Body fat in men with prolactinoma

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ABSTRACT. ***Objective:*** **(a) To evaluate body fat in men with prolactinoma and healthy controls, using whole body dual energy x-ray absorptiometry (DXA), and (b) to correlate DXA results with anthropometry and clinical aspects of male prolactinomas.** ***Material and methods:*** **A cross-sectional study was performed in two University referral centers. Eleven newly-diagnosed men with prolactinoma and 9 with normal PRL levels due to dopamine agonist treatment were submitted to DXA and blood analysis (PRL, testosterone, dihydrotestosterone, estradiol, and SHBG) by the time of their clinical evaluation. They were compared with 14 control men of similar age and body mass index distribution.** ***Results:*** **Newly-diagnosed men with prolactinoma had higher fat percentage in the arms and the total body, when compared with patients treated with dopamine agonists and controls. The former group also presented higher fat percentage in the legs than the controls. Truncal fat percentage of the newly-diagnosed patients was lower than the dopamine agonist treated group. The 3 groups had similar android and gynoid fat contents. Fat percentage of the 6 sites correlated with PRL, testosterone, and dihydrotestosterone levels.** ***Conclusion:*** **Newly-diagnosed men with prolactinomas had higher body fat content. Body fat was linked to disease control, especially to the PRL and androgen levels. Consequently, adequate control of hyperprolactinemia should be pursued in order to reduce the risk of obesity and its metabolic complications in men with prolactinoma.**
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INTRODUCTION

Although prolactinomas, tumors that produce PRL, predominate in women, men are prone to developing complications of the disease, such as visual field defects, hypopituitarism, infertility, and osteoporosis (1-3). Besides the influence on bone density, recent studies have suggested that PRL could alter body composition by influencing body fat. Studies in animals have concluded that PRL stimulates hyperphagia (4, 5) and increases abdominal fat (6). A similar effect could be present in humans, whose abdominal adipose tissue presents 4 PRL receptor isoforms (7). In fact, clinical studies in humans have shown that patients with prolactinoma may present weight gain (8, 9). PRL may influence body weight through the regulation of leptin, an adipocyte-derived hormone that increases satiety (10). On the other hand, leptin could counteract by stimulating PRL and LH secretion (11). PRL secretion is enhanced in obese women in proportion to body mass index (BMI) and particularly associated with visceral fat size (12). Moreover, normalization of PRL levels induced by dopamine agonist treatment results in weight loss (8, 9, 13). However, these drugs could influence body composition independently of hyperprolactinemia, since the dopaminergic tone itself has been suggested to influence body weight (13).

The metabolic consequences of obesity are currently well known. Factors such as hyperlipidemia and insulin resistance can converge and further elevate the cardiovascular disease risk (14, 15). Considering that scarce data is available on body fat in hyperprolactinemia, we were interested in investigating this aspect in men with prolactinoma. The aims of the present study were: (a) to evaluate body fat in men with prolactinoma and healthy controls, using whole body dual energy x-ray absorptiometry (DXA), and (b) to correlate DXA results with anthropometry and clinical aspects of male prolactinomas.

MATERIALS AND METHODS

Eleven newly-diagnosed men with prolactinoma, 9 men with prolactinoma but normal PRL levels as a consequence of dopamine agonist treatment, and 14 controls were evaluated in a cross-sectional study of body fat, using DXA. Data regarding the clinical aspects of the disease (age at diagnosis, disease and treatment duration, and treatment modalities) and anthropometric measures, such as BMI, abdominal and hip circumferences, waist to hip ratio (WHR), and waist to height ratio (WHER), were collected. Biochemical evaluation included PRL, testosterone, dihydrotestosterone (DHT), estradiol, and SHBG. DXA results were analyzed simultaneously with anthropometry, biochemical data, and clinical aspects of the prolactinoma, in order to identify correlations.

Patients

Twenty patients with prolactinoma were invited to participate in the study by the time of their clinical evaluation at the two centers involved in the study between October 2004 and July 2007 (Table 1). Eleven subjects were newly-diagnosed patients and, consequently, had never been treated with dopamine agonists. The other 9 patients were already in treatment with cabergoline (mean weekly dose=0.9±0.4 mg), 77.8% of these having

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Table 1 - *Clinical profile. Newly-diagnosed, cabergoline-treated patients, and controls.*

	Newly-diagnosed (no.=11)	Cabergoline-treated (no.=9)	Controls (no.=14)
Age (yr)	34.6±9.3	35.3±10.7	35.5±11.6
Age at diagnosis (yr)	30.6±12.4	32.9±10.3	-
Disease duration (yr)	1.1±0.8	2.6±2.6	-
Erectile dysfunction prevalence	30.6±12.4	32.9±10.3	-
Treated surgically	0	77.8%	-
Treatment duration (yr)	0	2.1±2.0	-
PRL (mIU/l)	24,846.4±24,867.6	201.4±78.4	234.9±88.8
Testosterone (nmol/l)	8.2±4.1	17.4±5.0	24.0±10.0
Dihydrotestosterone (pmol/l)	56.0±36.2	333.5±259.6	283.9±144.1
Estradiol (pmol/l)	75.5±25.0	87.2±25.3	136.4±55.6
SHBG (nmol/l)	32.2±4.2	32.4±11.0	40.1±16.4
Free androgen index	256.5±128.0	560.2±135.3	624.8±259.2
Free estrogen index	2.4±0.8	3.0±1.6	3.9±2.1
Body mass index (kg/m^2)	27.6±2.8	24.3±2.3	26.9±3.2
Waist circumference (cm)	104.1±7.8	87.1±5.0	92.0±8.2
Hip circumference (cm)	98.3±8.1	95.±3.8	96.4±15.7
Waist to hip ratio	1.1±0.0	0.9±0.1	1.0±0.3
Waist to height ratio	0.6±0.5	0.5±0.1	0.5±0.2

been previously submitted to pituitary surgery. The mean age of the newly-diagnosed group and of the cabergoline-treated patients was similar (34.6±9.3 *vs* 35.3±10.7 yr; p=0.89). The mean disease duration was 1.1±0.8 yr (median=1 yr) in the former and 2.6±2.6 yr (median=1 yr) in the latter (p=0.09).

Both micro- and macroprolactinoma patients were included in the study (no.=8 and 12, respectively). The term microprolactinoma refers to tumors with maximal diameter below 1 cm (at computed tomography and/or magnetic resonance imaging), while macroprolactinomas refers to those with maximal diameter ≥1 cm (16). In order to avoid the "hook effect", serum samples of patients with macroadenomas but modestly elevated PRL levels were diluted.

Exclusion criteria were the diagnosis of obesity (BMI≥30 kg/m^2), GH deficiency, hypothyroidism, and adrenal insufficiency. Twenty-five patients were initially evaluated, but 5 were excluded: 4 due to obesity and 1 to hypopituitarism. Hypothyroidism was diagnosed on the basis of TSH, and free T_4 antibodies levels. Patients with macroprolactinomas were submitted to an insulin tolerance test in order to detect associations with adrenal insufficiency and GH deficiency. GH deficiency was also diagnosed based on low IGF-I levels for age and gender.

Controls

The control group consisted of 14 healthy men with age, BMI, socioeconomic, and geographic distribution similar to that of the two patient groups (Table 1). Dietary habits of controls were also similar to the patients'. Their mean age was 35.5±11.6 yr.

Dual energy x-ray absorptiometry

Fat mass measurement was performed with a DXA scanner (Lunar Prodigy Advance, GE Healthcare). Six sites were analyzed: arms, legs, trunk, android, gynoid, and total body.

Anthropometry

Total body weight was measured on a spring balance scale (Filizola, Brazil) with participants dressed in underwear. Weights were recorded to the nearest 0.1 kg.

Standing height was measured without shoes with a stadiometer (Filizola, Brazil) and recorded to the nearest 0.5 cm.

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

Using a flexible measuring tape, with the subject standing, the waist circumference was measured in the mid-distance between the lower costal margin and the iliac crest and recorded to the nearest 1 mm. Hip was the maximum circumference at the level of the femoral trochanters.

WHR was calculated by dividing the waist circumference (cm) by the hip circumference (cm).

WHER was calculated by dividing the waist circumference (cm) by the height (cm).

Assays

Serum FSH, GH, IGF-I, LH, PRL, SHBG, and TSH were assessed using Immulite immunometric assays commercial kits. The intra- and interassay coefficients of variation (CV) were 2.5 and 6.3%, 5.3 and 5.7%, 3.9 and 7.7%, 3.6 and 6.8%, 2.2 and 6.9%, 6.1 and 8.0%, and 5.1 and 6.4%, respectively. Normal ranges in our laboratory were as follows: FSH=0.7-11.1 mIU/ml; IGF-I=15.1-46.5 nmol/l (21-25 yr), 15.2-42.8 nmol/l (26-30 yr), 15.0-39.9 nmol/l (31-35 yr), 14.2-36.9 nmol/l (36-40 yr), 13.1-34.7 nmol/l (41-45 yr), 12.2-32.8 nmol/l (46-50 yr), 11.3-30.9 nmol/l (51-55 yr), 10.5-29.3 nmol/l (56-60 yr), 9.8-27.6 nmol/l (61-65 yr); LH=0.8-7.6 mIU/ml; PRL=53.0-360.4 mUI/l; SHBG=13.0-71.0 nmol/l; TSH=0.4-4.0 µIU/ml. Normal GH peak during the insulin tolerance test corresponded to levels ≥7.8 mIU/l. Cortisol, estradiol, and testosterone were assessed using Immulite competitive immunoassays commercial kits. The intra- and interassay CV were 7.5 and 8.4%, 9.9% and 16%, and 10% and N/I (not informed), respectively. Normal ranges in our laboratory were as follows: cortisol (08:00 h) =138.0-689.8 nmol/l, estradiol ND (not detectable)-205.6 pmol/l, and testosterone =9.1-55.2 nmol/l (20-49 yr) or 6.3-26.3 nmol/l (>50 yr). DHT was assessed by a DSL-9600 Active DHT coated-tube radioimmunoassay kit. The intra- and interassay CV were 6.2% and 8.5%, respectively. Nor-

mal range in our laboratory was: 172.0-688.0 pmol/l. Free T_4 was assessed by an Immulite competitive analog immunoassay commercial kit. The intra- and interassay CV were 7.5 and 9.0%, respectively. Normal range in our laboratory was: 10.3-24.5 pmol/l.

Free androgen and estrogen indexes

Free androgen (FAI) and estrogen indexes (FEI) were calculated respectively by dividing testosterone (nmol/l) or estradiol (nmol/l) by the SHBG levels (nmol/l) and multiplying to a constant (10^4).

Ethical aspects

The present study was approved by the research and Ethics Committees of the two centers involved and informed consent was obtained from all patients and controls.

Statistical analysis

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

The unpaired T test was used to compare means between 2 groups and Fisher's exact test analyzed categorical variables. When more than 2 groups were studied, the one-way analysis of variance test (ANOVA) was used to compare means and categorical variables were analyzed using the chi-square test. Bonferroni's Multiple comparison test was performed after the one-way ANOVA test in order to evaluate all the pairs of columns. Whenever necessary, data were transformed with the purpose of allowing the analysis by parametric tests. Time data were transformed through inversions (time=1/time), measurements were log base 10 transformed (measurement=Log measurement), and ratios were square root transformed (ratio=square root of ratio). The Kolmogorov-Smirnov test was used to analyze the residuals for normality (when α=0.05, data passes this normality test). Whenever data did not pass the normality test, the Mann-Whitney test was used to compare means between 2 groups and the Kruskal-Wallis test, to compare 3 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.

Relationships between 2 numeric variables were studied by linear regression, Pearson parametric and Spearman non-parametric correlation; multiple regression was employed for the multivariate analysis. The statistical significance was set as 5%.

The analyses were carried out using GraphPad Prism version 4.02 for Windows, GraphPad Instat version 3.05 for Win 95/NT (GraphPad Software, San Diego, California, USA), and Epi Info™ version 3.3.2 (Centers for Disease Control and Prevention, USA).

RESULTS

Newly-diagnosed vs *dopamine agonist-treated patients and controls*

When compared with the cabergoline-treated patients and the controls, the newly-diagnosed group had higher PRL (p<0.01 in both post tests) and lower testosterone (p<0.05 in both post tests), DHT levels (p<0.01 in both post tests), and FAI (p<0.01 in both post tests) (Table 1). The comparison between cabergoline-treated patients and controls revealed no differences regarding the biochemical and hormonal data.

Newly-diagnosed men with prolactinoma had higher fat percentage in the arms and total body, when compared with patients treated with cabergoline (Fig. 1) and controls (Fig. 2). The former group also presented higher fat content than the controls in the legs. Truncal fat percentage of the newly-diagnosed patients was higher than that of the cabergoline-treated group. The 3 groups had similar android and gynoid fat contents. Additionally, no difference was obtained when fat percentages of cabergoline-treated patients and controls were compared (Fig. 3). Although the 3 groups had similar BMI (Table 1) (p>0.05 in the 3 comparisons), the newly-diagnosed group had a higher waist circumference than the other 2 groups (Table 1) (p<0.01). The same results were obtained when WHR was compared (Table 1) (p<0.01). WHER was higher in the newly-diagnosed than in the cabergoline-treated group (Table 1) (p<0.01). The comparison between the cabergoline-treated and the controls groups revealed no significant differences in the aspect of anthropometric measures.

Correlations

Fat percentage of the 6 sites evaluated with DXA correlated with PRL (r: arms=0.87, legs=0.76, trunk=0.67, android=0.55, gynoid=0.59, and total body =0.76; p<0.01), testosterone (r: arms =–0.73, legs =–0.71, trunk =–0.82, android =–0.74, gynoid =–0.67, and total body =–0.81; p<0.01), FAI (r: arms =–0.79, legs =–0.72, trunk =–0.61, android =–0.49, gynoid =–0.58, and total body =–0.68; p<0.01, except for the android region, where p=0.02), and DHT (r: arms =–0.95, legs =–0.78, trunk =–0.80, android =–0.75, gynoid =–0.65, and total body =–0.89; p<0.01).

Regarding anthropometry, arm, leg, truncal, android, gynoid, and total fat percentages were correlated with BMI

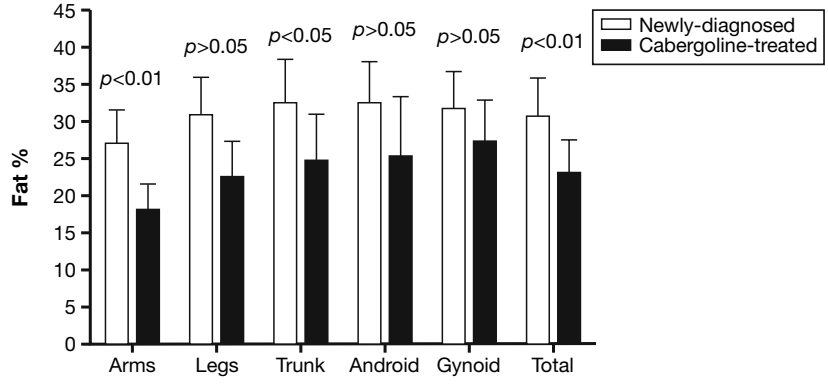

Fig. 1 - *Body fat %. Newly-diagnosed* vs *cabergoline-treated patients.*

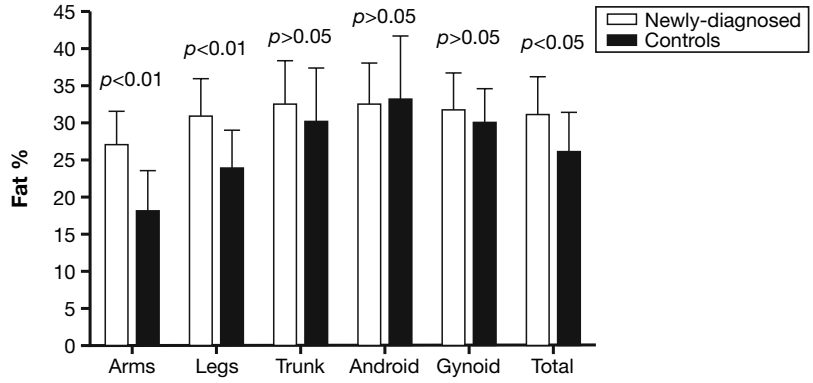

Fig. 2 - *Body fat %. Newly diagnosed patients* vs *controls.*

(r=0.70, 0.67, 0.73, 0.59, 0.47, and 0.72, respectively; $p<0.01$, except for the gynoid region, where $p=0.03$), waist circumference (r=0.90, 0.73, 0.71, 0.63, 0.55, and 0.78, respectively, $p<0.01$), hip circumference (r=0.47, 0.51, 0.53, 0.50, 0.63, and 0.57; $p=0.03$, 0.02, 0.01, 0.02, <0.01, and <0.01, respectively), and WHER (r=0.83, 0.79, 0.81, 0.76, 0.68, and 0.86, respectively; $p<0.01$). The arm, leg, truncal, and total body fat contents also correlated with WHR (r=0.74, 0.53, 0.50, and 0.56; $p<0.01$, except for the truncal region, where $p=0.03$).

Multivariate analysis

A multivariate analysis (Table 2) was performed with the purpose of identifying the influence of PRL, testosterone, DHT, and FAI on DXA results, when these factors were analyzed together. Multiple regression models indicated that: (a) the arm fat percentage correlated with PRL and DHT levels, (b) the leg and gynoid fat percentages correlated with the PRL levels, (c) the truncal and android fat percentages, with the testosterone levels, and (d) the total body fat percentage, with the PRL and testosterone levels.

DISCUSSION

Although men do not go through the lactation process, hyperprolactinemia may influence human male physiology in various ways, with a number of harmful effects, including osteoporosis and infertility (2, 3). Regarding body composition, it was suggested that PRL increases body fat in men, (9) which would put these patients at risk for the development of obesity and its metabolic consequences (hyperlipidemia, hypertension, and hyperglycemia) (17). Hyperprolactinemia could also influence body fat through secondary hypogonadism.

A limitation of using DXA instead of computed tomography or magnetic resonance imaging with the purpose of body fat evaluation is that DXA does not provide direct assessment of visceral fat, which is considered more metabolically active (17). This is partially compensated by the analysis of the android area and the correlations with waist circumference, considered the best clinical measure of abdominal fat (17). On the other hand, DXA provides adequate estimation of truncal fat, which was suggested to have a greater impact than abdominal fat on cardiovascular and metabolic syndrome risk factors (18). Another important advantage of DXA, in the case of developing countries such as Brazil, is its lower cost.

Considering the financial implications of body fat evaluation, one of the objectives of the study was to correlate DXA and anthropometric data. Abdominal and hip circumferences are very frequently used with the purpose of estimating body fat in the general population and the DETECT Study suggested that WHER is the best anthropometric indicator of cardiovascular risk (19). The present study confirmed the literature concerning the reliability of anthropometric measures in the evaluation of Brazilian men with prolactinoma.

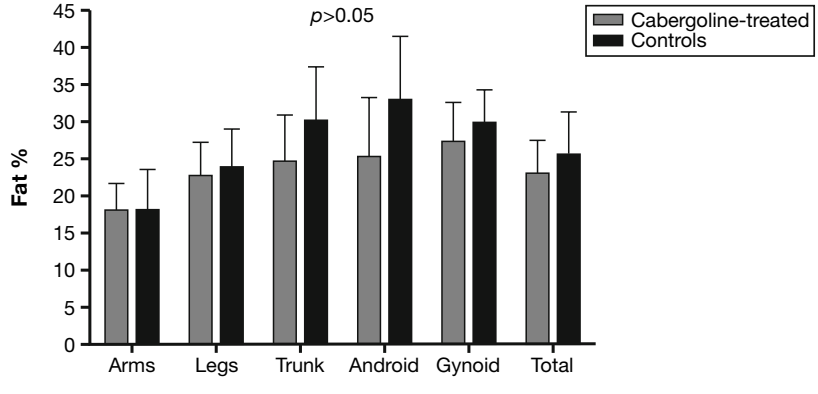

Fig. 3 - *Body fat %. Cabergoline-treated patients* vs *controls.*

Table 2 - *Multiple regression.*

DXA site	Correlation	r^2
Arm fat %	PRL DHT	82.9%
Leg fat %	PRL	66.8%
Truncal fat %	Testosterone	72.1%
Android fat %	Testosterone	56.5%
Gynoid fat %	PRL	66.8%
Total fat %	PRL Testosterone	73.2%

$p<0.01$ in all the multiple regression models. DXA: whole body dual energy x-ray absorptiometry; DHT: dihydrotestosterone.

As the prevalence of prolactinomas is much lower in men than women, another limitation of the present study is the small cohort analyzed. However, our group of patients was very similar in number to other studies reported in the literature. Macroprolactinomas predominated over microprolactinomas (2, 8, 20) and age at diagnosis was only slightly lower than that reported by others (20, 21). Moreover, cabergoline doses were lower (2, 20, 22). In Brazil, these findings can be attributed to the fact that many patients cannot support the medication costs and depend on the government for their acquisition. Hence, data obtained from this small cohort could provide interesting points for discussion on a subject as scarcely studied *in vivo* as body fat in men with prolactinomas.

In the present study, both PRL levels and fat content were higher in newly-diagnosed men with prolactinoma than in healthy subjects and cabergoline-treated patients. Moreover, the latter presented normal PRL levels and body fat content similar to the controls'. These results are in accordance with the literature, including another study developed by the present group of authors using Brazilian women with prolactinomas (23). Previous studies have suggested that PRL stimulates the development of adipose tissue (6, 8, 9), some of them observing a particular effect on the increase of abdominal fat (6). To the best of our knowledge, no previous study has focused on the correlations between body fat and disease control in men with prolactinoma. The present study results favor the hypothesis of a direct stimulatory effect of PRL on the development of adipose tissue, considering that the newly-diagnosed group differed from the others concerning PRL levels, with which body fat correlated. Additionally, there were also correlations between body fat and androgens, such as testosterone and DHT, which also supports the influence of secondary hypogonadism. The literature has numerous data on androgen influence on body fat. Androgen deficiency facilitates body fat increase and lean mass reduction (24). Bioavailable testosterone levels are predictive of fat deposition in the subcutaneous adipose tissue of both truncal and peripheral areas. Induced hypogonadism in men with prostate cancer results in adverse body composition changes (24). On the other hand, testosterone replacement decreases fat mass in hypogonadal men (25, 26). Additionally, androgen treatment reduces truncal and visceral adipose tissue (27). It also leads to a drop in leptin levels (28).

We excluded obese subjects (BMI≥30 kg/m^2) and patients with GH deficiency, hypothyroidism, and adrenal insufficiency since all these conditions can affect body composition independently of PRL. Obese subjects were excluded due to the association between obesity and the metabolic syndrome, which is characterized by increased abdominal fat (17). This characteristic pattern of fat distribution could result in increased android fat (17). Adverse body composition and lipid abnormalities can be found in patients with hypopituitarism and reversed by GH replacement (29).

The present results suggest that adequate control of hyperprolactinemia and hypogonadism is important in order to avoid deleterious consequences on body composition and the development of the metabolic syndrome.

CONCLUSION

Newly-diagnosed men with prolactinomas with elevated PRL and low testosterone levels had higher body fat content than cabergoline-treated patients and controls. Body fat was linked to disease control (PRL and androgen levels). Consequently, adequate control of hyperprolactinemia should be pursued in order to reduce the risk of obesity and its metabolic complications in men with prolactinoma.

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