 10 were under treatment with metformin, and one with insulin, while the other 11 patients received only nutritional orientation. Mean HbA_{1c} among DM patients was 7.34 ± 2.2%; 82% of them (18 out of 22) did not meet the criteria for cure.

Table 1 shows clinical characteristics of the patients according to the presence of diabetes. Patients with DM were more often hypertensive (73% *vs.* 46%, p = 0.04), and used statins more frequently (64% *vs.* 21%, p = 0.004) compared with those without DM. As predicted, DM patients had superior fasting glucose levels.

Table 1. Clinical characteristics of acromegalic patients, according to the presence of diabetes

	With DM (N = 22)	Without DM (N = 36)	p
Age (years)	56 ± 13	55 ± 11	0.60
Male	10 (45)	17 (46)	0.97
Hypertension	16 (73)	17 (46)	0.04
SBP (mmHg)	137 ± 23	127 ± 15	0.17
DBP (mmHg)	86 ± 16	81 ± 10	0.25
Statins	14 (64)	8 (21)	0.004
BMI (kg/m²)	30 ± 4	28 ± 6	0.31
Waist circumference	101 ± 9	94 ± 10	0.10
Fasting glucose (mg/dL)	117 ± 45	94 ± 11	0.004
Hb_{A1c}(%)	7.3 ± 2.2	-	-
Insulin (mcUI/mL)	6.6 (2.8-15.2)	4.0 (1.8-7.4)	0.08
HOMA-IR	1.1 (0.8-5.0)	0.8 (0.5-1.5)	0.20
Total cholesterol (mg/dL)	213 ± 52	192 ± 41	0.30
HDL cholesterol (mg/dL)	45 ± 8	56 ± 16	0.16
LDL cholesterol (mg/dL)	98 ± 57	114 ± 35	0.38
Triglycerides (mg/dL)	132 (91-175)	99 (72-138)	0.06
IGF-1 (ng/mL)	351 (97-453)	226 (162-426)	0.85
Basal GH (ng/mL)	1.4 (0.56-2.35)	1.5 (0.38-4.37)	0.94
Creatinine (mg/dL)	0.83 (0.76-1.07)	0.83 (0.67-0.96)	0.52
UAE (mg/min)	3.6 (0.0-23.05)	0 (0.0-15.30)	0.41
Cure (%)	4 (25)	13 (50)	0.10
Cure + controlled (%)	9 (40.9)	24 (66.7)	0.05

Data expressed as mean ± SD, number of patients (%), or median (P25-P75%). SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; HOMA-IR: Homeostasis Model Assessment; IGF-1: Insulin-like Growth Factor 1; GH: growth hormone; UAE: urinary albumin excretion.

Patients without DM were more often cured or had the disease controlled than DM patients (66.7% *vs.* 40.9%, p = 0.05), with borderline significance. There was no difference regarding age, BMI, waist circumference, insulin, IGF-1, basal GH, creatinine, and UAE levels. Pharmacological therapy for acromegaly did not differ between patients with and without DM: cabergoline (4.5% *vs.* 16%, p = 0.18), octreotide-LAR (64% *vs.* 59.5%, p = 0.75, and pegvisomant (9% *vs.* 3%, p = 0.21). There was also no difference associated with RT (23% *vs.* 16%, p = 0.53). However, DM patients underwent transsphenoidal surgery for acromegaly control more often (97% *vs.* 82%, p = 0.04) than patients without DM.

Multiple regression analysis was performed in order to establish factors associated with DM. Table 2 shows all logistic regression models. The dependent variable was the presence of DM, and the independent variables were age (biological importance), acromegaly status after treatment (cured or not cured, patients with controlled disease were not included in this phase), presence of hypertension, and SSAs use (model 1). After regression analysis, hypertension was associated with diabetes [odds ratio (OR): 8.3 (95% CI: 1.4-48), p = 0.02], and cure was associated with the absence of the diabetes [OR: 0.10 (95% CI: 0.02 – 0.68), p = 0.02]. This association was independent of age and SSAs use. When patients with controlled disease were included in the same group of cured subjects (model 2), similar results were observed: hypertension was associated with diabetes [odds ratio (OR): 9.28 (95% CI: 1.59 – 54), p = 0.01], and acromegaly cure was associated with absence of diabetes [OR: 0.17 (95% CI: 0.03 – 0.78), p = 0.02], independent of age and SSAs use.

Table 2. Odds ratio for presence of diabetes in the cohort of the acromegalic patients

	OR (CI: 95%)	p
Model 1		
Age	0.99 (0.92-1.0)	0.73
Acromegaly status*	0.10 (0.02-0.68)	0.02
Hypertension	8.3 (1.4-48)	0.02
SSAs	3.0 (0.7-11)	0.11
Model 2		
Age	1.0 (0.94-1.07)	0.92
Acromegaly status**	0.17 (0.03-0.78)	0.02
Hypertension	9.28 (1.59- 54)	0.01
SSAs	2.32 (0.58-9.28)	0.23

* Cured acromegaly *vs.* Active disease; ** Cured + controlled acromegaly *vs.* active disease; SSAs: somatostatin analogues.

DISCUSSION

Previous studies reported the prevalence of diabetes as being around 19% to 56%, depending on the population (1). A Brazilian series of cases of acromegalic patients showed a prevalence of 23% for DM (18), in contrast with 38% in the present study.

Prevalence of DM was higher in patients with active acromegaly. Hypertension and use of statins were more frequent in DM patients than in non-DM patients. However, absolute levels of GH and IGF-1 did not differ between these two groups of patients. Patients' mean age (55 years old) was similar to previous reports, ranging from 40 to 50 years of age (4).

Data in the literature concerning the use of dopaminergic agonists and glucose homeostasis in acromegalic patients are scarce (2). Pegvisomant has had favorable outcomes regarding glucose control in acromegalic patients (2). Cabergoline was used in seven subjects and pegvisomant in three individuals. Although 35 patients were on SSAs, there was no association between SSAs use and the presence of diabetes. In fact, previous studies about SSAs reported inconsistent results regarding glucose metabolism (19), and a meta-analysis suggested minor clinical impact of this class of drugs on glucose homeostasis of acromegalic patients (20). Somatostatin is a potent inhibitor of insulin and glucagon release from pancreatic islets. Tzanela and cols. recently reported a negative effect on pancreatic beta-cell function in acromegalic patients whose disease was controlled by SSAs (21).

Nabarro (22) showed that age, higher GH levels and longer course of disease were risk factors for decreasing glucose tolerance. Growth hormone levels were 19 times above the normal upper limit in acromegalic DM patients, compared with a 10-time increase in patients without DM. Patients with DM were 5 years older at the diagnosis of acromegaly (38 *vs.* 33 years), and had 3.7 more years of diagnosed acromegaly. In contrast, only active acromegaly was associated with the presence of DM in this cross-sectional study.

In acromegaly, the co-existence of diabetes and hypertension has been associated with more severe damage to cardiac function, and even with higher risk of cardiovascular death (1,23). An important association between DM and hypertension, independent of the status of acromegaly and age, was found in this cohort. Higher frequency of hypertension in DM patients (77%) was observed in this study, in contrast with

the frequencies reported by Espinosa-de-los-Monteros and cols. (24) and by Colao and cols. (23), 59.7% and 46.6%, respectively.

In contrast with the general population (25), age was not associated with presence of diabetes in this sample. Our patients with diabetes had same age of non-diabetic patients, especially because most of our sample was made up of older people. A large observational study (26) with 206 acromegalic patients suggested superior diabetes incidence in females, another association that was not found in the present study.

Previous reports in the literature (27) showed superior prevalence of diabetes in patients who were not cured by transsphenoidal surgery. In a study with 66 patients with acromegaly (28), normal post-surgery IGF-1 values were more suggestive of insulin sensitivity than random GH measure. Another study (2) reported that fasting glucose and insulin increase in patients with acromegaly returned to normal values after curative transsphenoidal surgery. These data are similar to our result; diabetes was associated with acromegaly activity, confirming the importance of achieving acromegaly control to prevent metabolic complications such as diabetes.

The criteria for cure suggested by Giustina and cols. (15) were applied because they had been previously used in this cohort (28). Nonetheless, four patients changed category (from cured to not cured) due to the application of new criteria recently reported in the last consensus (29), which did not alter the association between diabetes and active disease.

Cardiovascular disease is responsible for 60% of deaths in patients with acromegaly (13,30). Alterations in glucose metabolism should be carefully evaluated and treated, as they may be implicated in the high mortality of these patients caused by cardiovascular disease (23,30,31).

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