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Prolactin Levels in Brazilian Patients Evaluated Because of Weight Gain: A Correlation with the Anthropometric and Biochemical Profiles?

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Authors' contributions

This work was carried out in collaboration between all authors. Author ECON designed the study, wrote the protocol, performed the statistical analysis, managed the literature searches and wrote the first draft of the manuscript. Authors VTOR and TRF performed data collection and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To investigate if basal measures of serum prolactin correlate with biochemical and anthropometric data of Brazilian patients.
Methodology: This study consists of a cross-sectional evaluation of basal serum prolactin levels and its correlations with biochemical (fasting glucose, lipid profile, uric acid, insulin, Homeostasis Model Assessment-Insulin Resistance - HOMA) and anthropometric data (body mass index - BMI, waist circumference - WC, Visceral Adiposity Index - VAI) in 356 patients who sought Endocrinological evaluation in order to lose weight (242 women, 114 men; age range 16-80 years). Most patients were obese (43.63%), 36.52% were overweight and 16.85% had normal BMI. Patients were divided among four quartiles according to the prolactin levels: The first containing the patients with the lowest, and the forth, those with the highest levels.
Results: The fourth prolactin quartile had significantly lower BMI (*P*= .02), WC (*P*= .003), glucose

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(*P* <.001), total cholesterol (*P*= .02), LDL (*P*= .04), triglycerides (*P*= .02), HOMA (*P*= .04), and VAI (*P*= .04), and fewer diagnostic criteria for the Metabolic Syndrome (*P* <.001). In addition, the fourth quartile had lower prevalences of obesity (*P*= .02) and Diabetes Mellitus (*P*= .02). There were correlations between PRL and BMI (r= -.17, *P*= .001), WC (r= -.21, *P* <.001), glucose (r= -.25, *P* <.001), total cholesterol (r= -.14, *P*= .01), HDL (r= .14, *P*= .01), LDL (r= -.12, *P*= .02), triglycerides (r= -.17, *P* <.001), HOMA (r= -.13, *P*= .03), VAI (r= -.21, *P* <.001), and the number of diagnostic criteria for the Metabolic Syndrome (r= -.23, *P* <.001).

Conclusion: Patients with higher levels of prolactin had a more favorable anthropometric and biochemical profile. Basal levels of prolactin correlate well with anthropometric and biochemical data and may be a useful tool for the estimation of serotoninergic activity in patients who seek Endocrinological evaluation for weight reduction.

Keywords: Prolactin; serotonin; obesity; serotoninergic activity; cardiovascular risk.

1. INTRODUCTION

Obesity can be defined as a body mass index (BMI) above 30 kg/m². It develops as a consequence of energy imbalance - when calorie intake surpasses depletion [1].

Obesity is frequently associated with a series of risk factors for the development of cardiovascular disease: Elevation of glucose levels, dyslipidemia, arterial hypertension, insulin resistance, pro-thrombotic and pro-inflammatory status [2-5]. The combination of these factors is termed the Metabolic Syndrome [6,7].

Besides its well-known influence in mood and behavior, serotonin (5-HT) has also been linked to autonomic and neuroendocrine modulation; serotoninergic circuits also affect eating behavior [8]. It is a vasoactive monoamine that possesses amphibaric properties indicated by its ability to elicit either vasoconstriction with elevation of the blood pressure or vasodilation and hypotension, depending on the site of application, time of observation, concentration, and local factors [9,10]. Central 5-HT1A, 5-HT2, and 5-HT3 receptors are the major receptor subtypes important in cardiovascular regulation [11]. The mechanism for blood pressure control involves sympathoexcitation and vasopressin activation of a central angiotensinergic pathway [9]. Furthermore, low central serotoninergic responsivity has been associated with carotid artery thickening, which indicates preclinical vascular disease [11].

Polymorphisms of genes that affect serotoninergic neurotransmission have been linked with cardiovascular disease. Additionally, an abnormal production rate of the 5-HT2A receptor gene product might lead to the development of central obesity, probably due to the destabilization of the serotonin-hypothalamic-pituitary-adrenal system [12-14]. Polymorphisms of 5-HT2A receptor gene have also been associated with the development of the Metabolic Syndrome [14].

Central serotoninergic responsivity has been shown to be inversely associated with body mass, insulin resistance, dyslipidemia, and the development of the Metabolic Syndrome [15-17]. The 5-HT2C receptor has been suggested to perform an essential role in the regulation of food intake. Ablation of neurons from the ventromedial hypothalamus, a region that contains 5-HT2C, result in obesity, while mutations and polimorphisms of the 5-HT2C gene cause chronic hyperphagia, obesity, Diabetes Mellitus and hyperinsulinemia [8,18-20].

It has been demonstrated that treatment with the selective serotoninergic reuptake inhibitor (SSRI) citalopram favorably modifies metabolic risk factors, such as waist circumference, glucose, HDL cholesterol, triglycerides, and insulin sensitivity, reducing body weight [21]. On the other hand, it seems that the interference of serotoninergic tone may also influence metabolism independently of modifications in body fat. Another SSRI, escitalopram, has been shown to restore the hypothalamic-pituitary corticosteroid feedback and improve insulin sensitivity [22].

Prolactin (PRL) release from the pituitary is regulated, in part, by hypothalamic serotoninergic signals, and serotoninergic drug challenges result in increased PRL release in a dose dependent manner that is blocked by serotoninergic receptor antagonists [23,24]. Consequently, the measure of PRL responses to pharmacological challenges with 5-HT agonists provides a validated and minimally invasive method of estimation of central serotoninergic function [25,26]. Interestingly, as previously

mentioned, the PRL response to serotoninergic challenges has also been inversely associated with blood pressure, atherosclerotic disease, sedentary lifestyle, insulin resistance, and the prevalence of the Metabolic Syndrome [11,15-17]. Besides the serotoninergic challenge tests, simpler measures of PRL, e.g. salivary PRL, correlate positively with central 5-HT function and its measure has been indicated as an index of central 5-HT turnover in humans [27].

The aim of the present study was to investigate if basal measures of serum PRL correlated with biochemical and anthropometric data of Brazilian patients that sought Endocrinological evaluation in order to lose weight.

2. MATERIALS AND METHODS

The present study consists of a cross-sectional evaluation of basal serum PRL levels and its correlations with biochemical and anthropometric data in 356 patients who sought Endocrinological evaluation in order to lose weight.

2.1 Patients

Patients of both genders were included in the present study by the time of their endocrinological evaluation from January/2009 to October/2014 at the Endocrine Unit under supervision of the corresponding author (E.C.O.N.). Patients' age ranged from 16 to 80 years.

2.1.1 Exclusion criteria

(1) Pharmacological treatment with possible inducers of hyperprolactinemia, such as hormonal contraceptives, estrogen or androgen replacement therapy, antipsychotics, antidepressants, anticonvulsants, and metoclopramide; the diagnosis of (2) polycystic ovary syndrome (PCOS), (3) thyroid dysfunction, (4) prolactinomas or (5) non-functioning pituitary adenomas; (6) pregnancy; (7) lactation.

From the 583 patients consecutively considered to participate in this study, 146 were excluded due to the use of possible inducers of hyperprolactinemia, 59 to thyroid dysfunction, 13 to prolactinomas, and nine to PCOS.

2.2 Measurements

Total body weight was measured on a standardized spring balance scale (Filizola, São Paulo, Brazil) with participants dressed uniquely in underwear. Weights were recorded to the nearest .1 kg.

Standing height was measured without shoes with a stadiometer (Filizola, São Paulo, Brazil) and recorded to the nearest .5 cm.

BMI was calculated by dividing the total body weight (kg) to the squared standing height (m^2).

A non-elastic flexible measuring tape was used to measure waist circumference (WC). Measures were recorded to the nearest .1 cm. WC was measured at the mid- distance between the lower rib and the iliac crest. Circumferences above 88 cm in women and 102 cm in men were considered high.

Blood pressure was measure in the right arm with a standard aneroid sphygmomanomater (Tycos, USA). Systolic arterial hypertension was defined as a systolic pressure above 130 mmHg and diastolic arterial hypertension as a diastolic pressure above 85 mmHg according to the criteria of the III report of the NCEP (National Cholesterol Education Program Criteria; 2002) [2].

PRL was assessed using the electrochemi-luminescence immunoassay Prolactin II (Roche Diagnostics, Indianapolis, USA). Reference values for women were 3.6-25.0 ng/dL and, for men, 2.5-17.0 ng/dL.

Besides PRL, fasting glucose, lipid profile, uric acid, and insulin concentrations were also measured. Reference values were: Glucose = 70-99 mg/dL, Total cholesterol < 200 mg/dL, HDL > 50 mg/dL (women) and > 40 mg/dL (men), LDL < 130 mg/dL, Triglycerides < 151 mg/dL, uric acid < 6.5 mg/dL (women) and < 7.0 (men), insulin < 16 UI/mL.

The Homeostasis Model Assessment-Insulin Resistance (HOMA) was calculated by dividing the fasting insulin (mUI/L)-glucose (mmol/L) product by 22.5.

The Visceral Adiposity Index (VAI) was calculated respectively for men and women by the following formulas reported by Amato et al. [28]: [WC/(39.68 + 1.88 x BMI)] x (Triglycerides/1.03) x (1.31 x HDL) and [WC/(36.58 + 1.89 x BMI)] x (Triglycerides/0.81) x (1.52 x HDL).

2.3 Metabolic Syndrome – National Cholesterol Education Program Criteria

The diagnosis of Metabolic Syndrome was based on the presence of three or more of the following criteria: (1) plasma glucose > 110 mg/dL; (2) plasma triglycerides > 150 mg/dL; (3) plasma HDL < 50 mg/dL, in women, and < 40 mg/dL, in men; (4) blood pressure > 130/85 mmHg or the treatment with antihypertensive drugs; and (5) waist circumference > 88 cm, in women, and 102 cm, in men.

2.4 Statistical Analysis

Data are shown as mean ± SD, unless otherwise specified.

The unpaired Student T test was used to compare means between two groups and the Fisher's exact test analyzed categorical variables. When more than two groups were studied, the one-way ANOVA test was used to compare means and categorical variables were analyzed using the chi-square test. The Bonferroni's multiple comparison test was performed after the one-way ANOVA test in order to evaluate all the pairs of columns.

The Kolmogorov-Smirnov test was used to analyze the residuals for normality. (When alpha = .05, data passed this normality test). Whenever data did not pass the normality test, the Mann-Whitney test was used to compare means between two groups and the Kruskal-Wallis test, to compare three or more groups. The Dunn's Multiple comparison test was performed after the Kruskal-Wallis test in order to evaluate all the pairs of columns.

Regarding the comparisons between different BMI groups, a sample size of 60 in each group has a 80% power to detect a difference between means of PRL of 2.58 ng/mL with a significance level of .05 (two-tailed). Considering the comparisons between the PRL quartiles, a sample size of 70 in each group has a 99% power to detect a difference between means of BMI of 1.46 kg/m² with a significance level of .05 (two-tailed).

Relationships between two numeric variables were studied by linear regression and Pearson parametric correlation, except when data distribution was not normal and the Spearman non-parametric correlation was used. Non-parametric tests were also done in parallel with the parametric ones with confirmatory purposes. Correlations between prolactin and anthropometric measures were adjusted for age, using multiple regression. Correlations between PRL and other biochemical data were adjusted for age, BMI, and waist circumference using multiple regression. The statistical significance was set as 5%.

The analysis were carried out using GraphPad Prism version 6.05 2014 for Windows (GraphPad Software, San Diego, California, USA), GraphPad Instat version 3.05 for Win 95/NT (GraphPad Software, San Diego, California, USA), GraphPad StatMate version 2.00 for Windows (GraphPad Software, San Diego, California, USA), and Epi Info™ version 7.1.0.6 (Centers for Disease Control and Prevention, USA).

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Gender

Table 1 show the clinical and biochemical profile of the 356 patients evaluated in the present study as well as the comparison between genders. Men had higher BMI, WC, systolic and diastolic pressures, glucose, total cholesterol, triglycerides, uric acid, insulin, HOMA, a greater number of criteria for the diagnosis of the Metabolic Syndrome and lower HDL and PRL levels.

3.1.2 Body Mass Index classification

Most patients analyzed in the present study were obese (43.63%), while 36.52% were overweight and 16.85% had normal BMI. The frequency of patients with high waist circumference was 62.02%. Table 2 exhibits the clinical and biochemical profile of obese, overweight, and normal BMI subjects and the comparisons between these three groups. Obese subjects presented higher BMI, WC, systolic and diastolic pressures, glucose, total cholesterol, triglycerides, uric acid, insulin, HOMA, and VAI (Fig. 1), a greater number of criteria for the diagnosis of the Metabolic Syndrome and lower HDL and PRL levels.

Table 1. Patients' profile and the comparison between women and men

	Patients	Women	Men	*P*
N	356	242	114	-
Age (years)	41.1±12.9	42.2±12.8	38.8±12.9	.02
Body mass index (kg/m²)	30.14±6.39	29.23±6.39	32.03±5.71	*< .001*
Obesity (%)	46.64	41.74	57.02	.003
Overweight (%)	36.52	37.19	35.09	.003
Waist circumference (cm)	98.4±17.3	93.5±14.8	109.1±17.5	*< .001*
High waist circumference (%)	62.02	61.30	63.55	.75
Systolic pressure (mmHg)	120.3±8.8	118.5±8.0	124.1±9.2	*< .001*
Diastolic pressure (mmHg)	79.2±5.2	78.9±4.8	80.0±5.8	*.02*
Prolactin (mIU/L)	11.0±5.5	11.5±6.2	9.7±3.5	*.048*
Elevated prolactin (%)	3.10	3.32	2.63	1.00
Glucose (mg/dL)	96.4±25.6	93.8±22.7	102.1±30.3	*< .001*
Diabetes (%)	5.65	3.33	10.53	.01
Increased fasting glucose (%)	19.49	18.76	21.93	.01
Total cholesterol (mg/dL)	196.2±41.4	198.7±38.1	191.1±47.2	*.08*
Elevated cholesterol (%)	42.82	43.83	40.71	.64
HDL (mg/dL)	48.1±13.3	51.6±13.3	40.9±12.7	*< .001*
Low HDL (%)	49.15	46.86	53.98	.25
LDL (mg/dL)	113.6±34.4	113.5±33.7	113.5±35.9	*.79*
Elevated LDL (%)	30.11	29.71	30.97	.81
Triglycerides (mg/dL)	134.9±75.4	122.9±66.7	160.0±86.0	*< .001*
Elevated triglycerides (%)	32.67	25.23	48.25	< .001
Insulin (mUI/L)	11.1±8.4	9.7±6.8	14.3±10.6	*< .001*
HOMA	2.73±2.50	2.25±1.77	3.78±3.41	*< .001*
Uric acid (mg/dL)	5.03±2.69	4.44±2.69	6.21±2.91	*< .001*
Elevated uric acid (%)	13.72	6.82	27.78	< .001
Visceral Adiposity Index	5.59±4.10	4.85±3.40	7.14±4.95	*< .001*
Metabolic Syndrome (%)	29.49	23.97	41.23	.001
Number of MS criteria	1.8±1.3	1.6±1.3	2.1±1.3	*.002*

** HOMA: Homeostasis Model Assessment- Insulin Resistance; MS: Metabolic Syndrome (NCEP). The 5th column contains the P values for the comparison between women and men. P values in italics refer to results of non-parametric tests.*

3.1.3 Prolactin quartiles

Most patients (97.5%) had PRL values within the normal range. The minimum PRL value obtained in the present study was 1.3 ng/mL and the maximum, 40.0 ng/mL. Patients were divided according to their respective levels of PRL among four quartiles: the first one gathered patients with the lowest levels of PRL and the forth, those with the highest levels. Table 3 presents the data of patients located in these quartiles and the comparison between the four groups. Multiple comparisons between patients of the first and the fourth quartiles reinforced the results of the simultaneous comparison between the four groups, showing that the fourth PRL quartile had significantly lower BMI (Fig. 2), WC (Fig. 3), glucose, total cholesterol, LDL, triglycerides (Fig. 4), HOMA (Fig. 5), and VAI (Fig. 1), and fewer criteria for the diagnosis of the Metabolic Syndrome (Fig. 6). In addition, the fourth quartile had lower prevalences of obesity, Diabetes Mellitus, and increased fasting glucose.

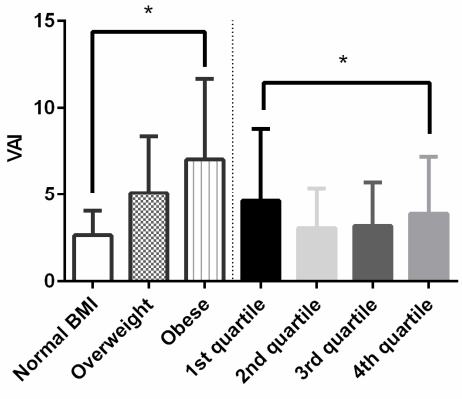

Fig. 1. Comparisons of Visceral Adiposity Index among different categories of body weight and PRL quartiles

Table 2. Data from obese, overweight and normal BMI patients

	Obese	Overweight	Normal BMI	*P*
N	166	130	60	-
Age (years)	44.1±13.3	39.3±11.6	36.9±13.0	.001
Body mass index (kg/m²)	35.18±5.77	27.08±1.37	22.83±1.52	*< .001*
Waist circumference (cm)	111.3±15.1	90.5±7.3	79.4±6.8	*< .001*
High waist circumference (%)	98.14	40.17	6.78	< .001
Systolic pressure (mmHg)	123.2±8.6	119.1±8.2	114.8±7.4	*< .001*
Diastolic pressure (mmHg)	79.2±5.2	78.9±4.8	80.0±5.8	*< .001*
Prolactin (mIU/L)	10.4±5.7	10.9±5.6	12.6±4.7	*.002*
Elevated prolactin (%)	3.01	3.88	1.67	.71
Glucose (mg/dL)	104.5±33.4	90.3±13.5	87.4±9.4	*< .001*
Diabetes (%)	10.3	2.33	0	.002
Increased fasting glucose (%)	40.61	14.73	10.00	< .001
Total cholesterol (mg/dL)	203.0±41.1	192.4±44.3	185.7±32.1	*.005*
Elevated cholesterol (%)	50.31	38.89	30.51	.02
HDL (mg/dL)	45.5±14.4	47.6±11.6	56.3±9.9	*< .001*
Low HDL (%)	56.36	53.54	20.00	< .001
LDL (mg/dL)	120.0±36.2	109.6±32.2	104.8±30.6	*.003*
Elevated LDL (%)	43.29	20.31	15.00	< .001
Triglycerides (mg/dL)	160.3±82.2	125.0±64.4	85.6±40.3	*< .001*
Elevated triglycerides (%)	45.18	28.57	6.67	< .001
Insulin (mUI/L)	15.4±9.4	7.6±4.3	6.5±5.4	*< .001*
Elevated insulin (%)	36.69	5.05	1.89	< .001
HOMA	4.01±2.94	1.65±1.01	1.39±1.22	*< .001*
Uric acid (mg/dL)	5.46±1.70	4.95±3.88	3.95±1.16	*< .001*
Elevated uric acid (%)	22.44	6.84	3.64	< .001
Visceral Adiposity Index	7.04±4.67	5.10±3.25	2.63±1.40	*< .001*
Metabolic Syndrome (%)	49.40	16.92	1.67	< .001
Number of MS criteria	2.6±1.2	1.4±1.1	0.4±0.6	*< .001*

** HOMA: Homeostasis Model Assessment- Insulin Resistance; MS: Metabolic Syndrome (NCEP). P values in italics refer to results of non-parametric tests.*

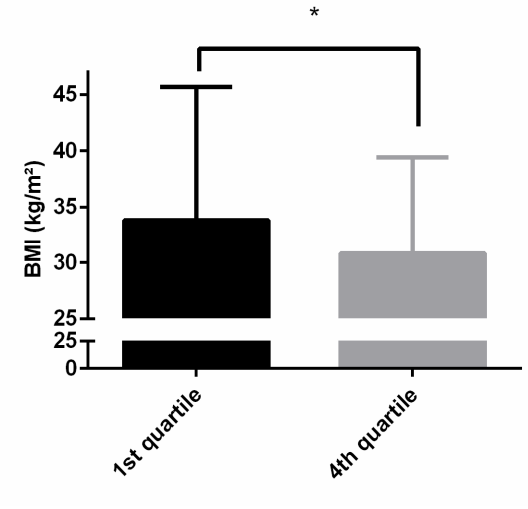

Fig. 2. Comparison of body mass index between the first and the fourth PRL quartiles

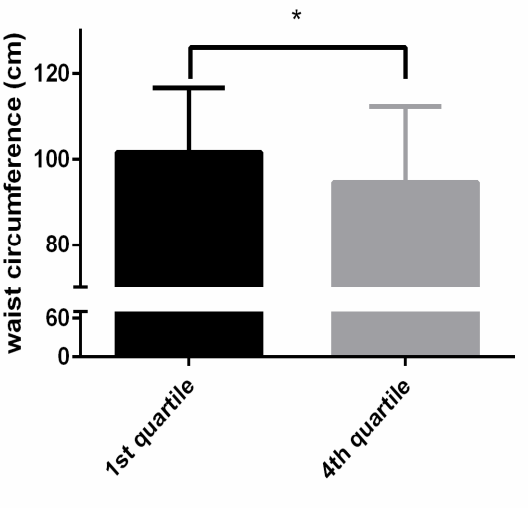

Fig. 3. Comparison of waist circumference between the first and the fourth PRL quartiles

Table 3. Data from the four prolactin quartiles

	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	*P*
N	94	99	70	93	-
Age (years)	46.9±12.9	42.5±13.5	37.1±9.9	38.5±13.3	.05
BMI (kg/m²)	33.85±11.83	33.83±15.24	31.66±11.89	30.82±8.6	*.02*
Obesity (%)	57.45	48.00	40.00	39.78	.02
Overweight (%)	35.11	39.00	35.71	35.48	.012
WC (cm)	101.7±14.9	99.9±17.7	97.2±18.24	94.7±17.7	*.003*
High WC (%)	74.16	61.05	53.73	54.02	.02
Systolic pressure (mmHg)	121.4±7.7	120.0±9.0	120.2±8.3	119.5±10.0	*.29*
Diastolic pressure (mmHg)	80.0±4.8	78.3±5.7	79.4±4.6	79.5±5.3	*.19*
PRL (mIU/L)	5.4±1.5	8.8±1.0	11.7±1.1	18.3±4.8	*< .001*
Glucose (mg/dL)	102.5±32.8	100.1±30.5	92.0±13.6	89.7±13.8	*< .001*
Diabetes (%)	8.60	10.00	0.00	2.15	.02
IFG (%)	26.88	21.00	15.94	13.98	.02
Total cholesterol (mg/dL)	208.3±45.1	192.4±35.0	196.9±42.5	187.0±40.5	*.02*
Elevated cholesterol (%)	50.54	37.11	48.53	36.26	.11
HDL (mg/dL)	46.1±14.6	47.7±12.4	49.1±13.1	49.3±13.1	*.11*
Low HDL (%)	62.37	45.00	42.65	45.65	.03
LDL (mg/dL)	122.3±37.7	109.2±27.1	115.9±38.8	107.7±33.0	*.04*
Elevated LDL (%)	32.26	26.00	32.84	30.11	.74
Triglycerides (mg/dL)	160.4±94.1	129.3±60.6	128.2±72.5	120.0±63.8	*.02*
Elevated triglycerides (%)	43.62	28.00	35.29	24.18	.03
Insulin (mUI/L)	11.8±8.0	12.1±10.1	10.2±8.5	10.2±6.5	*.04*
Elevated insulin (%)	25.97	21.95	19.30	11.84	.16
HOMA	3.00±2.23	3.15±3.39	2.46±2.42	2.27±1.63	*.04*
Uric acid (mg/dL)	4.85±1.79	5.52±4.23	5.01±1.73	4.63±1.45	*.07*
Elevated uric acid (%)	13.48	18.95	13.85	7.5	.19
VAI	4.62±4.17	3.04±2.33	3.16±2.56	3.87±3.30	.04
MS (%)	45.74	28.00	22.86	19.35	< .001
Number of MS criteria	2.3±1.4	1.8±1.4	1.6±1.3	1.5±1.3	*< .001*

** BMI: Body mass index; WC: waist circumference; PRL: prolactin; IFG: Increased fasting glucose; HOMA: Homeostasis Model Assessment- Insulin Resistance; VAI: Visceral Adiposity Index; MS: Metabolic Syndrome (NCEP). P values in italics refer to results of non-parametric tests.*

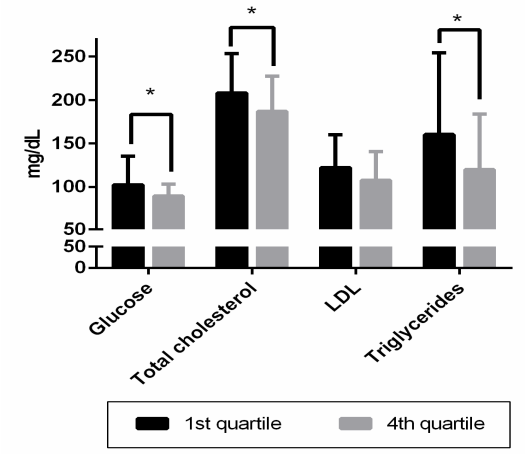

Fig. 4. Comparison of glucose and lipid profile between the first and the fourth PRL quartiles

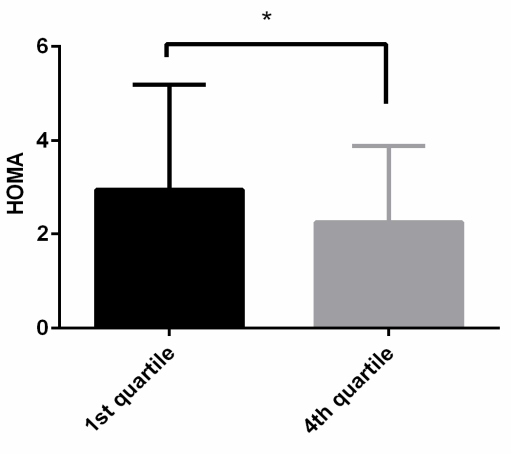

Fig. 5. Comparison of HOMA between the first and the fourth PRL quartiles

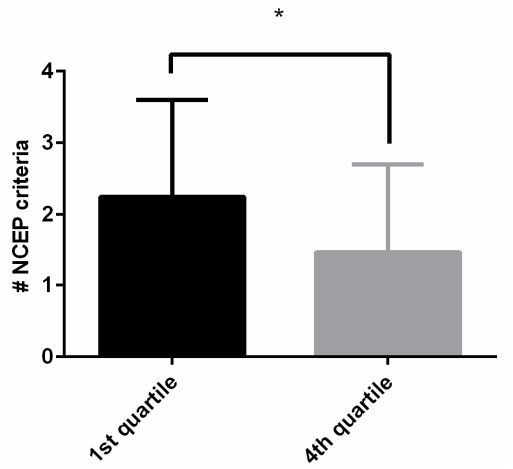

Fig. 6. Comparison of the number of NCEP criteria between the first and the fourth PRL quartiles

3.1.4 Correlations

There were statistically significant correlations between PRL and age (r = -.28, *P* < .001), BMI (r = -.17, *P* = .001), WC (r = -.21, *P* < .001), glucose (r = -.25, *P* < .001), total cholesterol (r = -.14, *P* = .01), HDL (r = .14, *P* = .01), LDL (r = -.12, *P* = .02), triglycerides (r = -.17, *P* < .001), HOMA (r = -.13, *P* = .03), VAI (r = -.21, *P* < .001), and the number of NCEP diagnostic criteria for the Metabolic Syndrome (r = -.23, *P* < .001).

There were also statistically significant correlations between BMI and WC (r = .81, *P* < .001), glucose (r = .36, *P* < .001), total cholesterol (r = .14, *P* = .009), HDL (r = -.31, *P* < .001), LDL (r = .19, *P* < .001), triglycerides (r = .40, *P* < .001), insulin (r = .57, *P* < .001), HOMA (r = .57, *P* < .001), and the number of NCEP diagnostic criteria for the Metabolic Syndrome (r = .57, *P* < .001).

Regarding WC, there were statistically significant correlations between this variable and glucose (r = .39, *P* < .001), total cholesterol (r = .15, *P* = .005), HDL (r = -.41, *P* < .001), LDL (r = .19, *P* < .001), triglycerides (r = .51, *P* < .001), insulin (r = .62, *P* < .001), HOMA (r = .64, *P* < .001), and the number of NCEP diagnostic criteria for the Metabolic Syndrome (r = .69, *P* < .001).

The correlations between VAI and age (r = .16, *P* = .003), glucose (r = .31, *P* < .001), total cholesterol (r = .31, *P* < .001), LDL (r = .30, *P* < .001), insulin (r = .48, *P* < .001), HOMA (r = .51, *P* < .001), and the number of NCEP diagnostic criteria for the Metabolic Syndrome (r = .72, *P* < .001) were also statistically significant. Since WC, BMI, HDL, and triglycerides are variables included in the formula for the calculation of VAI, we did not study the correlations between VAI and these factors.

Finally, significant correlations were obtained between age and BMI (r = .19, *P* < .001), WC (r = .22, *P* < .001), glucose (r = .41, *P* < .001), total cholesterol (r = .27, *P* < .001), LDL (r = .21, *P* < .001), triglycerides (r = .22, *P* < .001), HOMA (r = .13, *P* = .02), and the number of NCEP diagnostic criteria for the Metabolic Syndrome (r = .31, *P* < .001).

3.1.5 Multiple regression

After the adjustment for age, the correlation between PRL and WC remained statistically significant (r^2 = .07, *P* < .001).

Regarding the biochemical data, after the adjustment for the influence of age, BMI, WC, and VAI, only the correlation between PRL and HDL remained statistically significant (r^2 = .07, *P* < .001).

3.2 DISCUSSION

As expected, the obese subjects included in the present study had higher WC and an increased prevalence of Diabetes Mellitus, dyslipidemia and insulin resistance. BMI is correlated with all-cause mortality. However, it is not a good predictor of mortality risk and is not directly associated with visceral adiposity [29]. The latter is associated with increased cardiovascular risk through the production of adipokines, proinflammatory and prothrombotic activity, and the deterioration of insulin sensitivity [2,7,30]. The present study did not evaluate visceral adiposity through imaging techniques such as magnetic resonance imaging, computed tomography scan, or Dual-energy X-ray absorptiometry, but evaluated WC and VAI. The measure of WC has been tightly linked with the metabolic risk factors and considered the best clinical estimation of obesity [7]. However, WC alone is not able to distinguish between subcutaneous and visceral adiposity [31]. In order to complement the evaluation of fat distribution, VAI was calculated for the present sample. Amato et al. [28] showed that all the components of the Metabolic Syndrome increased significantly across the VAI quintiles. These authors also identified an association

between VAI, insulin resistance and cardio- and cerebrovascular events, presenting VAI as a valuable indicator of "visceral adipose function" and cardiometabolic risk [28].

Basal PRL levels of the 356 Brazilian patients included in the present study were evaluated and subjects were divided according to these levels among PRL quartiles, which provided interesting results. Subjects with normal BMI had higher levels of PRL, when compared with those with obesity and overweight. Moreover, subjects with the highest levels of PRL presented lower BMI, WC, glucose, total cholesterol, LDL, triglycerides, and HOMA. In addition, this subgroup of patients had lower prevalence of Diabetes Mellitus. In addition, PRL levels were inversely correlated with anthropometric (BMI, WC) and biochemical data (glucose, total cholesterol, LDL, triglycerides, HOMA) and directly correlated with HDL levels. Our data is in accordance with the studies of Muldoon et al. [11,15,16] and Horacek et al. [32], which evaluated central serotoninergic responsivity with the fenfluramine and citalopram tests and with data from Lindell et al. [27], which investigated salivary PRL as an indicator of central serotoninergic turnover. PRL response to fenfluramine has been inversely related to obesity, fasting levels of glucose, triglycerides, and insulin [16]. Muldoon et al. [16] also observed that the associations between the PRL response to fenfluramine and the metabolic risk factors were maintained after the exclusion of obese patients. The literature also presents reports of lowered fasting glucose and glycated hemoglobin as a result of the amelioration of central serotoninergic tone with SSRI treatment [33,34].

In the present study, insulin resistance was not evaluated through gold-standard glucose clamping techniques, being estimated by the calculation of HOMA-IR, which could be considered a limitation. However, despite being a simple method of evaluation of insulin resistance, HOMA results have been shown to approximate those of the clamping techniques [35]. Both insulin and HOMA were higher in patients with lower PRL levels. Insulin itself may affect the function of central serotoninergic neurons. Diabetic rats present altered affinity of 5-HT receptors and a reduced content of 5-HT in the cerebral cortex and the brain stem [36,37].

The prevalence of the Metabolic Syndrome and the number of diagnostic criteria for this syndrome were higher in patients with lower levels of basal PRL, in the present study. If low levels of PRL are considered an indicator of reduced serotoninergic activity, these data are in accordance with that of Herrera-Marquez et al. [38], who detected a state of depressed serotoninergic brain activity in adolescents with the Metabolic Syndrome. In addition, these data are supported by studies on 5-HT receptors: type 2 diabetics have a higher concentration of brain 5-HT receptors and polimorphisms of 5-HT 2A and 2C receptors [8,12,13,39]. And the presence of the Metabolic Syndrome and insulin resistance have been associated with reduced brain serotoninergic activity, reflected in a blunting of the PRL response to a serotoninergic challenge [15,16,32]. On the other hand, selective 5-HT reuptake inhibitors and 5-HT releasing agents are able to transiently improve insulin resistance and beneficially change the components of the Metabolic Syndrome [21,40]. Weight loss and modulation of the sympathetic nervous system and/or the hypothalamus-pituitary-adrenal axis have been suggested as mechanisms for the favorable metabolic effects of SSRI treatment [21].

There was no difference in systolic or diastolic blood pressures when the four quartiles of PRL were compared. Although the difference in PRL levels suggests the presence of different serotoninergic central activity in these four quartiles, our data is not in accordance with studies that indicated an influence of 5-HT on blood pressure. Besides acting on 5-HT receptors, 5-HT may affect blood pressure control and metabolic processes through the autonomic nervous system and the hypothalamic-pituitary axis [9,41], producing insulin resistance and glucose intolerance [42]. Ultrasound assessment of carotid arteries was not performed in the present study. The adverse effects of low central serotoninergic tone on metabolism can also result in an increase in atherosclerosis and cardiovascular risk. Muldoon et al. [11] correlated a blunted response to citalopram with carotid artery thickening and carotid artery plaque, which are considered good indicators of preclinical vascular disease. These authors concluded that the association between central serotoninergic responsivity and preclinical vascular disease was partially mediated by components of the Metabolic Syndrome. Moreover, treatment of depression with SSRI may reduce the incidence of death and recurrent myocardial infarct [43,44]. However, since 5-HT challenge tests are more complex to execute, the

authors attempted to use basal levels of PRL as a screening tool to identify these subjects in the present study.

The present study did not evaluate dietary habits or the degree of physical activity. Besides the influence on PRL secretion, serotoninergic pathways may also affect eating habits and physical activity, contributing to the development of obesity and its complications. Studies have suggested an interaction between 5-HT with other pathways, since serotoninergic control of eating behavior is influenced by glucose and hormones such as insulin, corticosterone, and leptin [45]. Experiments in animals have shown that stimulation of different 5-HT receptor subtypes can either induce anorexia or increase appetite [46].

When the analysis of the associations between PRL and the biochemical data were adjusted for the influence of age, BMI, body fat, and cardiometabolic risk, only the correlation with HDL remained significant. Consequently, the results of the multivariate analysis, allied with the cross-sectional profile of the present study, preclude the present study to infer the presence of causal relationships between PRL secretion and body composition and/or metabolism. Nevertheless, the correlation between PRL and WC remained significant in the multivariate analysis, which indicates that PRL levels could be used as a marker of obesity in this cohort of Brazilian patients. The present results also suggest that basal PRL may be used as a simple marker of serotoninergic activity in routine evaluation of obese and overweight Brazilian patients.

4. CONCLUSION

Patients with higher levels of PRL had a more favorable anthropometric and biochemical profile. The present study suggests that basal levels of PRL correlate well with BMI, waist circumference and biochemical data and may be useful as a tool for the estimation of serotoninergic activity in Brazilian patients who seek Endocrinological evaluation for weight reduction.

ETHICAL APPROVAL AND INFORMED CONSENT

The present study was approved by the research and ethics committee of the Federal University of Rio de Janeiro (project registered as 178/04) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all the patients.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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