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# Evaluation of Glucose Metabolism in Women with Prolactinomas

Adilson Lamounier Filho[1], Rafaela Marchon de Sousa[2] Mariana Coelho Botelho[2], João Bosco Nascimento[2], Erika Cesar de Oliveira Naliato[3] and Alice Helena Dutra Violante[4*]

1 Department of Clinical Medicine Endocrinology, Federal University of Espirito Santo, Vitoria, Brazil

2 Department of Medicine-Scientific Initiation Program, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

3 Department of Medicine, Ricardo AT Castilho Center of Studies-Teresopolis Medical Association, Teresopolis, Brazil

4 Department of Clinical Medicine-Endocrinology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

***Corresponding author:**
Alice Helena Dutra Violante

aliceviolante@hucff.ufrj.br

Department of Clinical Medicine-Endocrinology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

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## Abstract

Prolactin (PRL) affects many organic functions, including metabolism control, glucose tolerance, and insulin resistance. This study aimed at evaluating the relationship between PRL and basal glucose metabolism in 17 women with microprolactinomas. Fasting glycemia, insulin, Homeostatic Model Assessment-Insulin Resistance (HOMA-IR), and Homeostatic Model Assessment-beta (HOMA-beta) were evaluated in six non-diabetic non-obese patients with Normoprolactinemia (NPRL), 11 with hyperprolactinemia (EPRL), and 11 healthy controls. Patients were also compared according to dopamine agonist use and menstrual status. Normo and hyperprolactinemic patients and controls had serum PRL levels of 15.5 ± 8.3 vs 73.5 ± 44.9 vs 13.8 ± 5.7 ng/mL, respectively. Glycemia, insulinemia, HOMA-IR and HOMA-beta were not statistically different between these three groups (p:0.3359, 0.8951, 0.8681, and 0.2098, respectively). The four variables did not correlate with PRL levels.

Metabolic parameters did not differ between eumenorrheic and oligomenorrheic women (p:0.1247, 0.2994, 0.1954, and 0.1767 for glycemia, insulinemia, HOMA-IR, and HOMA-beta, respectively). Bromocriptine (BC) users showed lower fasting glycemia than non-users of dopamine agonist (p=0.0021). We concluded that hyperprolactinemia did not result in impairment of glucose metabolism in women with prolactinoma.

**Keywords:** Prolactin; Glucose metabolism; Insulin resistance; Hypogonadism

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## Introduction

Prolactin secreting pituitary tumors (prolactinomas) is the main cause of pathologic hyperprolactinemia. Their clinical manifestations are prompted by prolactin excess (PRL), a hormone which secretion is inhibited by hypothalamic dopamine [1].

PRL has pleiotropic effects, influencing lactation, reproduction, osmoregulation, behavior, immune regulation, growth and metabolism [2]. Binding with its receptor (PRLR) results mainly in the activation of the JAK/STAT pathway [3]. However, other pathways, such as the Insulin Receptor Substrate 1 (IRS-1), Phosphoinositide 3'-Kinase (PI3K), and MAP-Kinase (MAPK) can also be activated in different cell lines [4,5]. Moreover, PRL can increase expression of genes related to growth and differentiation and decrease the expression of those related to apoptosis.

One of PRL target organs is the pancreas, with stimulation of beta-cell proliferation, increase in insulin production due to transcription gene induction at the islets, decreased in glucose response threshold and increased beta cell binding [6-9]. PRL and glucose seem to act synergistically on insulin gene expression stimulation. PRL can induce glucose intolerance, hyperinsulinemia and insulin resistance, in animals and humans, increasing the risk of obesity, Diabetes Mellitus and Metabolic Syndrome [10,11].

On the other hand, Bromocriptine (BC), a dopamine receptor agonist (DA) used for the treatment of prolactinomas, reduces

insulin resistance by lowering PRL central levels, and inhibits leptin secretion by the adipocytes *via* sympathetic nervous system suppression [12].

Considering the above, the PRL can regulate glycemic metabolism. In this sectional study, we assessed basal glycemia and insulinemia in non-diabetic non-obese Brazilian women with prolactinomas and hyper-or normoprolactinemia.

# Methods

We selected 17 patients with microprolactinoma that had regular follow-up visits at the Endocrinology outpatient clinics of Hospital Universitario Clementino Fraga Filho (HUCFF), during 1 year period. The study was developed by the Hyperprolactinemia Research Line of the Endocrinology Post-graduation Program of Faculdade de Medicina-Universidade Federal do Rio de Janeiro-UFRJ- Brazil. The average follow-up time corresponded to 58.7 months. All patients who agreed to participate in the research signed an informed consent form.

Women with diagnosis of prolactinoma were studied (symptoms+pituitary tumor<10 mm evidenced in computed tomography or magnetic resonance+PRL ≥ 100 ng/mL in basal dosage and/or PRL tumor positivity on immunohistochemistry). Patients with previous diagnosis of Diabetes Mellitus or glucose intolerance, use of medications or other situations that could lead to alterations on the gluco-insulin metabolism, non-compensated deficiency of pituitary hormones, obesity (Body Mass Index (BMI) ≥ 30 kg/m$^2$), age under 18 years, and menopause (amenorrhea in more than 6 months and FSH ≥ 30 mUI/mL) were excluded from the protocol.

Patients were compared to a control group of 11 non-diabetic non-obese women. This study had the approval from the Research Ethics Committee of the Faculdade de Medicina and HUCFF-UFRJ-Brazil.

## Methodology

In this sectional study, the clinical-biochemical data of women with prolactinoma and controls were compared. Patients were divided into subgroups. PRL levels (normoprolactinemia: PRL ≤ 25,0 ng/mL, hyperprolactinemia: PRL>25 ng/mL), gonadal function (eumenorrheic: eight or more menstrual cycles/year and regular menses in the three months prior to inclusion in the study; oligomenorrheic: less than eight cycles/year with menstrual irregularity in the three months prior to inclusion in the study), and DA use by the time of study insertion (Bromocriptine-BC, Cabergoline-CB, or DA absence). The subgroups were compared between each other and with the control group.

## Variables

The demographic variables analyzed in the study were: Age (years), time of prolactinoma diagnosis (months), weight (in kg, measured with Welmy® mechanical scale), calibrated in a 0,1 kg scale, with the patient wearing light clothes), height (cm, evaluated on a 0,5 cm scale stadiometer), waist circumference (WC-larger abdominal circumference, in cm, measured on a 0.1 cm scale), hip circumference (measured at the level of the acetabular line, in cm, on a 0.1 cm scale), Body Mass Index (BMI) calculated by the formula: Weight (kg)/height(m$^2$) and Waist-to-Hip Ratio (WHR).

The laboratory variables analyzed were: PRL (ng/mL), fasting glucose (mg/dL), fasting insulin (µUI/mL), HOMA-IR and HOMA-beta indices. The HOMA-IR was obtained by the formula: (fasting glucose (mMol/L) × fasting insulin (µUI/mL)/22.5) and the HOMA-beta, by the formula: (20 × fasting insulin (µUI/ mL)/(fasting glucose (mMol/L)-3.5)) [13].

## Statistical analysis

To compare numerical variables between two groups, student's t-test was used, for samples with normal distribution, or the Mann-Whitney test (non-parametric). To compare numerical variables between three (or four) groups, one-way Analysis Of Variance (ANOVA) or Kruskal-Wallis (non-parametric) was executed; multiple groups were compared with Tukey's multiple comparisons test (parametric) or the corresponding non-parametric test was used.

Categorical variables were compared using the chi-square or Fisher's exact test. Spearman and Pearson correlation coefficients were used to measure the relationship between numerical variables. Statistical significance was set as the 95% level ($p<0.05$).

# Results

## General characteristics of patients with microprolactinoma

The clinical and biochemical data of the 17 women with microprolactinoma evaluated in the present study **(Table 1)**. Their mean age corresponded to 40.18 years ± 8.13 years, and the time since diagnosis was 62.8 months ± 35.9 months, while mean weight was 63.1 kg ± 8.8 kg, BMI 24.86 ± 2.81 kg/m$^2$, WC 87.3 cm ± 6.7 cm, hip 100.3 cm ± 6.9 cm, and WHR 0.87 ± 0.04. In the biochemical analysis, the following mean values were found: PRL 50.64 ± 44.96 ng/mL, fasting glucose 85.8 ± 7.9 mg/dL, fasting insulin 7.70 ± 2.65 mUI/mL, HOMA-IR 1.65 ± 0.64, HOMA-beta 139.9 ± 75.41, Follicle-Stimulating Hormone (FSH) 10.22 ± 17.19 mIU/mL, Luteinizing Hormone (LH) 8.77 ± 12.98 IU/L, Estradiol 81.16 ± 62.38 pg/mL, Growth Hormone (GH) 0.53 ± 0.44 ng/mL, and Insulin-like Growth Factor 1 (IGF-1) of 247.7 ± 89.59 µg/L. Regarding pharmacological treatment, five patients were receiving BC, five CB, and seven were not undergoing DA treatment at the time of the evaluation. Three patients had been surgically treated *via* transsphenoidal approach.

## Comparison between patients and controls

The patient group was significantly older than the control (40.18 ± 8.13 *vs* 32.45 ± 7.42 years, respectively, p=0.0175). WC (87.32 ± 6.68 *vs* 79.32 ± 12.36 cm, p=0.0349) and WHR (0.87 ± 0.05 *vs* 0.80 ± 0.09; p=0.0099) were higher in patients. However, the groups did not have any relevant difference in terms of weight, BMI, or hip circumference.

**Table 1:** Clinical-biochemical data of women with microprolactinoma and controls.

| Variable | Groups | Average | Standard deviation | Minimum value | Maximum value | p |
|---|---|---|---|---|---|---|
| **Age (years)** | Patients | 40.18 | 8.13 | 28 | 49 | 0.0175 |
| | Controls | 32.45 | 7.42 | 20 | 43 | |
| **Weight (kg)** | Patients | 63.13 | 8.8 | 45.9 | 77.2 | 0.9403 |
| | Controls | 62.82 | 8.32 | 52 | 72.4 | |
| **BMI (kg/m²)** | Patients | 24.86 | 2.82 | 18.95 | 29.06 | 0.6704 |
| | Controls | 24.33 | 3.76 | 19.1 | 29.93 | |
| **Waist (cm)** | Patients | 87.32 | 6.68 | 74 | 98.5 | 0.0349 |
| | Controls | 79.32 | 12.36 | 63 | 99 | |
| **Hip (cm)** | Patients | 100.3 | 6.9 | 85 | 115 | 0.6999 |
| | Controls | 99.2 | 7.4 | 89 | 113 | |
| **WHR** | Patients | 0.87 | 0.05 | 0.76 | 0.96 | 0.0099 |
| | Controls | 0.8 | 0.09 | 0.69 | 0.96 | |
| **PRL (mg/mL)** | Patients | 50.64 | 44.96 | 8.1 | 165.4 | 0.0014 |
| | Controls | 13.82 | 5.74 | 5.4 | 22.7 | |
| **Glucose (mg/dL)** | Patients | 85.76 | 7.88 | 69 | 99 | 0.1366 |
| | Controls | 81.27 | 7.02 | 71 | 94 | |
| **Insulin (µUI/mL)** | Patients | 7.7 | 2.65 | 3.42 | 13.94 | 0.7904 |
| | Controls | 7.44 | 2.34 | 4.3 | 11.1 | |
| **HOMA-IR** | Patients | 1.65 | 0.64 | 0.66 | 3.41 | 0.6058 |
| | Controls | 1.52 | 0.6 | 0.8 | 2.58 | |
| **HOMA-β** | Patients | 139.9 | 75.4 | 75.3 | 292.2 | 0.0817 |
| | Controls | 155.7 | 46.7 | 110 | 271.8 | |
| **FSH (UI/L)** | Patients | 10.22 | 17.19 | 1.14 | 74.5 | 0.397 |
| | Controls | 6.9 | 6.9 | 1.2 | 20.9 | |
| **LH (mUI/mL)** | Patients | 8.77 | 12.98 | 1.5 | 57 | 0.2688 |
| | Controls | 11.17 | 18.49 | 0.8 | 56.7 | |
| **Estradiol (pg/mL)** | Patients | 81.16 | 62.38 | 20 | 22 | 0.7201 |
| | Controls | 81.29 | 63.36 | 18.9 | 196 | |
| **GH (ng/mL)** | Patients | 0.53 | 0.44 | 0.07 | 1.48 | 0.0028 |
| | Controls | 1.76 | 1.17 | 0.22 | 3.75 | |
| **IGF-1 (µg/L)** | Patients | 247.7 | 89.59 | 99.4 | 375.1 | 0.8659 |
| | Controls | 253.3 | 75.27 | 163.5 | 428.6 | |

As expected, mean PRL was significantly higher in patients (50.64 ± 44.96 ng/mL) than controls (13.82 ± 5.74 ng/mL, p=0.0014). The opposite was observed in relation to GH, considerably higher in the control group (1.76 ± 1.17 *vs* 0.53 ± 0.44 ng/mL, p=0.0028). Other laboratory values, such as fasting glucose, fasting insulin, HOMA-IR, HOMA-beta, FSH, LH, estradiol and IGF-1, did not differ significantly among groups.

## Comparison according to prolactin level

Among prolactinoma patients, six had normal PRL levels (NPRL: 15.25 ± 6.924 ng/mL) and 11, hyperprolactinemia (EPRL: 69.95 ± 45.27 ng/mL). One third of NPRL patients were on pharmacological treatment by the time of the study (one with BC and one with CB), while 72.2% of the EPRL group were using DA (four patients with BC and four with CB).

Mean PRL of the NPRL group was not significantly different from that obtained in the controls (p>0.9999). Comparisons between NPRL, EPRL and controls are shown **(Table 2)**.

Data presented as mean ± SD; EPRL=patients with high PRL values; NPRL=patients with normal PRL values; p-PRL=p from comparison between controls, EPRL and NPRL; EU=Eumenorrhea; Oligo=oligomenorrhea; p-men=p from comparison between controls, EU and Oligo.

There was no difference when groups were compared regarding age (p=0.0534), weight (p=0.9946), BMI (p=0.8913), WC (p=0.1124), or hip circumference (p=0.6708). The clinical follow-up duration for NPRL and EPRL was similar (p=0.8394). EPRL had a significantly higher WHR than controls (p=0.0292). However, there was no significant difference when the WHR of NPRL was compared to those of EPRL and controls (p: 0.6107 and 0.1058, respectively).

At biochemical evaluation, EPRL patients had lower GH levels than controls (0.4964 ± 0.3815 *vs* 1.760 ± 1.173 ng/mL, respectively; p=0.0275). GH levels of NPRL did not differ significantly from those of controls (p=0.0756) or EPRL (p=0.9999). There was no significant difference in fasting glucose values (p=0.3359), fasting insulin (p=0.8951), HOMA-IR (p=0.8681), HOMA-beta (p=0.2098), FSH (p=0.6835), LH (p=0.4364), E2 (p=0.8557), and IGF-1 (p=0.9633), when the three groups were compared.

**Table 2:** Group comparison.

| Variable | Controls | NPRL | EPRL | p-PRL | EU | Oligo | p-men |
|---|---|---|---|---|---|---|---|
| Age (years) | 32.45 ± 7.42 | 38.67 ± 9.81 | 41.00 ± 7.46 | 0.0534 | 39.30 ± 9.11 | 41.43 ± 7.00 | 0.054 |
| Weigth (kg) | 62.82 ± 8.32 | 62.92 ± 10.38 | 63.25 ± 8.36 | 0.9946 | 61.70 ± 24.69 | 65.17 ± 6.66 | 0.725 |
| BMI (kg/m$^2$) | 24.33 ± 3.76 | 24.62 ± 3.64 | 25.00 ± 2.46 | 0.8913 | 24.69 ± 3.37 | 25.11 ± 2.00 | 0.883 |
| Waist (cm) | 79.32 ± 12.36 | 87.00 ± 8.72 | 87.49 ± 5.77 | 0.1124 | 85.49 ± 7.92 | 88.5 ± 4.71 | 0.102 |
| Hip (cm) | 99.20 ± 7.35 | 98.37 ± 10.03 | 101.3 ± 4.68 | 0.6708 | 100.0 ± 8.12 | 100.6 ± 5.17 | 0.918 |
| WHR | 0.80 ± 0.09 | 0.89 ± 0.04 | 0.86 ± 0.05 | 0.0244 | 0.87 ± 0.05 | 0.87 ± 0.05 | 0.038 |
| PRL (ng/mL) | 13.82 ± 5.74 | 15.25 ± 6.92 | 69.95 ± 45.27 | <0.0001 | 27.46 ± 14.09 | 83.74 ± 54.04 | 0.002 |
| Glucose (mg/dL) | 81.27 ± 7.02 | 85.50 ± 5.43 | 85.91 ± 9.19 | 0.3359 | 83.60 ± 7.03 | 88.86 ± 8.51 | 0.124 |
| Insulin (µUI/mL) | 7.44 ± 2.34 | 8.03 ± 2.69 | 7.52 ± 2.73 | 0.8951 | 6.92 ± 2.60 | 8.82 ± 2.45 | 0.299 |
| HOMA-IR | 1.52 ± 0.60 | 1.68 ± 0.50 | 1.63 ± 0.73 | 0.8681 | 1.43 ± 0.53 | 1.96 ± 0.70 | 0.195 |
| HOMA-beta | 155.7 ± 46.7 | 142.2 ± 81.2 | 138.7 ± 76.2 | 0.2098 | 141.1 ± 84.6 | 138.2 ± 66.5 | 0.176 |
| FSH (UI/L) | 6.90 ± 6.90 | 18.13 ± 28.40 | 5.90 ± 3.36 | 0.6835 | 5.67 ± 5.20 | 16.71 ± 25. 76 | 0.215 |
| LH m (UI/mL) | 11.17 ± 18.49 | 14.60 ± 21.25 | 5.59 ± 3.51 | 0.4364 | 9.534 ± 16.86 | 7.68 ± 4.53 | 0.331 |
| Estradiol (pg/mL) | 81.29 ± 63.36 | 92.78 ± 79.92 | 74.83 ± 53.91 | 0.8557 | 100.2 ± 70.4 | 54.01 ± 38.47 | 0.256 |
| GH (ng/mL) | 1.76 ± 1.17 | 0.58 ± 0.56 | 0.50 ± 0.38 | 0.0152 | 0.50 ± 0.43 | 0.57 ± 0.47 | 0.014 |
| IGF1 (µg/L) | 253.3 ± 75.3 | 253.8 ± 104.6 | 244.4 ± 85.6 | 0.9633 | 232.8 ± 107.3 | 268.9 ± 57.0 | 0.682 |

## Comparisons according to menstrual cycle

In the present sample, there were seven oligomenorrheic patients (41.17%) and 10 (58.83%) eumenorrheic; most oligomenorrheic patients had PRL levels above the normal range (85.83%). Among the seven oligomenorrheic patients, one was being treated with BC, three with CB and three were not receiving DA treatment. In the eumenorrheic group, four patients were using BC, two CB and four were not under pharmacological treatment by the time of the study.

Table 2 presents the results of the comparisons between patients with eumenorrhea, oligomenorrhea and controls. The mean age of the three groups was similar (p=0.0545) and clinical follow-up duration was similar in the two groups of patients (p=0.7066). There was no significant statistical difference between the three groups regarding weight (p=0.7256), BMI (p=0.8833), WC (p=0.1029), or hip circumference (p=0.9188). Oligomenorrheic and eumenorrheic patients had higher WHR than controls (p=0.0380). However, oligomenorrheic and eumenorrheic individuals had similar WHR (p=0.9933).

There was no significant difference when the three groups were compared in terms of HOMA-IR (p=0.1954), HOMA-beta (p=0.1767), fasting glucose (p=0.1247), fasting insulin (p=0.2994), FSH (p=0.2154), LH (p=0.3315), estradiol (p=0.2564), GH (p=0.0146), and IGF1 (p=0.6829). However, oligomenorrheic patients had significantly higher PRL than controls (p=0.0017), with no difference compared to eumenorrheic patients. Mean GH was significantly higher in controls than in eumenorrheic individuals (p=0.0210), with no significant difference between controls and oligomenorrheic individuals or between the two groups of patients.

## Comparisons according to pharmacological treatment

When patients were divided according to type of DA (none, BC, or CB) and compared to controls, there were no differences in age (none=42.1 ± 48.3 years, BC=42.8 ± 8.3 years, CB=34.8 ± 6.4 years; p=0.9509), weight (none=67.9 ± 7.5 kg, BC=61.4 ± 9.7 kg, CB=58.2 ± 7.5 kg; p=0.1878), BMI (none=26.03 ± 1.80 kg/m$^2$, BC=25.33 ± 3.62 kg/m$^2$, CB=22.76 ± 2.36 kg/m$^2$; p=0.1285), WC (none=91.2 ± 5.2 cm, BC=87.0 ± 7.5 cm, CB=82.2 ± 4.8 cm; p=0.0728), hip circumference (none=102.3 ± 6.6 cm, BC=101.6 ± 4.8 cm, CB=96.1 ± 8.3 cm; p=0.4546), or WHR (none=0.88 ± 0.04, BC=0.86 ± 0.07, CB=0.86 ± 0.04; p=0.0753). Clinical follow-up duration of patients treated with BC and CB was similar to that of the group without DA (none=71.3 ± 31.4, BC=63.6 ± 43.8, CB=50.2 ± 38.0 months; p=0.6345).

Patients treated with CB had significantly higher PRL than the control group (77.1 ± 57.2 *vs* 13.8 ± 5.7 ng/mL; p=0.0085). Patients treated with BC had lower fasting glucose (77.0 ± 7.7 mg/dL) than those without DA (89.4 ± 5.2 mg/dL; p=0.0021) and the ones treated with CB (89.4 ± 3.7 mg/dL; p=0.0220 **(Figure 1)**. HOMA-beta was higher in the BC-treated group (none=125.3 ± 44.3, BC=206.8 ± 103.9, CB=93.4 ± 18.2; p=0.0347). GH levels of patients without DA were lower than those of controls (0.4 ± 0.3 *vs* 1.8 ± 1.2 ng/mL; p=0.0439). No significant difference was found when comparing the levels of insulin (none=9.0 ± 2.9 mUI/mL, BC=6.7 ± 2.8 mUI/mL, CB=6.8 ± 1.5 mUI/mL; p=0.3443), HOMA-IR (none=2.0 ± 0.7, BC=1.3 ± 0.6, CB=1.5 ± 0.4; p=0.2089), FSH (none=15.8 ± 23.3 mUI/mL, BC= 7.2 ± 7.2 mUI/mL, CB=5.4 ± 1.1 mUI/mL; p=0.8160), LH (none=6.5 ± 4.6 mUI/mL, BC=14.7 ± 23.9 mUI/mL, CB=6.0 ± 3.1 mUI/mL; p=0.7583), estradiol (none=72.6

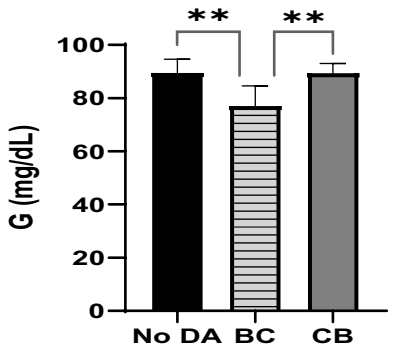


**Figure 1** Glucose levels and DA treatment.

± 46.8 pg/mL, BC=103.9 ± 99.1 pg/mL, CB=70.4 ± 39.1 pg/mL; p=0.9805), or IGF1 (none=239.7 ± 81.1 µg/L, BC=229.5 ± 133.8 µg/L, CB=277.1 ± 52.3 µg/L; p=0.8265) between the four groups.

## Relations between variables: Linear regression

We investigated the relationship between potential independent variables, such as PRL, estradiol, GH, WC and DA treatment, and the other variables through linear regressions.

As for the relationship between PRL and clinical-biochemical parameters, linear regression showed a significant relation between PRL and glucose levels (p=0.0333; $r^2$=0.1627).

Linear regression was also statistically significant for the relation between estradiol and weight (p=0.0361; $r^2$=0.1581), BMI (p=0.0335; $r^2$=0.1623) e LH (p=0.0013; $r^2$=0.3343).

Regressions involving GH and the following variables were statistically significant: weight (p=0.1596; $r^2$=0.0352), BMI (p=0.0046; $r^2$=0.2700), WC (p<0.0001; $r^2$=0.5798), hip circumference (p=0.0081; $r^2$=0. 2403), WHR (p=0.0002; $r^2$=0.4284), and fasting glucose (p=0.0040; $r^2$=0.2704). Significant relations between the measurement of WC and BMI (p<0.0001; $r^2$=0.7682), blood glucose (p=0.0030; $r^2$=0.2919), insulin (p=0.0002; $r^2$=0.4301), and HOMA-IR (p<0.0001; $r^2$=0.4554) were also identified. Finally, regarding pharmacological treatment, a relation was found between treatment with BC and fasting glucose (p=0.0007; $r^2$=0.5479).

## Relations between variables: Multivariate analysis

Since significant relations involving estradiol and WC were found in linear regression, both independent variables were used in a multivariate analysis model for BMI. In this statistical model, only the relation between WC and BMI remained significant (p<0.0001, $r^2$=0.8355).

The same type of approach was used to assess the variables identified as potential determinants of fasting glucose. In the statistical model that included WC and BC treatment, only the influence of BC treatment on fasting glucose remained significant (p=0.0020, $r^2$=0.6159).

# Discussion

The aim of this study was to assess the effects of hyperprolactinemia and its control on the basal metabolism of glucose and insulin in non-diabetic non-obese Brazilian women with prolactinoma. When women with microprolactinoma and controls were compared, there was no significant difference in fasting blood glucose or insulin levels and HOMA. These results corroborate those of Posawetz et al. who did not observe differences in these parameters or markers, such as homocysteine, C-reactive protein, or adiponectin, despite higher levels of Low-Density Lipoprotein (LDL) and lower levels of High-Density Lipoprotein (HDL) in their patients with prolactinoma [14]. Fasting insulinemia found in patients and controls (7.70 µUI/mL and 7.44 µUI/mL, respectively) included in the present study was lower than those found by Lee et al. in 492 non-diabetic non-obese Korean women (11.0 µUI/mL), and Bravata et al. in a sample of 6511 Americans (11.2 µUI/mL) [15,16].

The HOMA-IR results of our patients (1.65) and controls (1.52) were lower than the 2.8 reported by Bravata et al. and 1.96, by Acosta et al. for 120 non-obese Chileans of both genders [17]. In the Brazilian population, Gelonese et al. found a mean HOMA-IR of 1.6, in 240 non-obese women, and a value of 2.71 corresponding to the 90$^{th}$ percentile of the sample (240 women and 72 men), above which they considered insulin resistance [18]. In our study, the secretory activity of pancreatic beta-cells was estimated using the HOMA-beta index. We found no significant difference patients and controls, suggesting a similar insulin secretory activity in these two groups. However, HOMA-beta must be interpreted with caution, since pre-diabetic individuals may present compensatory hyperfunction of beta-cells and normal individuals do not secrete insulin identically for a given glycemia [19].

Prolactinomas represent the most frequent type of clinically functioning pituitary adenoma 40%-60% of the secretory tumors. They are more frequent in women among the second and third decades of life [20]. Although our patients were older than the control group and the literature indicates an effect of age on the prevalence of Diabetes Mellitus and changes in insulin sensitivity, there was no significant difference in blood glucose, insulin, HOMA-IR or HOMA-beta levels, when these two groups were compared [21].

The treatment of prolactinoma aims to control symptoms and, in macroadenomas, tumors with dimensions above 1 cm, to reduce tumor volume. More than half of our sample was being treated with DA. These medications are the first therapeutic option for prolactinomas. This treatment induces normalization of PRL levels in 80%-90% of patients and a decrease in tumor volume in 70% (22.23%). In Brazil, CB and BC were the only DA commercially available at the time of this study. Among the 10 patients undergoing pharmacological treatment, half used

CB and half used BC. The former has greater selectivity for D2 dopaminergic receptors and longer half-life than BC, allowing for greater dosage convenience and fewer side effects. Three patients had been treated with transsphenoidal surgery before inclusion in the study. In microprolactinomas, cure rates of up to 85%-90% have been reported. Surgery should be considered in small tumors and DA intolerance and/or resistance [22].

In the present cohort, patients treated with BC had lower glycemia than those treated with CB or without DA. In addition, the multivariate analysis indicated BC treatment as a determinant of lower blood glucose. These findings corroborate the data shown by Igata et al and Oshige et al on the improvement of glycemic levels in patients with prolactinoma treated with BC [23]. The effect of BC on glycemia can be direct, due to decrease in the hepatic production of glucose and release of free fatty acids and triglycerides, with a consequent reduction in insulin resistance. In 2010, the use of BC for the treatment of Type 2 Diabetes Mellitus was approved by the US Food and Drugs Administration.

Although our 17 patients did not have diabetes or obesity, nor alterations in blood glucose or fasting insulin, our results indicate an action of BC on blood glucose. The results do not seem to have been affected by control of hyperprolactinemia or menstrual status. However, it is noteworthy that, at the time of the study, most patients with hyperprolactinemia (72.2%) were being treated with DA, which may have prevented the deleterious consequences of hyperprolactinemia on glucose-insulin metabolism in our sample.

Foss et al. observed that insulinemia response to glucose administration was higher in patients with hyperprolactinemia, who did not present increase in muscle glucose uptake, which suggested a higher insulin resistance status. Furthermore, hyperprolactinemic patients had less suppression of free fatty acids, indicating a reduction in the anti-lipolytic effect of insulin, when compared to controls [24].

Pala et al. compared hyperprolactinemic patients before and after treatment with CB to controls with similar BMI, observing higher levels of glucose, cholesterol, and triglycerides in the patients. After six months of treatment with CB, there was a significant reduction in these three biochemical parameters [11]. Atmaca, et al. found higher basal insulinemia, HOMA-IR, and HOMA-beta in premenopausal women with hyperprolactinemia [10]. The authors also identified a positive correlation between PRL and blood glucose levels. However, in our study, the evidence of a relation between PRL and glucose was not confirmed after correction for the influence of other variables. Therefore, our data do not indicate greater secretory activity of beta-cells nor peripheral insulin resistance in hyperprolactinemic patients.

Our hyperprolactinemic patients had a higher frequency of oligomenorrhea (58.3%) than normoprolactinemic patients and controls. These data are consistent with the known effect of hyperprolactinemia on the gonadal axis. Although the literature has established a potential effect of gonadal steroids on the glucose-insulin metabolism, there were no differences in the metabolic parameters of eumenorrheic, oligomenorrheic and control women in our series.

Yang et al. verified that PRL was positively related to glycemia in patients with polycystic ovary syndrome [25]. Similarly to our cohort, sex estrogen and androgen levels did not differ between patients and controls, and the authors considered a role for PRL in sex steroid-independent insulin resistance. It is known that body composition, especially visceral fat deposition, can negatively influence the glucose-insulin metabolism, contributing to the development of the Metabolic Syndrome. To limit the influence of body weight on the results, patients with obesity were excluded from the present study. Despite that, our patients had higher waist and WHR than controls. The relations between waist and fasting glucose, insulin, and HOMA-IR corroborate literature data on the influence of abdominal fat on glucose-insulin metabolism [26].

There is also evidence that DA may indirectly influence glucose-insulin metabolism through changes in body composition. We have previously reported that normoprolactinemic women with prolactinomas treated with DA had lower body fat, including at the visceral compartment, and their body fat content was influenced by regular DA administration [27]. Naliato et al. and Posawetz et al. have also shown that newly diagnosed males with prolactinomas had higher body fat content, which was linked to disease control, especially to the PRL and androgen levels [14,28].

GH opposes insulin actions on glucose metabolism, and, in acromegaly, there is an increase in prevalence of Diabetes Mellitus and insulin resistance. Despite this and the potential for GH co-secretion by the prolactinomas, our study did not show an increase in GH levels in patients with microprolactinoma. Additionally, the relation between the levels of this hormone and blood glucose was ruled out after the adjustment for other variables.

Some of the limitations of the present study were its sectional nature, the lack of assessment of the glucose-insulin profile through dynamic tests, the heterogeneity regarding the type and frequency of DA treatment, and the heterogeneity in time elapsed since the diagnosis of microprolactinoma and with PRL levels in the normal range.

## Conclusion

We conclude that this group of non-diabetic non-obese Brazilian women with microprolactinomas had insulin and HOMA-IR levels lower than those obtained by other studies in non-obese patients. This finding can be attributed to the fact that most patients were being treated with DA by the time of the study. Our data do not point to hyperprolactinemia as a significant factor in the glucose-insulin metabolism in women with microprolactinomas, but the use of DA, especially BC, seems to have been decisive in controlling glycemia and insulin resistance.

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The authors declare that no competing interests exist.

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