ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

Parathormone-Related Peptide Is Not Associated with Bone Mineral Density in Eugonadal Prolactinoma

ORIGINAL ARTICLE
Endocrinol Res Pract. 2023;27(3):158-163

ABSTRACT

Objective: One of many theories for the cause of osteoporosis in prolactinoma is the increased level of the parathyroid hormone-related peptide. We aimed to assess the parathyroid hormone-related peptide levels and its potential effects on bone mineral density in patients with eugonadal prolactinoma.

Methods: We enrolled 29 eugonadal prolactinoma patients and 31 controls. Serum prolactin, thyroid function tests, calcium, phosphorus, albumin, gonadal steroids, parathyroid hormone, 25-OH vitamin D, alkaline phosphatase, 24-hour urine calcium, parathyroid hormone-related peptide, and bone mineral density were measured.

Results: No statistically significant difference was observed in parathyroid hormone-related peptide levels between the prolactinoma and the control groups ($P = .288$). The parathyroid hormone-related peptide levels were significantly higher in men in both groups ($P < .05$). No relationship was observed between the parathyroid hormone-related peptide levels and bone mineral density in g/cm^2 for lumbar vertebrae, femur, and radius ($P > .05$). Although there was also no significant correlation between parathyroid hormone-related peptide and *Z* scores of lumbar vertebrae and femur ($P > .05$), *Z* scores of radius were significantly correlated with parathyroid hormone-related peptide ($P = .001$, $r = -0.575$).

Conclusion: To the best of our knowledge, contrary to hypotheses that the elevated level of parathyroid hormone-related peptide may be one of the factors contributing to osteoporosis in prolactinoma patients, this is the first study revealing that parathyroid hormone-related peptide has no significant impact on osteoporosis in eugonadal prolactinoma patients. Furthermore, this is the first study to demonstrate gender differences in physiological parathyroid hormone-related peptide levels. However, additional studies with large samples are required to confirm these findings.

Keywords: Prolactinoma, osteoporosis, parathyroid hormone-related peptide, BMD

Introduction

Prolactinoma is the most common type of prolactin-secreting pituitary adenoma, which arises from lactotroph cells in the pituitary gland. Amenorrhea, galactorrhea, and infertility are characteristics of prolactinomas in female patients, and decreased libido, gynecomastia, and impotence are characteristics of prolactinomas in male patients. These symptoms are related to hypogonadism resulting from a decrease in gonadotropin-releasing hormone levels due to prolactin increase and consequently decreased gonadotropin and estrogen/testosterone secretion.[1,2] In addition to these symptoms, increased bone resorption and decreased bone mineral density (BMD) have been demonstrated in women and men with prolactinoma.[3] According to studies, the reduction in BMD was 4%-23% in the peripheral bones and 8%-23% in the axial bones. Osteopenia was first demonstrated in patients with prolactinoma in 1980. Although osteopenia was previously thought to be associated with prolactin-related hypogonadism in the first studies, recent studies have also shown increased osteopenia and fracture incidence in patients with normal gonadal function.[4,5] Prolactin acts directly and indirectly on bone metabolism. The factors affecting bone metabolism may include increased calcium resorption from the bone, inhibition of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) pulsatile release, and release of prolactin-dependent parathyroid hormone-related peptide (PTHrP).[6,7]

Parathyroid hormone-related peptide was initially identified as a crucial factor in cancer-induced hypercalcemia. Due to its similarity to the parathyroid hormone's aminoterminal end, it may interact with the same receptors (via renal and bone).[8] Although PTHrP levels were found to be increased in many tumor tissues, mRNAs belonging to PTHrP were also

Arzu Okyar Baş[1]
Murat Cinel[2]
Özgür Demir[2]

[1]*Department of Internal Medicine, Ankara University Faculty of Medicine, Ankara, Turkey*
[2]*Endocrinology and Metabolic Diseases Subdivision,Department of Internal Medicine, Ankara University Faculty of Medicine, Ankara, Turkey*

This Study's Abstract was Previously Presented at World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO) on 26-28th August 2021.

Corresponding author:
Arzu Okyar Baş
✉ arzu0506@hotmail.com

Received: February 10, 2023
Revision Requested: March 3, 2023
Last Revision Received: April 19, 2023
Accepted: April 28, 2023
Publication Date: July 4, 2023

Cite this article as: Okyar Baş A, Cinel M, Demir Ö. Parathormone-related peptide is not associated with bone mineral density in eugonadal prolactinoma. *Endocrinol Res Pract.* 2023;27(3):158-163.

DOI: 10.5152/erp.2023.23223

identified in nontumor tissues like lactating breast tissue, parathyroid gland, pituitary, and adrenal glands.[9] Parathyroid hormone-related peptide was produced in animal studies from lactating breast tissue, and rising serum prolactin levels were linked to rising PTHrP mRNA levels.[10] In massive breast hyperplasia, increased PTHrP is associated with hypercalcemia, and, it may suggest that in nonlactating breast tissue, PTHrP can also be secreted into the systemic circulation and may have systemic effects.[11] In patients with prolactinoma with similar features to lactating breast tissue, it has been suggested that the level of the PTHrP may be increased and may be related to a reduction in BMD.[12]

There is solely one study evaluating the clinical relationship between increased serum parathyroid hormone-associated peptide levels in prolactinoma patients and in the study mentioned above, although the possible effect of gonadal functions could not be excluded, it has been suggested that there might be a decrease in BMD due to an increase in PTHrP level.[12]

By excluding the detrimental effects of prolactin on the gonadal system, this study sought to assess PTHrP levels and their potential effects on BMD in premenopausal women and men with normal gonadal function.

Material and Methods

The study was planned as a prospective, observational study and consisted of patients with prolactinoma admitted to the Endocrinology and Metabolism Diseases Outpatient Clinic for a 6-month period.

Men between the ages of 18 and 65 and premenopausal women between the ages of 18 and 55 who were being monitored while taking dopamine agonists (cabergoline) and had no history of transsphenoidal surgery were included. Patients with symptomatic or laboratory-proved hypogonadism, a history of transsphenoidal surgery, and known osteoporosis or pathological fractures were excluded. All possible participants (both for prolactinoma and the control groups) were also evaluated with laboratory tests and detailed history to exclude participants with osteoporosis risk. Thus patients with previous osteoporosis/osteopenia diagnoses, previous history of fractures, severe vitamin deficiencies including 25-OH vitamin D, history of surgeries causing hormonal deficiencies (i.e., thyroidectomy and ovariectomy), long-term use of certain medications, such as corticosteroids, proton pump inhibitors, and antiepileptic medications, any known electrolyte alterations (calcium, phosphorus), and altered levels of hormones (thyroid function tests, known hypogonadism) were also excluded. The control group consisted of healthy participants with the same demographic characteristics as the prolactinoma group, no known osteoporosis, and clinically normal gonadal functions. Only laboratory tests, including PTHrP levels, were taken from the control group, as the primary purpose of enrolling a control group was to compare PTHrP levels between groups, given that the ELISA kit used did not indicate a normal range for PTHrP levels.

MAIN POINTS

- Although parathyroid hormone-related peptide (PTHrP) relates to osteoporosis and the situations/tissues that remain prolactinoma, such as lactating breast tissue, our study on eugonadal prolactinoma patients showed that PTHrP levels did not differ between osteoporotic and nonosteoporotic groups.
- Although no statistically significant relationship was observed between serum levels of PTHrP and bone mineral density in g/cm^2 value, PTHrP levels were only correlated with *Z* scores of radius. It is possible that PTHrP's similar physiology to parathyroid hormone is the reason for its correlation with the radius *Z* score. However, when taken together, it was determined that this was insufficient evidence to conclude that PTHrP plays a role in the etiology of osteoporosis in prolactinoma.
- Parathyroid hormone-related peptide levels were significantly higher in male patients. The physiological differences in PTHrP levels according to gender were shown for the first time, and larger sampled studies are needed to confirm that finding.

Age, gender, body mass index, duration of prolactinoma diagnosis, tumor diameter, and volume, detailed menstrual history for female patients (menarche history, oligomenorrhea, if any), the presence of known osteoporosis, and the history of pathological or traumatic fracture were noted.

Prolactin level (with peg), gonadotropin (FSH, LH) levels, estrogen/testosterone, progesterone, thyroid function tests [thyroid-stimulating hormone (TSH), free thyroxine 3 (fT3), free thyroxine 4 (fT4)], 25-OH vitamin D, serum calcium, serum phosphorus, serum albumin, parathyroid hormone level, alkaline phosphatase level, 24-hour urine calcium, and creatinine were measured.

Serum samples were taken for the PTHrP levels and were stored at -80° C after centrifugation for 20 minutes right after collection. The collected samples were evaluated using the Cloud Clone brand kit using the ELISA method.

Bone mineral density was measured from the lumbar spine, femur, and radius bones. All BMD analyses were performed via GE Hologic Explorer dual x-ray absorptiometry with a dual-energy fan-beam protocol. As a general principle, it is advised to utilize a *Z*- score for populations under 50 years old and a *T* score for populations over 50 years old. Although the majority of participants in the prolactinoma group, the group for whom BMD analysis was conducted, were under the age of 50, a small number of participants aged 50 and beyond were also included in the study. For this reason, both *T* and *Z* scores are shown in Tables 1-3. However, considering certain limitations of *T* and *Z* scores, BMD was also given in g/cm^2. Therefore, this parameter has been acknowledged as the primary parameter.

Ethics Approval

The study was approved by the Clinical Research Ethics Committee of Ankara University School of Medicine Clinical Research Ethics Committee (Date: December 11, 2017, Decision No: 20-1252-17). The ethical guidelines of the institutional and/or national research committee, the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards, were followed in all procedures carried out in studies involving human participants.

Informed Consent

Written informed consent was obtained.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 22.0 (IBM Corp., Armonk, NY, USA).[13] For sample size determination, a power analysis was performed in light of previous studies.[12] The proper study group size with a margin of error of 0.05

Table 1. Comparison of the Characteristics and Laboratory Results of Prolactinoma and Control Groups

	Prolactinoma Group	Control Group	*P*-Value
Sex, n (%)			
Female	19 (65.5 %)	13 (41.9%)	.553
Male	10 (34.5 %)	18 (58.1%)	
Age, mean ± SD	40.48 ± 11.23 years	41.28 ± 9.91 years	.734
Duration of diagnosis, median (minimum–maximum)	48 (4-288 months)	N/A	N/A
Body mass index, median (minimum–maximum)	24.2 (19.1-33 kg/m^2)	25.3 (20.2-31.0 kg/ m^2)	.378
Parathormone-related peptide, mean ± SD	364.5 ± 173.1 pg/mL	386.7 ± 149.6 pg/mL	.288
Prolactin (PEG) median (minimum–maximum)	14 (0.5-696.0 ng /mL)	5.95 (3.4-16.8 ng/mL)	.027
Estradiol, median (minimum–maximum)	87 (25.0-261.0 pg/dL)	88.5 (34.0-261.0 pg/dL)	.778
Progesterone, median (minimum–maximum)	1.4 (0.11-16.20 ng/mL)	1.6 (0.13-19.0 ng/mL)	.687
Total testosterone, mean ± SD	303 ± 83 ng/mL	291.4 ± 12.6 ng/mL	.696
25-OH vitamin D, mean ± SD	25 ± 3.2 ng/mL	28 ± 4.9 ng/mL	.458
TSH, median (minimum–maximum)	2 (0.6-5.9 mIU/L)	2.7 (0.9-4.8 mIU/L)	.530
Free T4, mean ± SD	9.8 ± 1.5 pmol/L	8.3 ± 1.2 pmol/L	.492
Free T3, mean ± SD	5.0 ± 0.7 pmol/L	4.3 ± 0.9 pmol/L	.788
Serum calcium, mean ± SD	9.6 ± 0.4 mg/dL	9.4 ± 0.7 mg/dL	.693
Serum phosphorus, mean ± SD	3.4 ± 0.5 mg/dL	3.8 ± 1.2 mg/dL	.455
Serum creatinine, mean ± SD	0.695 ± 0.147 mg/dL	0.732 ± 0.180 mg/dL	.877
Serum albumin, mean ± SD	4.54 ± 0.32 g/L	4.87 ± 0.45 g/L	.769
Serum alkaline phosphatase, median (minimum–maximum)	65 (45-222 U/L)	75 (35-182 U/L)	.465
Serum parathormone, median (minimum–maximum)	46 (20-235 pg/mL)	49 (18-259 pg/mL)	.723
24-hour urine calcium, mean ± SD	180 ± 109 mg/day	172 ± 89 mg/ day	.322
Radius bone mineral density, g/cm^2, mean ± SD	0.555 ± 0.053 g/cm^2	N/A	N/A
Femur bone mineral density, g/cm^2, mean ± SD	0.960 ± 0.148 g/cm^2	N/A	N/A
Lumbar bone mineral density, g/cm^2, mean ± SD	0.993 ± 0.137 g/cm^2	N/A	N/A
Radius bone *T* score, mean ± SD	-0.892 ± 1.03	N/A	N/A
Femur bone *T* score, mean ± SD	-0.064 ± 1.12	N/A	N/A
Lumbar bone *T* score, mean ± SD	-0.717 ± 1.31	N/A	N/A
Radius bone *Z* score, mean ± SD	-0.517 ± 0.93	N/A	N/A
Femur bone *Z* score, mean ± SD	0.207 ± 1.31	N/A	N/A
Lumbar bone *Z* score, mean ± SD	-0.396 ± 1.30	N/A	N/A

(alpha) and power of 90 was calculated as 28 participants. Thus, we enrolled 29 prolactinoma patients and 31 healthy controls. Visual (histogram, probability plots) and analytic (Kolmogorov–Smirnov test) methods were used to determine whether or not variables are normally distributed. The descriptive statistics were presented as mean SD for variables with a normal distribution, median (minimum–maximum) for variables with nonnormal distribution, and number (percentage, %) for categorical variables. Student's *t*-test was used to compare normally distributed variables. The Mann–Whitney *U*-test was used to compare variables that were disproportional between the 2 groups. On the basis of the variable distributions, Spearman or Pearson correlation tests were used to conduct correlation analyses. The correlation analysis of PTHrP with laboratory data and age was performed in the whole group. However, as only BMD data were available for the prolactinoma group, the correlation analysis of BMD data and PTHrP was only performed in the prolactinoma group. Results with a *P*-value < .05 were deemed statistically significant.

Results

A total of 40 participants with prolactinoma were screened. Eleven participants were excluded due to having various exclusion criteria. (Three patients had a history of transsphenoidal surgery, 6 patients were in the postmenopausal period, and 2 patients were reluctant to participate in the study.) Totally 29 patients with prolactinoma, 19 (65.5%) females and 10 (34.5%) males, were enrolled. The median age of the prolactinoma group was 40.48 ± 11.23 years. The mean duration of prolactinoma diagnosis was 59 months. As a control group, 31 individuals, 18 (58.1%) female and 13 (41.9%) male, were included in the study. The median age was 41.28 ± 9.91 years in the control group. The median body mass indexes were 24.2 (19.1-33 kg/m^2) and 25.3 (20.2-31.0 kg/m^2) in the prolactinoma and control groups, respectively.

Age, gender, body mass index, duration of prolactinoma and laboratory findings, including Prolactin level (with peg), gonadotropin (FSH, LH) levels, estrogen/testosterone, progesterone, thyroid function tests (TSH, fT3, fT4), 25-OH vitamin D, serum calcium, serum phosphorus, serum albumin, parathyroid hormone level, alkaline phosphatase level, 24-hour urine calcium and creatinine, PTHrP levels, and BMD of the lumbar spine, femur, and radius were given in Table 1 in comparison with 2 groups. All patients' gonadotropin (FSH, LH) levels, estrogen/testosterone, and progesterone were in the normal range by gender. In addition, in both prolactinoma and control groups, there was no hypogonadism-associated symptom (such as menstrual disorder, loss of libido, erectile dysfunction, constant

Table 2. Correlations Between Parathyroid Hormone-Related Peptide (PTHrP) Levels and bone mineral density Measurements

	PTHrP	
	r	*P*
Age*	-0.140	.469
Radius bone mineral density, g/cm²#,*	0.018	.818
Femur bone mineral density, g/cm²#,*	-0.187	.331
Lumbar bone mineral density, g/cm²#,*	-0.166	.189
Radius bone *Z* score#,*	-0.575	.001
Femur bone *Z* score#,*	-0.319	.098
Lumbar bone *Z* score#,*	-0.211	.181
Prolactin level°	-0.225	.240
Estradiol°	-0.293	.223
Progesterone°	-0.177	.468
Total testosterone*	-0.176	.627
Parathyroid hormone°	0.054	.780
Serum calcium*	0.180	.199
Serum phosphorus*	-0.203	.311
Serum creatinine*	-0.130	.112
Serum alkaline phosphatase°	0.120	.250

#Correlation analysis of marked variables was performed only for the prolactinoma group, other parameters were analyzed for the whole study sample (prolactinoma group and control group).
*Correlation analysis of marked variables was performed via Pearson correlation tests
°Correlation analysis of marked variables was performed via Spearman correlation tests

tiredness, loss of motivation and concentration, mood changes, increased body fat, enlargement of breast tissue, decreased muscle mass and physical strength, etc.) in symptom questioning.

Since the patient group population consists of premenopausal female and male patients, both BMD in g/cm² and, *T* and *Z* scores were taken into consideration (Table 1). According to the *T* (for participants aged ≥50 years) and *Z* scores (for participants aged < 50 years), for lumbar scores; 64.3% (n = 18) were normal, 32.1% (n = 9) were osteopenic, 3.6% (n = 2) were osteoporotic, for femur total scores, 89.3% (n = 25) were normal, 10.7% (n = 3) were osteopenic, and for radius scores 82.1% (n = 23) were normal, 10.7% (n = 3) were osteopenic, and 7.1% (n = 2) were osteoporotic. When patients were divided into osteoporotic and nonosteoporotic groups, there was no significant difference between groups regarding PTHrP serum levels ($P > .05$).

Serum levels of PTHrP were not statistically related to BMD in terms of g/cm² ($P = .330$ for femur, $P = .389$ for lumbar vertebrae, and .939 for radius). Although there was also no significant correlation between PTHrP and *Z* scores of lumbar vertebrae and femur ($P > .05$), *Z* scores of radius were significantly correlated with PTHrP ($P = .001$, $r = -0.575$).

No statistically significant association was found between the level of PTHrP and serum prolactin levels ($P = .240$). In addition, there was no statistically significant correlation between PTHrP and estradiol ($P = .223$), progesterone ($P = .468$) in females and total testosterone ($P = .627$) in males. Correlation analyses of PTHrP and other parameters were summarized in Table 2.

Although there was no statistically significant difference between groups in terms of PTHrP values ($P = .288$) (Table 1), in both groups, the PTHrP level was significantly higher in the males than the females ($P < .001$) (Table 3).

Discussion

There are several theories regarding the causes of osteoporosis in prolactinoma patients. In the first studies in the 1980s, when osteoporosis was identified in patients with prolactinoma, hypogonadism was thought as the primary cause, based on prolactin's negative impact on the gonadal system.[5] With a greater understanding of the biological structure and receptors of prolactin and a heightened awareness of osteoporosis in prolactinoma patients with normal gonadal functions, research into the etiology of osteoporosis has increased over time. The increased concentration of PTHrP is one of the implicated factors. In this study, we aimed to evaluate the effect of PTHrP on the presence of osteoporosis in eugonadal prolactinoma, and our results revealed no significant relationship between PTHrP and BMD in this specific population.

Parathyroid hormone-related peptide is produced physiologically in numerous tissues, such as lactating breast tissue, parathyroid, pituitary, and adrenal glands. Increased PTHrP in massive breast hyperplasia was found to be associated with hypercalcemia. Increased PTHrP in pregnancy also helps to meet the fetus's increased calcium requirement.[11,14] Recent studies showed that during pregnancy and lactation, PTHrP increases and causes pseudohyperparathyroidism , and it is associated with parity-related fragility and osteoporosis.[15] Considering the knowledge about the ability of PTHrP to increase bone turnover on osteoclasts in bone, PTHrP may be thought to have an impact on osteoporosis in prolactinoma patients.[11,14]

Only 1 study examines the potential effect of PTHrP in the etiology of osteoporosis in patients with prolactinoma.[12] In the aforementioned study, patients receiving medical or surgical treatment for prolactinoma, pre/postmenopausal women, and men, a heterogeneous group, were enrolled, and PTHrP levels were significantly higher in the prolactinoma group than in the healthy population. In addition, no noticeable difference was observed between the sexes and the increase in PTHrP was correlated with a decrease in BMD. However, the main limitation of the previous study was including postmenopausal women and hypogonadal men with low total testosterone levels carrying causative factors for osteoporosis. Therefore, the effect of gonadal hormones on osteoporosis has not

Table 3. The Comparison of the PTHrP Levels According to Gender

	Parathyroid Hormone-Related Peptide Levels	Mean ± SD	*P* Values Between Genders
The control group	Female gender	336.9 ± 120 pg/mL	<.001
	Male gender	450.65 ± 162.78 pg/mL	
The prolactinoma group	Female gender	290.62 ± 111.4 pg/mL	<.001
	Male gender	505 ± 240.4 pg/mL	

been excluded.[12] In our study, only men and women with normal reproductive functions were enrolled to exclude the possible effect of sex steroids. We evaluated the relationship between PTHrP level and BMD in g/cm^2 under normal gonadal functions, and no statistically significant association was observed. However, when *Z* scores were taken into account, even though there was no correlation between the lumbar vertebrae and femur *Z* scores and PTHrP, PTHrP levels and *Z* scores of radius bone have a negative and moderate correlation. When the PTHrP level in the prolactinoma group was compared with the control group, there was no difference in serum PTHrP level between the 2 groups. Parathyroid hormone-related peptide has a similar physiological structure to PTH, and, like PTH, PTHrP may also primarily affect the radius bone that is rich in cortical bone.[16] However, considering that the *Z* score is less sensitive than the g/cm^2 value in predicting bone density in this subgroup, PTHrP levels did not differ between nonosteoporotic and osteoporotic groups and the PTHrP level was not different in the healthy and prolactinoma groups, it may not be accurate to reveal that PTHrP is exactly responsible for the development of osteoporosis in eugonadal prolactinoma.

Although previous studies focused on PTH levels claim biological variations in blood samples between genders,[17] studies in PTHrP showed null variability in gender.[18,19] In contrast to other studies, in our study, PTHrP levels were significantly higher in males than in females in both the prolactinoma and control groups. Our finding revealing gender-associated PTHrP level variation in both groups is substantial since our study is the first study claiming higher PTHrP levels in males than females. Since PTHrP is one of the proteins synthesized from the parathyroid hormone-like hormone (PTHLH) gene region on chromosome 12, and the autosomal dominant inheritance pattern is known to affect both genders equally,[20,21] it is challenging to example this novel finding in the lights of current information. More and larger sampled studies are warranted to confirm and clarify this finding.

The major limitations of our study are the limited number of the patient group and not having of information on the BMD measurement of the control group. Since the main aim of the study was to evaluate the relationship between PTHrP and BMD in eugonadal prolactinoma patients, despite the small sample size, we divided patients into groups according to their BMD (*T* or *Z*) scores and give in the results if there is a significant relationship between PTHrP and BMD. However, we acknowledge that the small percentage of osteoporosis (defined via *T* or *Z* score) may affect the possible relationship and is also a limitation. Therefore, since BMD in g/cm^2 may give more objective data than *T* or *Z* scores, by providing a correlation analysis of PTHrP and BMDs in g/cm^2, besides *T* and *Z* scores of the related areas, we tried to alleviate this limitation. The wide range of prolactin and gonadal steroid levels may also be seen as a limitation. Since the main aim of the study was evaluating the prolactinoma patients under medical treatment without a necessity of a normal prolactin serum level, the serum level of prolactin does have a wide range. Contrary, although the gonadal serum levels given in Table 1 seem to have a wide range, all patients' serum levels were in the normal range for our laboratory's standards. Therefore, since we aimed to evaluate prolactinoma patients with normal gonadal status plus with or without normal prolactin levels, the sample characteristics were proper for the design. Our study also has strengths: the homogeneous compound of the prolactinoma group, constituted by excluding other risk factors causing osteoporosis, such as decreased gonadal functions and having a control group to compare PTHrP levels between prolactinoma patients and healthy individuals.

Conclusion

Contrary to previous studies with heterogeneous patients, including postmenopausal and hypogonadal patients, we found that increased PTHrP could not be seen as a prominent factor for decreased BMD in eugonadal prolactinoma patients. Further studies are needed to evaluate the etiology of osteoporosis in prolactinoma patients with normal gonadal function. Furthermore, this is the first study to demonstrate gender differences in physiological PTHrP levels. Additional studies with large samples are required to confirm these findings.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Ankara University School of Medicine (Date: December 11, 2017, Decision No: 20-1252-17).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.O.B., Ö.D.; Design – A.O.B., Ö.D.; Supervision – M.C., Ö.D.; Resources –Ö.D.; Materials – A.O.B., M.C.; Data Collection and/or Processing – A.O.B., M.C.; Analysis and/or Interpretation – A.O.B., Ö.D.; Literature Search – A.O.B., Ö.D.; Writing Manuscript – A.O.B., Ö.D.; Critical Review – Ö.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

References

1. Kars M, Dekkers OM, Pereira AM, Romijn JA. Update in prolactinomas. *Neth J Med*. 2010;68(3):104-112.
2. Klibanski A. Clinical practice. Prolactinomas. *N Engl J Med*. 2010;362(13):1219-1226. [CrossRef]
3. Shibli-Rahhal A, Schlechte J. The effects of hyperprolactinemia on bone and fat. *Pituitary*. 2009;12(2):96-104. [CrossRef]
4. Mazziotti G, Mancini T, Mormando M, et al. High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas. *Pituitary*. 2011;14(4):299-306. [CrossRef]
5. Greenspan SL, Oppenheim DS, Klibanski A. Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. *Ann Intern Med*. 1989;110(7):526-531. [CrossRef]
6. Sumathy S. *A Study on Serum Prolactin in Reduced Bone Mineral Density*. Chennai: Madras Medical College; 2007.
7. Kovacs CS, Chik CL. Hyperprolactinemia caused by lactation and pituitary adenomas is associated with altered serum calcium, phosphate, parathyroid hormone (PTH), and PTH-related peptide levels. *J Clin Endocrinol Metab*. 1995;80(10):3036-3042. [CrossRef]
8. Henderson JE, Shustik C, Kremer R, Rabbani SA, Hendy GN, Goltzman D. Circulating concentrations of parathyroid hormone-like peptide in malignancy and in hyperparathyroidism. *J Bone Miner Res*. 1990;5(2):105-113. [CrossRef]
9. Ikeda K, Mangin M, Dreyer BE, et al. Identification of transcripts encoding a parathyroid hormone-like peptide in messenger RNAs from a variety of human and animal tumors associated with humoral hypercalcemia of malignancy. *J Clin Invest*. 1988;81(6):2010-2014. [CrossRef]
10. Thiede MA, Rodan GA. Expression of a calcium-mobilizing parathyroid hormone-like peptide in lactating mammary tissue. *Science*. 1988;242(4876):278-280. [CrossRef]

11. Khosla S, van Heerden JA, Gharib H, et al. Parathyroid hormone-related protein and hypercalcemia secondary to massive mammary hyperplasia. *N Engl J Med*. 1990;322(16):1157. [CrossRef]
12. Stiegler C, Leb G, Kleinert R, et al. Plasma levels of parathyroid hormone-related peptide are elevated in hyperprolactinemia and correlated to bone density status. *J Bone Miner Res*. 1995;10(5):751-759. [CrossRef]
13. Allen P, Bennett K, Heritage B. *SPSS Statistics Version 22: A Practical Guide*. Australia: Cengage Learning; 2014.
14. Kovacs CS. Bone development and mineral homeostasis in the fetus and neonate: roles of the calciotropic and phosphotropic hormones. *Physiol Rev*. 2014;94(4):1143-1218. [CrossRef]
15. Kovacs CS. Calcium and phosphate metabolism and related disorders during pregnancy and lactation. In Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext*. South Dartmouth, MA: MDText.com. 2000.
16. Silverberg SJ, Shane E, de la Cruz L, et al. Skeletal disease in primary hyperparathyroidism. *J Bone Miner Res*. 1989;4(3):283-291. [CrossRef]
17. Ercan M, Akbulut ED, Avcı E, et al. Determining biological variation of serum parathyroid hormone in healthy adults. *Biochem Med (Zagreb)*. 2019;29(3):030702. [CrossRef]
18. Lv Z, Wu X, Cao W, et al. Parathyroid hormone-related protein serves as a prognostic indicator in oral squamous cell carcinoma. *J Exp Clin Cancer Res*. 2014;33(1):100. [CrossRef]
19. Nordholm A, Rix M, Olgaard K, Lewin E. Parathyroid hormone-related peptide plasma concentrations in patients on hemodialysis. *Scand J Clin Lab Investig*. 2014;74(3):206-212. [CrossRef]
20. Reyes M, Bravenboer B, Jüppner H. A heterozygous splice-site mutation in PTHLH causes autosomal dominant shortening of metacarpals and metatarsals. *J Bone Miner Res*. 2019;34(3):482-489. [CrossRef]
21. Kamalakar A, Washam CL, Akel NS, et al. PTHrP(12-48) modulates the bone marrow microenvironment and suppresses human osteoclast differentiation and lifespan. *J Bone Miner Res*. 2017;32(7):1421-1431. [CrossRef]