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# Bone density in women with prolactinoma treated with dopamine agonists

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**Abstract** *Objectives* (1) to evaluate bone density in women with prolactinoma treated with dopamine agonists and healthy controls, using dual energy x-ray absorptiometry (DXA), (2) to classify the results according to the current International Society for Clinical Densitometry (ISCD) criteria, and (3) to correlate bone density with lean and fat masses, biochemical data and clinical aspects of prolactinomas.

*Materials and methods* A cross-sectional study was performed in two University referral centers. Forty-five premenopausal women with prolactinoma were submitted to DXA and blood analysis (prolactin, estradiol, testosterone, SHBG, calcium, phosphorus, PTH, C-telopeptides of type 1 collagen, and osteocalcin) by the time of their clinical evaluation. They were compared with 25 control women of similar age and body mass index distribution.

*Results* Women with prolactinoma had lower lumbar spine *Z*-score than controls. Femoral neck, trochanter, and total proximal femur *Z*-scores were similar in patients and controls. Twenty-two percent of the patients had *Z*-scores below the expected age range vs. 4% in the control group. Lumbar spine, femoral neck, and total proximal femur *Z*-scores were mainly correlated with the amenorrhea duration. The trochanter *Z*-score was associated with the gynoid lean/fat mass ratio.

*Conclusions* Based on the current ISCD criteria, bone density evaluation in women with prolactinoma reveals bone loss, especially of trabecular type. Bone density in these patients was particularly associated with the duration of amenorrhea, which reinforces the importance of the adequate disease control in women with prolactinoma in order to avoid complications of this disease.

**Keywords** Prolactinoma · Bone density · Hyperprolactinemia · Women

**Abbreviations**

| | |
|---|---|
| NPNE | Patients with normal PRL and estradiol levels |
| EPNE | Patients with elevated PRL and normal estradiol levels |
| EPLE | Patients with elevated PRL and low estradiol levels |

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## Introduction

Previous studies have shown that patients with prolactinoma are susceptible to developing osteopenia and osteoporosis [1–6]. The prolactinoma-related bone loss can be severe and affect young patients, since it can restrict peak bone mass acquisition [5]. Although men are less prone to present osteoporosis, those with prolactinoma are as equally affected as women by bone loss [4, 6]. In Brazil, the prevalence of osteopenia and osteoporosis in patients with prolactinomas is also high [3, 6]. In this country, a significant portion of these patients remain hyperprolactinemic during long periods, since many are not able to support the medication cost and interrupt treatment or use suboptimal doses of dopamine agonists.

These previous studies on bone loss in patients with prolactinoma were developed considering the criteria based on the *T*-score that compares subjects with the young adult. However, the current International Society for Clinical Densitometry (ISCD) criteria for premenopausal women are based on the *Z*-score, which compares subjects with age-matched ones [7]. Currently, the normal ISCD criteria for age is a *Z*-score of –2.0 SD or greater [7].

The aims of this study were: (1) to evaluate bone density in women with prolactinoma and healthy controls, using dual energy x-ray absorptiometry (DXA), (2) to classify the results according to the current ISCD criteria, and (3) to correlate bone density with lean and fat masses, biochemical data, and clinical aspects of prolactinomas.

## Patients and methods

The present study consists of a cross-sectional evaluation of BMD in 45 Brazilian premenopausal women with prolactinoma and 25 healthy women from a control group, using DXA. The latter was also employed in the analysis of fat and lean masses of patients and controls. Subjects were additionally evaluated for prolactin (PRL), estradiol, testosterone, SHBG, calcium, phosphorus, PTH, C-telopeptides of type 1 collagen (CTX), and osteocalcin levels. Bone densitometry results were analyzed simultaneously with fat and lean masses, biochemical data, and clinical aspects of the prolactinomas, in order to identify correlations.

## Patients

Patients with prolactinoma, already receiving dopamine agonist treatment for the disease, were invited to participate in the study by the time of their clinical evaluation at the Hyperprolactinemia Unit of HUCFF and the Pituitary Unit of IEDE between October 1st 2004 and September 30th 2006. Patients' age ranged from 20 to 48 years [34.1 ± 7.9 years (mean ± SD)]. The mean disease duration was 5 ± 2.8 years.

Both micro- and macroprolactinoma patients were included in the study ($n = 33$ and 12, respectively). The diagnosis of prolactinoma had been based on the presence of clinical features of hyperprolactinemia and/or hypogonadism, associated with the detection of at least two samples with elevated PRL levels, and an image exam showing a pituitary tumor. The term microprolactinoma refers to tumors with PRL levels at diagnosis ≥50 μg/L and maximal diameter below 1 cm (at computed tomography and/or magnetic resonance imaging), while macroprolactinomas, to those with PRL levels at diagnosis ≥200 μg/L and maximal diameter ≥1 cm.

Patients with macroprolactinoma, and those with microprolactinoma and low cortisol levels (<5 μg/dL), were submitted to an insulin tolerance test in order to detect associations with GH deficiency and/or secondary adrenal insufficiency. GH deficiency was also diagnosed based on the existence of low IGF-I levels for age and sex. Hypothyroidism was diagnosed on the basis of TSH and free T4 basal levels, whereas hypogonadism, on basal levels of FSH, LH, and estradiol. No patient had excess of other pituitary hormones.

Exclusion criteria were: previous occurrence of nontraumatic fractures, pituitary surgery, diagnosis of GH deficiency, adrenal insufficiency, hypothyroidism, primary hypogonadism, and other diseases or use of medications that could affect bone metabolism. From the 58 patients consecutively invited to participate in this study, eight patients were excluded due to GH deficiency, two to pituitary surgery, two to hyperparathyroidism, and one to primary hypogonadism.

### Controls

The control group consisted of healthy premenopausal women with age, socioeconomic, and geographic distribution similar to the patient group. Their ages ranged between 22 and 46 years (37.5 ± 7.8 years). All controls denied a previous occurrence of nontraumatic fractures. The prevalence of smoking, alcohol use, calcium intake, and regular physical activity in the control group was compatible with that of the patient group.

### Dual energy X-ray absorptiometry

Bone density measurement of all subjects was performed with the same DXA scanner (Lunar Prodigy Advance, GE Healthcare). Four sites were analyzed in bone densitometry: lumbar spine, femoral neck, trochanter, and total

proximal femur. Subjects' BMD was classified according to *Z*-score. BMD of those with a *Z*-score of –2.0 or lower was defined as below the expected range for age and that of the ones with a *Z*-score above –2.0 SD was within the expected range for age.

Fat and lean masses were measured with a whole body DXA. Six sites were analyzed: arms, legs, trunk, android, gynoid, and total body. The arm region was defined as the tissue distal to the vertical lines passing through the shoulder joints. The leg region was defined as the tissue below the oblique lines passing through the hip joints. The trunk region was delineated by an upper horizontal border below the chin, vertical borders lateral to the ribs, and a lower border formed by the oblique lines passing through the hips, excluding the gynoid region (hips and thighs). The android region was determined by an upper horizontal border between T12 and L1, lateral borders set just outside the soft tissue, and a lower horizontal border superior to the iliac crest. The lean/fat mass ratio (LFR) of each site was calculated by dividing lean mass (*g*) to fat mass (*g*).

### Body mass index

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

### Assays

Serum FSH, GH, IGF-I, LH, PRL, PTH, 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%, 3.8 and 5.4%, 3.6 and 6.7%, 2.2 and 6.9%, 6.3 and 8.6%, 6.1 and 8.0%, and 5.1 and 6.4%, respectively. Normal ranges in our laboratory were as follows: FSH (follicular phase, premenopausal) = 2.8–11.3 mIU/mL; IGF-I = 127.0–424.0 μg/L (20 years), 116.0–358.0 μg/L (21–25 years), 117.0–329.0 μg/L (26–30 years), 115.0–307.0 μg/L (31–35 years), 109.0–284.0 μg/L (36–40 years), 101.0–267.0 μg/L (41–45 years), 94.0–252.0 μg/L (46–50 years); LH = 0.8–7.6 mIU/mL; PRL = 3.6–25.0 μg/L; PTH = 7–53 pg/mL; SHBG = 13–71 nmol/L; and TSH = 0.4–4 μIU/mL. GH levels above 3 ng/mL were consistent with a normal peak at the insulin tolerance test. 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%, respectively. Normal ranges in our laboratory were as follows: cortisol (8:00 h) = 5.0–25.0 μg/dL, estradiol not detectable—160.0 pg/mL, and testosterone = 63.0–120.0 ng/dL. Free T4 was assessed by an Immulite competitive analog immunoassay commercial kit. The intra- and interassay CV were 7.5 and 9.0%, respectively. The normal range in our laboratory for free T4 was 0.8–1.9 ng/dL. Patients who presented menstrual cycles, even if irregular, were studied in the early follicular phase (days 1–7 from bleeding).

### Free estrogen and androgen indexes

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

### Ethical considerations

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 Student's *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 mean values 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. Relationships between two numeric variables were studied by linear regression and Pearson parametric correlation; stepwise multiple regression was employed for the multivariate analysis. Whenever necessary, data were transformed with the purpose of allowing the analysis by parametric tests. The statistical significance was set as 5%.

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

## Results

### Patients vs. controls

The mean lumbar spine *Z*-score was lower in patients as compared with controls ($p = 0.0046$). The *Z*-scores of the

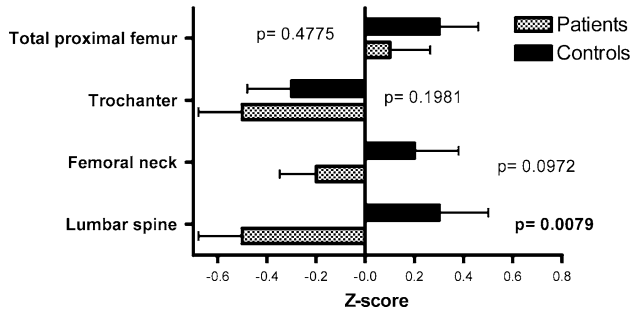


**Fig. 1** *Z*-scores of patients and controls

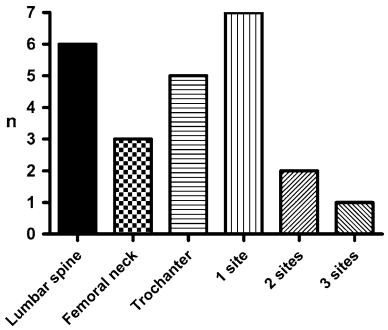


**Fig. 2** *Z*-scores below the expected range for age in patients

other three skeletal sites were similar in patients and controls (Fig. 1 and Table 1). Ten patients (22%) had *Z*-scores below the expected range for age in one or more sites. In most patients in this situation, a single site was affected. Figure 2 exhibits these findings according to location and number of sites involved. Only one of the controls (4%) had a trochanter *Z*-score of –2.1 SD ($p = 0.0447$).

Body mass index and LFR of arms, legs, trunk, android regions, and total body were similar in patients and controls. However, patients had higher gynoid LFR than controls. Calcium, phosphorus, PTH, CTX, and osteocalcin levels of patients and controls were also comparable (Table 1). Only one patient (2.2%) and one control (4%) had elevated CTX levels ($p = 1.0000$). No patient or control had elevated osteocalcin levels.

**Table 1** Patients and controls

| | Patients | Controls | *p*-Value |
|---|---|---|---|
| *N* | 45 | 25 | – |
| Age (years) | 34.5 ± 7.9 | 37.5 ± 7.7 | 0.1086 |
| BMI (kg/m$^2$) | 27.7 ± 6.1 | 25.1 ± 7.4 | 0.3234 |
| PRL (μg/L) | 121.5 ± 242.9 | 11.8 ± 5.4 | <0.0001 |
| Estradiol (pg/mL) | 112.7 ± 147.1 | 83.8 ± 43.9 | 0.7610 |
| Testosterone (ng/dL) | 89.9 ± 136.0 | 72.8 ± 74.4 | 0.9609 |
| SHBG (nmol/L) | 59.0 ± 30.4 | 79.9 ± 40.3 | 0.0267 |
| FEI | 76.8 ± 64.4 | 48.6 ± 28.8 | 0.1341 |
| FAI | 801.5 ± 1638.0 | 385.3 ± 358.9 | 0.1341 |
| CTX (ng/mL) | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.8280 |
| Osteocalcin (ng/mL) | 20.5 ± 8.3 | 20.8 ± 7.7 | 0.9781 |
| Lumbar *Z*-score | –0.5 ± 1.2 | 0.3 ± 1.0 | 0.0047 |
| Neck *Z*-score | –0.2 ± 1.0 | 0.2 ± 0.9 | 0.0757 |
| Trochanter *Z*-score | –0.5 ± 1.2 | –0.3 ± 0.9 | 0.1981 |
| Total proximal femur *Z*-score | 0.1 ± 1.1 | 0.3 ± 0.8 | 0.2112 |
| Arm lean/fat mass ratio | 1.9 ± 0.8 | 1.8 ± 0.6 | 0.8098 |
| Leg lean/fat mass ratio | 1.5 ± 0.5 | 1.3 ± 0.4 | 0.1649 |
| Truncal lean/fat mass ratio | 1.6 ± 0.7 | 1.4 ± 0.6 | 0.8988 |
| Android lean/fat mass ratio | 1.5 ± 0.8 | 1.4 ± 0.7 | 0.9093 |
| Gynoid lean/fat mass ratio | 1.2 ± 0.3 | 1.0 ± 0.3 | 0.0397 |
| Total body lean/fat mass ratio | 1.7 ± 0.6 | 1.5 ± 0.4 | 0.6657 |

## Patients with normal and elevated PRL levels

By the time they were enrolled in this study, all patients were receiving treatment with dopamine agonists (73.3% with bromocriptine and 26.7% with cabergoline). Mean treatment duration corresponded to 2.5 ± 2.5 years. The mean daily dose of bromocriptine was 4.9 ± 3.5 mg; the mean cabergoline weekly dose was 0.6 ± 0.4 mg. Age, age at diagnosis of prolactinoma, disease and treatment duration, PRL, estradiol, testosterone, SHBG, calcium, phosphorus, PTH, CTX, and osteocalcin levels, and DXA results were similar in bromocriptine and cabergoline users (data not shown). Nevertheless, 33 patients (73.3%) had elevated PRL levels at study entry, with persistently elevated PRL levels during the previous year (129.0 ± 123.0 μg/L). The 12 well-controlled patients had a mean period of normoprolactinemia of 8.1 ± 6.5 months. When patients' clinical characteristics were studied, no significant difference involving these two groups was identified, with the exception of PRL levels (Table 2) and the prevalence of amenorrhea (42.4% vs. 0%, respectively).

Although *Z*-scores of the femoral DXA sites were lower in patients with elevated PRL levels, the difference between the two groups did not reach statistical significance (Fig. 3 and Table 2). Two patients with normal PRL (16%) and eight with elevated PRL levels (24%) had *Z*-scores below the expected range for age in one or more sites ($p = 0.7054$).

Patients with normal PRL had lower BMI, while LFR was higher in the same group. Calcium, phosphorus, PTH, CTX, and osteocalcin levels were equivalent in patients with normal and elevated PRL levels (Table 2). The only patient with high CTX had normal PRL levels.

## Patients with normal and low estradiol

No patient had been on treatment with estrogen or contraceptive pills since the diagnosis of prolactinoma was

**Table 2** Patients with normal vs. elevated prolactin levels at study entry

| | Normal PRL | Elevated PRL | *p*-Value |
|---|---|---|---|
| *N* | 12 | 33 | – |
| Age (years) | 34.8 ± 6.6 | 34.2 ± 8.4 | 0.8246 |
| Age at diagnosis (years) | 30.4 ± 6.9 | 28.9 ± 8.0 | 0.5683 |
| Disease duration (years) | 4.3 ± 2.6 | 5.3 ± 2.9 | 0.2886 |
| Amenorrhea duration (years) | 5.3 ± 8.9 | 5.9 ± 4.7 | 0.2128 |
| Treatment duration (years) | 1.6 ± 2.1 | 2.9 ± 2.6 | 0.1133 |
| BMI (kg/m$^2$) | 24.3 ± 4.7 | 28.9 ± 6.1 | 0.0235 |
| PRL (μg/L) | 11.7 ± 5.8 | 161.6 ± 273.6 | <0.0001 |
| Estradiol (pg/mL) | 82.9 ± 58.5 | 123.6 ± 167.7 | 0.9505 |
| Testosterone (ng/dL) | 83.0 ± 100.1 | 92.4 ± 148.2 | 0.7839 |
| SHBG (nmol/L) | 59.0 ± 31.1 | 56.5 ± 43.4 | 0.4248 |
| FEI | 61.0 ± 53.9 | 82.5 ± 67.6 | 0.5169 |
| FAI | 589.9 ± 698.2 | 878.4 ± 1870.0 | 0.7866 |
| CTX (ng/mL) | 0.3 ± 0.2 | 0.3 ± 0.2 | 0.3940 |
| Osteocalcin (ng/mL) | 22.4 ± 9.3 | 20.2 ± 7.6 | 0.4267 |
| Lumbar *Z*-score | –0.7 ± 1.1 | –0.4 ± 1.3 | 0.4257 |
| Neck *Z*-score | 0.2 ± 0.9 | –0.3 ± 0.9 | 0.1555 |
| Trochanter *Z*-score | 0.0 ± 1.5 | –0.7 ± 1.1 | 0.1619 |
| Total proximal fêmur *Z*-score | 0.5 ± 1.3 | 0.0 ± 1.0 | 0.1690 |
| Arm lean/fat mass ratio | 2.5 ± 0.9 | 1.7 ± 0.7 | 0.0043 |
| Leg lean/fat mass ratio | 1.9 ± 0.5 | 1.4 ± 0.4 | 0.0008 |
| Truncal lean/fat mass ratio | 2.1 ± 0.9 | 1.4 ± 0.6 | 0.0022 |
| Android lean/fat mass ratio | 2.0 ± 1.2 | 1.3 ± 0.6 | 0.0046 |
| Gynoid lean/fat mass ratio | 1.4 ± 0.4 | 1.1 ± 0.3 | 0.0030 |
| Total body lean/fat mass ratio | 2.1 ± 0.7 | 1.5 ± 0.5 | 0.0009 |

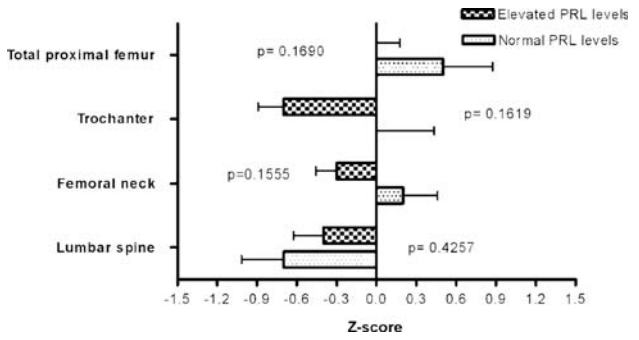


**Fig. 3** *Z*-scores: patients with normal vs. elevated prolactin levels

established. Most patients (48.9%) had normal estradiol levels, despite the presence of elevated PRL levels (EPNE). As mentioned before, 26.7% had normal PRL and estradiol levels (NPNE). The remaining 24.4% had elevated PRL and low estradiol levels (below 30 pg/mL, compatible with menopause—EPLE). On the subject of disease control, EPLE had higher PRL, with lower estradiol levels and FEI (Table 3). Sixty-four percent of EPLE complained of amenorrhea at study entry.

Although the four *Z*-scores were lower in EPLE, the difference between the three groups did not reach statistical significance (Fig. 4 and Table 3). In NPNE, the prevalence of *Z*-scores below the expected range for age corresponded to 16%, while the prevalence in EPNE and EPLE reached 18 and 36%, respectively ($p = 0.4285$).

Lean/fat mass ratio was higher in NPNE. The three groups had similar levels of calcium, phosphorus, PTH, CTX, and osteocalcin levels (Table 3).

### Correlations

Femoral neck, trochanter, and total proximal femur *Z*-scores correlated with age at diagnosis ($r = 0.3544$, 0.4415, and 0.3819; $p = 0.0169$, 0.0024, and 0.0090, respectively). All sites had *Z*-scores correlated with the approximate duration of amenorrhea/hypogonadism ($r$ and $p$: lumbar spine = –0.3106 and 0.0402; femoral neck = –0.3845 and 0.0100; trochanter = –0.3307 and 0.0284; total proximal femur = –0.3552 and 0.0180, respectively). The lumbar spine *Z*-score also correlated with the PRL levels ($r = -0.3609$, $p = 0.0149$).

In the patient group, there was no significant correlation between *Z*-scores and BMI. When *Z*-scores were studied together with LFR, femoral neck and trochanter *Z*-scores correlated with gynoid LFR ($r = 0.3066$ and 0.3793; $p = 0.0405$ and 0.0102, respectively). Trochanter *Z*-score also correlated with leg LFR ($r = 0.3362$, $p = 0.0240$). CTX and osteocalcin were not correlated with hormonal or DXA data.

### Multivariate analysis

Multivariate analysis was employed to identify factors that could have significantly affected lumbar spine (duration of amenorrhea and PRL levels) and femoral *Z*-scores (age at diagnosis, duration of amenorrhea, leg, and gynoid LFR) based on the correlation results. The stepwise multiple regression models showed that, after the adjustment for the influence of the other variables, the lumbar spine, femoral neck, and total proximal femur *Z*-scores were mainly correlated with the amenorrhea duration. The model created for the study of the trochanter *Z*-score showed an association with gynoid LFR (Table 4).

## Discussion

In agreement with the literature, including previous data on Brazilian patients, the present study shows that bone

**Table 3** Patients with normal PRL and estradiol levels, EPNE, and EPLE patients

| | NPNE | EPNE | EPLE | *p*-Value |
|---|---|---|---|---|
| *N* | 12 | 22 | 11 | – |
| Age (years) | 34.8 ± 6.6 | 35.5 ± 7.6 | 31.6 ± 9.6 | 0.4040 |
| Age at diagnosis (years) | 30.4 ± 6.9 | 30.4 ± 8.0 | 26.5 ± 8.0 | 0.3757 |
| Disease duration (years) | 4.3 ± 2.6 | 5.4 ± 3.0 | 5.3 ± 2.6 | 0.5311 |
| Amenorrhea duration (years) | 5.3 ± 8.9 | 6.1 ± 4.9 | 5.3 ± 4.4 | 0.4450 |
| Treatment duration (years) | 1.6 ± 2.1 | 3.0 ± 2.7 | 2.6 ± 2.6 | 0.2867 |
| BMI (kg/m$^2$) | 24.3 ± 4.7 | 28.6 ± 5.7 | 29.5 ± 7.2 | 0.0768 |
| PRL (μg/L) | 11.7 ± 5.8 | 87.1 ± 97.3 | 310.6 ± 427.9 | <0.0001 |
| Estradiol (pg/mL) | 82.9 ± 58.5 | 173.3 ± 187.3 | 24.5 ± 4.3 | <0.0001 |
| Testosterone (ng/dL) | 83.0 ± 100.1 | 73.6 ± 105.8 | 129.9 ± 210.8 | 0.3650 |
| SHBG (nmol/L) | 59.0 ± 31.1 | 62.4 ± 48.7 | 49.5 ± 41.0 | 0.5508 |
| FEI | 61.0 ± 53.9 | 110.4 ± 66.5 | 26.6 ± 14.0 | <0.0001 |
| FAI | 589.9 ± 698.2 | 564.9 ± 623.3 | 1506.0 ± 3119.0 | 0.3588 |
| CTX (ng/mL) | 0.3 ± 0.2 | 0.3 ± 0.1 | 0.3 ± 0.2 | 0.8031 |
| Osteocalcin (ng/mL) | 22.4 ± 9.3 | 20.4 ± 8.1 | 19.5 ± 6.8 | 0.7034 |
| Lumbar *Z*-score | –0.7 ± 1.1 | –0.1 ± 1.2 | –1.0 ± 1.3 | 0.2091 |
| Neck *Z*-score | 0.2 ± 0.9 | –0.3 ± 0.9 | –0.3 ± 1.0 | 0.3248 |
| Trochanter *Z*-score | 0.0 ± 1.5 | –0.6 ± 0.9 | –1.0 ± 1.2 | 0.1416 |
| Total proximal femur *Z*-score | 0.5 ± 1.3 | 0.1 ± 0.9 | –0.2 ± 1.3 | 0.3147 |
| Arm lean/fat mass ratio | 2.5 ± 0.9 | 1.7 ± 0.7 | 1.7 ± 0.8 | 0.0160 |
| Leg lean/fat mass ratio | 1.1 ± 0.5 | 1.4 ± 0.4 | 1.3 ± 0.5 | 0.0028 |
| Truncal lean/fat mass ratio | 2.1 ± 0.9 | 1.5 ± 0.6 | 1.4 ± 0.7 | 0.0081 |
| Android lean/fat mass ratio | 2.0 ± 1.2 | 1.3 ± 0.6 | 1.2 ± 0.6 | 0.0152 |
| Gynoid lean/fat mass ratio | 1.4 ± 0.4 | 1.1 ± 0.3 | 1.1 ± 0.3 | 0.0116 |
| Total body lean/fat mass ratio | 2.1 ± 0.7 | 1.5 ± 0.5 | 1.5 ± 0.6 | 0.0034 |

*NPNE* patients with normal PRL and estradiol levels, *EPNE* patients with elevated PRL and normal estradiol levels, *EPLE* patients with elevated PRL and low estradiol levels

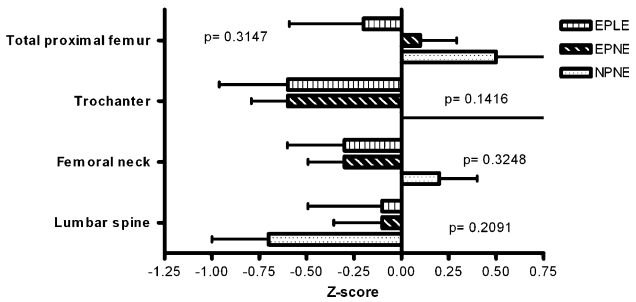


**Fig. 4** *Z*-scores in NPNE, EPNE, and EPLE patients

density is lower in women with prolactinoma than in healthy controls [1–3, 5]. As mentioned before, this study differs from all the previous ones as it is based on more modern densitometric diagnostic criteria for premenopausal women. BMD was analyzed on the basis of *Z*-scores, which establishes a comparison with age-matched subjects, following the current ISCD criteria [7]. According to the latter, the terms osteopenia and osteoporosis are not to be used in the classification of premenopausal women. However, results of *T*-scores confirmed the *Z*-score data. Patients had a significantly higher prevalence of lumbar spine osteopenia and osteoporosis than controls (29.6% vs. 4.2%, $p = 0.0178$) and no difference was observed when the femoral sites were taken into account. Additionally, patients with normal and elevated PRL had a similar prevalence of osteopenia and osteoporosis. It is worth noting that, although the diagnostic criteria were different, bone loss remains an important feature of prolactinoma: more than one-fifth of the patients had a BMD below the expected range for age in one or more skeletal sites.

**Table 4** Multiple regression

| *Z*-score | Influences | $r^2$ (%) | *p*-Value |
|---|---|---|---|
| Lumbar spine | Amenorrhea duration | 16.71 | 0.0236 |
| Femoral neck | Amenorrhea duration | 36.08 | 0.0034 |
| Trochanter | Gynoid lean/fat mass ratio | 38.14 | 0.0007 |
| Total proximal femur | Amenorrhea duration | 26.15 | 0.0065 |

In accordance with previously published data involving female and male patients with prolactinoma [4, 6, 8], the skeletal site in which the difference between patients and controls reached statistical significance was the lumbar spine. This site is formed basically by trabecular bone [9], which is especially affected by hormonal disturbances such as hyperprolactinemia and hypogonadism [1, 8].

The present study was limited by evaluating patients in different degrees of disease control and already in use of dopamine agonists. The authors tried to overcome this difficulty by confronting different groups (normal vs. elevated PRL; NPNE, EPNE vs. EPLE; amenorrheic vs. non-amenorrheic). However, no difference in bone density was obtained in these comparisons. Another limitation of the study was that the control group was not of the same size of the patients', which could have affected the results. Despite these limitations, patients still presented significantly lower bone density in the lumbar spine than controls.

Shaarawy et al. [10] detected higher levels of osteocalcin, a biomarker that reflects bone formation, and N-telopeptides of type 1 collagen, a biomarker of bone resorption, in newly-diagnosed women with amenorrheic hyperprolactinemia than in controls. These levels were consistent with high bone turnover and dropped after 12 months of bromocriptine treatment. In the present study, osteocalcin was used as a biomarker of bone formation and CTX, as a biomarker of bone resorption. Our group of women with prolactinoma did not present higher biomarker levels, which may be due to the fact that it consisted of patients with longer disease duration and previously treated with dopamine agonists. These factors may also explain the absence of correlations between biomarkers and BMD in our study.

Lean and fat masses were evaluated in order to investigate the effects of body composition on patients' BMD. Body fat can exert a protective effect on bone mass in women, including those with prolactinomas [11–13]. Some authors attribute this effect to the production of leptin in the adipose tissue. However, this notion is not unanimous. Some found no relationship between leptin and bone mass [14], while others argue that leptin levels are able to predict BMD [15]. In the present group of women with prolactinoma, BMD was associated with gynoid LFR. Interestingly, patients with normal PRL had lower body fat, as confirmed by a higher LFR in all DXA sites. Both dopamine agonist administration and PRL itself have been linked to body fat regulation and that could explain the difference between patients with normal and elevated PRL levels [16, 17]. However, this finding did not reflect on significant differences in BMD when these groups were compared. This suggests that, in this group of Brazilian women with prolactinoma, BMD suffered additional influences.

An object of interest of the present study was to evaluate the influence of hyperprolactinemia and hypogonadism on BMD. In women with hyperprolactinemia, the secondary hypogonadism seems to be the main responsible for bone loss. This concept has been reinforced by reports on bone loss in amenorrheic hyperprolactinemic women [1, 2, 11], but not in non-amenorrheic cohorts [1, 2, 11, 18]. Additionally, the bioavailable fraction of estrogen can be an important determinant of bone turnover and loss in women and men [19]. A study with Brazilian men with prolactinoma showed that bone loss was mainly associated with estradiol levels [6]. Estradiol inhibits the osteoblast and osteoclast apoptosis [20] and its osteoprotective effect is predominantly mediated by the control of osteoclast number and activity [21]. The present study showed that the main influence on lumbar spine, femoral neck, and total femur bone density was the duration of the hypogonadism. It is in accordance with the studies that suggest that hyperprolactinemia affects bone density indirectly through secondary hypogonadism.

In most cases, adequate dopamine agonist treatment is able to restore menstrual regularity in women with hyperprolactinemic amenorrhea [22]. Moreover, menstrual status has been mentioned as the most important predictor of progressive spinal osteopenia [2]. The present study did not detect differences in *Z*-scores when patients were compared according to PRL or estradiol levels and did not identify correlations between them and BMD. On the other hand, the lumbar spine, femoral neck, and total proximal femur *Z*-scores were associated with the duration of hypogonadism. Our findings are in agreement with those of Biller et al. [2] and Kayath et al. [3]. Other studies have detected the influence of hyperprolactinemia duration and PRL levels on the extent of bone damage [4, 5].

In most women with hyperprolactinemia, bone loss is reversed or at least interrupted once adequate disease control is established [2, 5, 11, 23]. One could argue that, based on disease and amenorrhea duration, our patients should have received dopamine agonist treatment sooner and be better controlled by the time of study entry. However, in our country, erratic dopamine agonists provision leads to irregular dopamine agonist regimens and increases the difficulty in establishing adequate control of hyperprolactinemia and hypogonadism. Our study confirms the influence of disease control on bone mass of women with prolactinoma. This reinforces the importance of achieving normoprolactinemia in order to avoid complications of the disease.

## Conclusion

Based on the current ISCD criteria, BMD evaluation in women with prolactinoma confirms previous studies,

showing bone loss, especially of trabecular type. Bone density in these patients was particularly associated with the duration of amenorrhea, which reinforces the importance of the adequate disease control in women with prolactinoma in order to avoid complications of this disease.

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