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Original Article

N-Terminal-pro-Brain Natriuretic Peptide Is Increased and Closely Related with Osteoporosis in Patients with Newly Diagnosed Primary Hyperparathyroidism

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ABSTRACT

Objective: The aim of this study is to determine the prevalence of osteopenia and osteoporosis in newly diagnosed primary hyperparathyroidism patients and to evaluate the relationship between the presence of osteoporosis and the primary hyperparathyroidism routine laboratory parameters including N-terminal-pro-brain natriuretic peptide.

Methods: This prospective study included 94 patients (mean age: 59.7 ± 11.7 years, female/male: 78/16) who have been diagnosed with primary hyperparathyroidism. For all patients participating in this study, laboratory tests were performed (routine tests and tests for diagnosing hyperparathyroidism), and dual-energy x-ray absorptiometry inspections were also performed. The participants of the study were divided into 3 groups according to T score in dual-energy X-ray absorptiometry as normal (group I or T score >−1), patients with osteopenia (group II or T score between −1 and −2.5), and the patients with osteoporosis (group III or T score ≤ −2.5).

Results: Notable level increase of blood urea nitrogen and N-terminal-pro-brain natriuretic peptide from group I to group III is seen in the results. In logistic regression analysis, it was found that levels of N-terminal-pro-brain natriuretic peptide and urine calcium independently determined the patients for osteoporosis ($P < .05$). According to the analysis, it was found that increasing levels of urine calcium (per 10 mg/day) and N-terminal-pro-brain natriuretic peptide (per 10 pg/mL) increase the risk of osteoporosis by 8.6% and 9.1% for patients, respectively. When we took N-terminal-pro-brain natriuretic peptide and urine calcium cut-off values as 200 pg/mL and 300 mg/day, respectively, it determines patients for osteoporosis with 82.6% sensitivity and 73.2% specificity, and 73.9% sensitivity and 63.4% specificity, respectively. N-terminal-pro-brain natriuretic peptide and urinary calcium levels were independently associated with T score in dual-energy X-ray absorptiometry.

Conclusion: The primary outcome of this study is N-terminal-pro-brain natriuretic peptide levels are significantly increased in newly diagnosed primary hyperparathyroidism patients and are independently associated with osteoporosis presence. In addition, apart from N-terminal-pro-brain natriuretic peptide level, urine calcium level is also independently associated with osteoporosis presence, in our study.

Keywords: Primary hyperparathyroidism, osteoporosis, NT-proBNP

INTRODUCTION

Primary hyperparathyroidism (pHPT) is frequently asymptomatic until the time of diagnosis.[1] During this asymptomatic period, bone loss and osteopenia or osteoporosis may occur.[2-4] For this reason, the diagnosis of pHPT should be kept in mind in cases of bone loss, which were detected by chance at relatively young ages. In addition, bone mineral density (BMD) should be measured as soon as possible after the diagnosis of pHPT. Dual-energy X-ray absorptiometry (DEXA) technique is recommended for BMD measurement in current guidelines.[5]

Bone mineral density score in patients with pHPT is associated with disease severity and a T score of <−2.5 as determined by DEXA is a surgical criterion.[5] Although there is a correlation between BMD and biochemical parameters related to pHPT in univariate analyses, this relationship has been reported to be not independent.[6-10] Bone mineral density measurement and degree can only be done with x-ray DEXA examination. However, if a biochemical marker is associated with osteoporosis, it may be important for patients with pHPT, especially at follow-up and osteoporosis.

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It has been shown that there is an increase in brain natriuretic peptide (BNP) without cardiac involvement in pHPT patients and also an increase in BNP with the presence of atherosclerotic heart disease and heart failure and cardiovascular prognosis in these patients.[11-14] Natriuretic peptides are known to be specifically synthesized from cardiac myocytes by pressure and volume excess. Natriuretic peptides have endocrine, paracrine, and autocrine effects. One of the endocrine effects is the increased endothelin-1 (ET-1) synthesis of parathyroid cells. Both atrial natriuretic peptide (ANP) and BNP cause an increase in ET-1 synthesis from parathyroid cells.[15] Endothelin-1 is known to be particularly clear in osteoporosis due to the feature of mediated vasoconstrictor tone increase of ET-1 in bone cells.[16-18] However, in the literature to the best of our knowledge, there is no study related to increased osteoporosis with increased BNP effect in pHPT patients. We hypothesized that in pHPT patients, osteoporosis or BMD reduction may be associated indirectly with BNP.

Therefore, our study aimed to determine the prevalence of osteopenia and osteoporosis in the newly diagnosed pHPT patients and to evaluate the relationship between the presence of osteoporosis and the pHPT routine laboratory parameters including N-terminal proBNP (NT-proBNP).

METHODS

The Population of the Study

This prospective study included 94 patients (mean age: 59.7 ± 11.7 years, female/male: 78/16) who have a diagnosis of pHPT. Primary hyperparathyroidism was defined as elevated or inappropriately normal intact parathyroid hormone level (PTH) level and accompanying elevated serum calcium corrected for serum albumin.[5] In this study, the patients who have inflammatory and hematological diseases, musculoskeletal diseases, vitamin D deficiency or treatment, presence of cancer, pregnancy, and renal failure were not included. The study protocol is approved by The Cukurova University by the Ministry of Health (Date: May 15, 2018 / Desicion No: 59) and written informed consent was obtained from each participant.

A detailed medical history and a complete physical examination was performed for all groups and final basal characteristics were recorded. After measuring weight and height, the body mass index (BMI) was calculated. Laboratory tests, renal ultrasound (US), and bone densitometry were performed for all patients. All patients were searched for the diagnosis of renal stone or nephrocalcinosis in renal US for surgical indications.

Main Points

- N-terminal-pro-brain natriuretic peptide (NT-proBNP) is significantly increased in newly diagnosed primary hyperparathyroidism (pHPT) patients.
- NT-proBNP is independently associated with osteoporosis presence.
- High NT-proBNP can be followed closely for osteopenia and osteoporosis.
- Our study is a first in the literature, and it needs to be supported by new studies and assessments.

According to the National Institutes of Health consensus panel, the following are considered as surgical criteria in symptomatic pHPT patients or the presence of any of them in asymptomatic pHPT patients: (i) serum calcium level elevation for 1 mg/dL, (ii) significant hypercalciuria (> 400 mg/24 h), (iii) DEXA T score <−2.5, (iv) patient under 50 years old (<50 age), and (v) decrease in creatinine clearance by more than 30%.[5]

Biochemical Measurements

Venous blood samples were collected in blood tubes from cubital veins of patients in the outpatient clinics. By using chemiluminescence immunoassay and Beckman Coulter DXI 800, serum PTH concentration and 25-hydroxyvitamin D level were measured. The reference range was accepted as 20-40 pg/mL. Complete blood count (white blood cell count, hematocrit, and platelet counts) was measured using a Beckman Coulter DXH 800 within 5 minutes after sample ingestion. Serum glucose, Hemoglobin A1c, blood urea nitrogen (BUN), creatinine, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALP), high sensitive C-reactive protein (hs-CRP), NT-proBNP, uric acid, serum calcium, serum phosphorus, and urine calcium levels were measured using an automated chemistry analyzer (Abbott Aeroset, Minn, USA) and using appropriate commercial kits (Abbott). By using the most commonly used formula in clinical practice, the corrected serum calcium levels were calculated (if serum albumin level was lower than 4 mg/dL: corrected calcium = measured total calcium (mg/dL) + 0.8 (4.0 − serum albumin [g/dL])).[19]

Measurement of Bone Densitometry by Dual-Energy x-Ray Absorptiometry

For all measurements, participants wore light clothes and removed all metal and plastic artifacts. A stadiometer and BMI-calibrated electronic scales were used for measuring the height, and the nearest millimeter was recorded. The BMD analysis of all patients in the anterior–posterior and lateral lumbar vertebrae (L1-L4) was performed with DEXA (Lunar iDXA, GE, Madison, Wis, USA).

One lumbar spine (L1eL4) scan and one total hip scan on both the iDXA and the Prodigy within 24 hours were performed for each participant. All lumbar spine scans were performed by elevating the legs and opening the intervertebral spaces to allow clear visualization of the vertebra. This positioning was assisted with the GE-Lunar spine positioning. For total hip scans, the GE-dual femur positioning device was used for allowing both legs to be abducted and inwardly rotated 25°. Scans were analyzed using Encore software versions 12.5 (Prodigy) and 13.5 (iDXA). The same experienced densitometry specialist performed the analysis of each scan, manually for the lumbar spine for the consistent placing of the intervertebral spaces and with the auto analysis used for the total hip. The specialists systematically monitored the point typing and bone edge profiles, and they acquired BMD (mean value of a pixel-by-pixel measurement of the BMD within a defined bone area), bone mineral content (a derived quantity obtained by multiplying BMD by bone area), and bone area data from each scan. The BMD T scores, BMD Z-scores, percentage tissue fat, and thickness parameters were also recorded.

Statistical Analysis

Variables were divided into 2 groups categorically and continuously. Kolmogorov–Smirnov test was used to assess whether continuous variables were suitable for normal distribution. Continuous variables were expressed as mean ± standard deviation (mean ± SD). Categorical variables are given in numbers and percentages. Continuous variables were compared by one-way analysis of variance (ANOVA) or Kruskal–Wallis one-way ANOVA test. For data with normal distribution, Scheffe and Games-Howell tests were used for multiple comparisons of groups with respect to homogeneity of variances. For non-normal distributed data, Bonferroni-adjusted Mann–Whitney *U* test was used for multiple comparisons of groups. The specialists used chi-square test for comparing the categorical variables for this study and performed multivariate logistic regression analysis with univariate analysis of $P < .05$ parameters for determining the patients with osteoporosis independently. A receiver operator characteristic (ROC) curve analysis was performed for re-evaluating the markers that are independent of detecting osteoporosis and for determining the limit value of these markers. As a measure of the accuracy of the test, the value of the area under the curve has been used. Pearson's correlation method was used, and univariate correlation analysis was performed for determining the DEXA-related parameters. A statistically significant parameter was included in a multivariate model, and linear regression analysis was performed with these parameters. Independent indicators affecting DEXA T scores were determined. For statistical significance, $P < .05$ was accepted. For all analyses, Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

The study has 3 groups of participants according to T score in DEXA as follows: normal (group I or T score >−1), patients with osteopenia (group II or T score between −1 and −2.5), and patients with osteoporosis (group III or T score ≤ −2.5). In this study, 23 of the pHPT patients (24.5%) who had osteoporosis were without any fractures in study groups.

Demographic and Laboratory Findings of Primary Hyperparathyroidism Patients According to T Scores in Dual-Energy X-Ray Absorptiometry

There was no statistical difference between groups for age and gender. In group I, group II, and group III, surgical treatment was applied in 45%, 63%, and 91% of patients, respectively, and this difference was significant between the groups. White blood cell, hematocrit, and platelet count were different between groups, and these parameters were significantly lower in group III than group II. Group III had the highest levels of creatinine, ALP, serum and urine calcium, and PTH, and there was statistical significance between group III and the other 2 groups (Table 1). High sensitive C-reactive protein level was significantly higher in group II and group III compared to group I (Table 1). Blood urea nitrogen and NT-proBNP levels increased significantly from group I to group III (Table 1). It was determined that BUN and NT-proBNP levels were statistically different between all study groups (Table 1). Other laboratory findings were similar among the groups (Table 1). In addition, 47.9% of all pHPT patients included in the study were found to have a value of NT-proBNP above 125 pg/mL.

Multivariate Logistic Regression Analysis for the Detection of Patients with T Score in Dual-Energy X-Ray Absorptiometry Score ≤−2.5

In multivariate logistic regression analysis, it was found that levels of NT-proBNP and urine calcium independently determined the patients for osteoporosis ($P < .05$ and Table 2). According to this analysis, it was found that increasing levels of urine calcium (per 10 mg/day) and NT-proBNP (per 10 pg/mL) increase the risk of osteoporosis by 8.6% and 9.1% for patients, respectively (Table 2).

Receiver Operating Characteristic Curve Analysis for the Detection of Patients with T Score in Dual-Energy X-Ray Absorptiometry Score ≤−2.5

In the ROC analysis, the area under the curve values were 0.867 and 0.728 for NT-proBNP and urine calcium, respectively ($P < .05$, Table 3 and Figure 1).When the NT-proBNP and urine calcium cut-off values were taken as 200 pg/mL and 300 mg/day, respectively, it determines patients for osteoporosis with 82.6% sensitivity and 73.2% specificity, and 73.9% sensitivity and 63.4% specificity, respectively (Table 3).

Parameters Associated with T Score in Dual-Energy X-Ray Absorptiometry

Correlation analysis was performed between T score in DEXA and other demographic and laboratory parameters (Table 4). Parameters that correlated significantly with T score in DEXA were used, and linear regression analysis was performed (Table 4). The levels of NT-proBNP and urinary calcium were found independently associated with T score in DEXA (Table 4). The relationship between T score in DEXA and NT-proBNP, and T score in DEXA and the urinary calcium level is shown in Figures 2 and 3.

DISCUSSION

The primary outcome of this study is that NT-proBNP levels are significantly increased in newly diagnosed pHPT patients and are independently associated with osteoporosis presence. In addition, apart from NT-proBNP, urine calcium level is also independently associated with osteoporosis presence, in our study. Both of these findings are not available in the literature as much as we have investigated.

Leere et al[6] evaluated the relationship between BMD and age, sex, BMI, and biochemical parameters, serum calcium, vitamin D, ALP, creatinine, PTH, and phosphorus levels, in a recent study involving 563 patients with pHPT. With some of these parameters being associated in the univariate analysis, it is reported that this relationship is not significant in multivariate analysis. Similar findings have been found in previous studies.[7-10] However, if a biochemical marker could be associated with osteoporosis, it may be important for patients with pHPT, especially those on follow-up and with osteoporosis. For this reason, BMD measurement and grading can only be evaluated by DEXA examination in patients with pHPT. However, DEXA is a radiation-related study. For this reason, it is important to obtain knowledge about

Table 1. Demographic and Laboratory Findings of pHPT Patients According to T Scores in DEXA

Variable	Group I, *n* = 20	Group II, *n* = 51	Group III, *n* = 23	*P*
Age (years)	57.1 ± 9.1	59.3 ± 11.5	62.9 ± 13.8	.256
Gender (female)	14	43	21	.069
Surgery, n (%)	9 (45)	32 (63)	21 (91.3)	**.001**
White blood cell (μL)	6.84 ± 1.22	7.04 ± 1.30 ¥	6.05 ± 1.31	**.010**
Hematocrit (%)	41.9 ± 3.6 α	41.5 ± 3.11 ¥	38.4 ± 3.84	**.001**
Platelet (K/mm^3)	242 ± 61	275 ± 49 ¥	232 ± 78	**.009**
Glucose (mg/dL)	106.5 ± 26.0	115.4 ± 33.6	103.8 ± 47.2	.373
HbA1c (%)	5.78 ± 0.29	6.16 ± 0.94	5.89 ± 1.49	.294
Blood urea nitrogen (mg/dL)	27.7 ± 7.3 α, β	32.2 ± 10.2 ¥	42.5 ± 24.7	**.001**
Creatinine (mg/dL)	0.65 ± 0.26 α	0.73 ± 0.27 ¥	1.32 ± 1.49	**.005**
Total protein (g/dL)	6.97 ± 0.32	7.09 ± 0.43	6.92 ± 0.35	.170
Serum albumin (g/dL)	4.38 ± 0.25	4.18 ± 0.43	4.12 ± 0.25	**.046**
Aspartate aminotransferase (U/L)	20.8 ± 10.6	25.1 ± 16.2	19.8 ± 10.7	.289
Alanine aminotransferase (U/L)	17.6 ± 8.6	22.6 ± 13.2	16.8 ± 9.7	.254
Alkaline phosphatase (U/L)	98.7 ± 46 α	107 ± 36 ¥	155 ± 117	**.008**
hs-CRP (mg/L)	0.28 ± 0.22 α, β	0.50 ± 0.39	0.54 ± 0.36	**.032**
NT-proBNP (pg/mL)	80 ± 27 α, β	170 ± 102 ¥	453 ± 381	**<.001**
Uric acid (mg/dL)	5.02 ± 1.09	5.51 ± 1.25	5.18 ± 1.31	.271
Serum calcium (mg/dL)	11.2 ± 0.81 α	11.3 ± 0.75 ¥	10.7 ± 0.89	**.016**
Urine calcium (mg/day)	244 ± 127 α	299 ± 198 ¥	400 ± 154	**.013**
Serum phosphorus (mg/dL)	2.60 ± 0.52	2.83 ± 0.56	2.84 ± 0.62	.255
Parathyroid hormone (pg/mL)	198 ± 101 α	242 ± 173 ¥	519 ± 513	**<.001**
25(OH) Vit D (ng/mL)	18.6 ± 8.4	19.8 ± 10.3	18.1 ± 12.7	.790

The values were shown as mean ± standard deviation or n (%). Bold values mean they are statistically significant.
Group I, normal DEXA score group; Group II, osteopenia group; Group III, osteoporosis group; 25(OH) Vit D, 25-hydroxyvitamin D; DEXA, dual x-ray absorptiometry; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N terminal pro-brain natriuretic peptide.
α, significant association between group I and group III ($P < .05$).
β, significant association between group I and group II ($P < .05$).
¥, significant association between group II and group III ($P < .05$).

bone microarchitecture with a simple biochemical parameter. In our study, in accordance with previous studies, the presence of osteoporosis was found to be associated with the white blood cell, hematocrit and platelet counts, BUN and creatinine, ALP, serum and urine calcium, PTH, hs-CRP, and NT-proBNP levels in univariate analysis. In multivariate analysis, however, only urine calcium and NT-proBNP levels were independently associated with osteoporosis presence. This finding is consistent with the literature, and as far as we have investigated, there were no data on the association between urine calcium and NT-proBNP and osteoporosis in previous studies.

As with our results in our study, vitamin D serum levels were decreased due to increased vitamin D turnover in pHPT patients with active disease.[20] Although it has been reported that there is a relationship between vitamin D levels and BMD,[8,10] there are also reports that there is no significant association in 2 recent studies.[6,21] In our study, vitamin D levels were low in all BMD

Table 2. Variable Regression Analysis for the Detection of pHPT Patients with Osteoporosis

Variable	Odds Ratio	95% CI	*P*
Urine calcium (10 mg/day)	1.086	1.030-1.145	.002
NT-proBNP (10 pg/mL)	1.091	1.029-1.156	.003

NT-proBNP, N terminal pro-brain natriuretic peptide; pHPT, primary hyperparathyroidism.

Table 3. ROC Analysis for the Detection of pHPT Patients with Osteoporosis

Variable	AUROC Curve	*P*	Cut–Off	Sensitivity (%)	Specificity (%)
Urine calcium	0.728 (0.616–0.840)	.001	300 mg/day	73.9	63.4
NT–proBNP	0.867 (0.789–0.945)	<.001	200 pg/mL	82.6	73.2

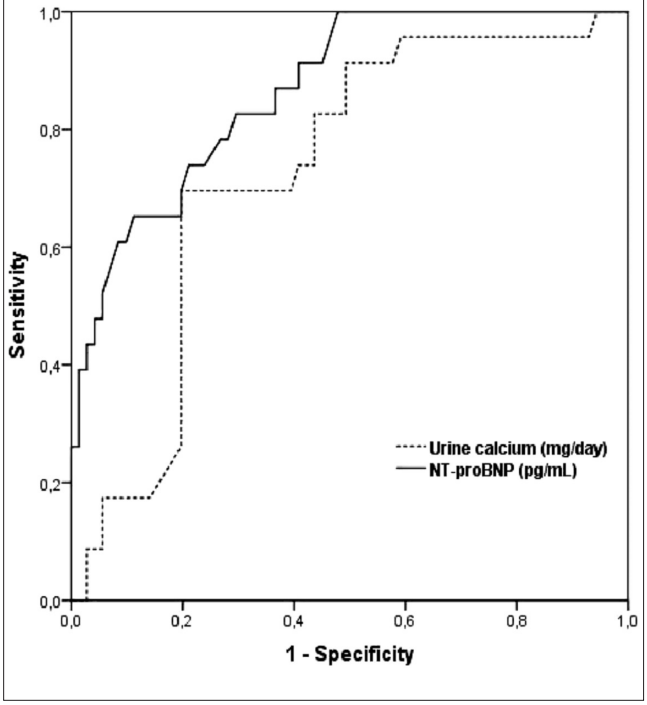
NT–proBNP: N terminal pro–brain natriuretic peptide; AUROC, area under the receiver operating characteristic curve.

groups in accordance with previous data and there was no significant relationship between the groups. So, there was no relation between vitamin D level and the presence of osteoporosis.

Natriuretic peptide follow-up is usually done in cardiac diseases. However, one of the most important problems in pHPT patients is the increased incidence of coronary artery disease, heart failure, and cardiovascular events, and therefore, several studies have been conducted on the use of BNP in pHPT patients.[11-14] The levels of NT-proBNP were shown to be above the normal reference value by 20% in patients with mild PHPT without cardiac involvement.[11] Several studies have reported that BNP increases with cardiac involvement.[12-14] In our study, the majority of patients with pHPT were serious and underwent surgical treatment, and NT-proBNP levels were found to be higher than the reference value of 125 pg/mL in 47.9% of all patients.

Several studies in pHPT patients have reported a close association between current bone disease and Left ventricular dysfunction.[22-25] However, the relationship between existing bone diseases and NT-proBNP has not been addressed in these studies. If the NT-proBNP assessment was done, the result of our study could be even more meaningful. One study that has been undertaken before the clinical use of natriuretic peptides has shown that ANP and BNP affect rat parathyroid cells by ET-1 synthesis in addition to PTH.[15] It is known that ET-1 is the most potent vasoconstrictor and also increases the osteoclastic activity and leads to osteopenia by changing intrauterine vascular tonus and causing a feeding problem.[16-18] For these reasons, it is a peptide associated with osteoporosis. We did not measure ET-1 levels in our study, but we concluded that the independent association between increased NT-proBNP and BMD is probably related with such a physio-pathological system. Our study was the first study that evaluated the relationship between NT-proBNP and osteoporosis and found that there was a meaningful relationship. In addition, we believe that our study should be considered as a preliminary study and more accurate data should be obtained by studies in which both NT-proBNP and ET-1 levels are measured and the presence of osteoporosis is evaluated together.

Figure 1. The receiver operator characteristic curve of values for N-terminal-pro-brain natriuretic peptide and urinary calcium levels for determining patients to be osteoporosis for primary hyperparathyroidism.



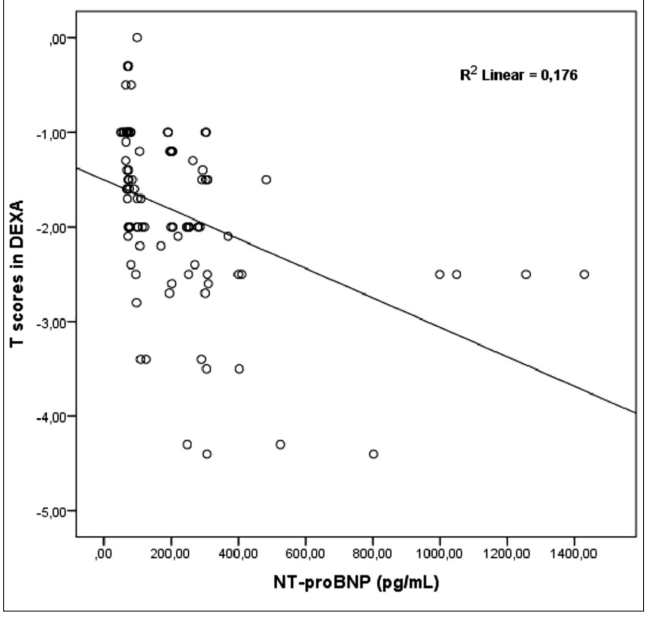
In accordance with the National Institutes of Health consensus panel, the following are considered as surgical criteria in symptomatic pHPT patients or the presence of any of them in asymptomatic pHPT patients: (i) serum calcium level elevation for 1 mg/dL, (ii) significant hypercalciuria (> 400 mg/24 h), (iii) DEXA T score <−2.5, (iv) patient under 50 years old (<50 years old), and (v) decrease in creatinine clearance by more than 30%.[5] Because of this reason, urine calcium level is used as a follow-up parameter in pHPT patients. Our study showed that there was an

Table 4. The Parameters Associated with T Scores in DEXA and Linear Regression Analysis for Parameters Significantly Correlated with T Scores in DEXA

	Univariate analysis		Multivariate analysis	
Variable	*P*	*r*	*P*	β
NT–proBNP (pg/mL)	<.001	0.418	<.001	0.361
Urine calcium (mg/day)	<.001	0.390	<.001	0.327
Parathyroid hormone (pg/ml)	.041	0.211	.733	0.042
Alkaline phosphatase (u/L)	.049	0.171	.756	0.033

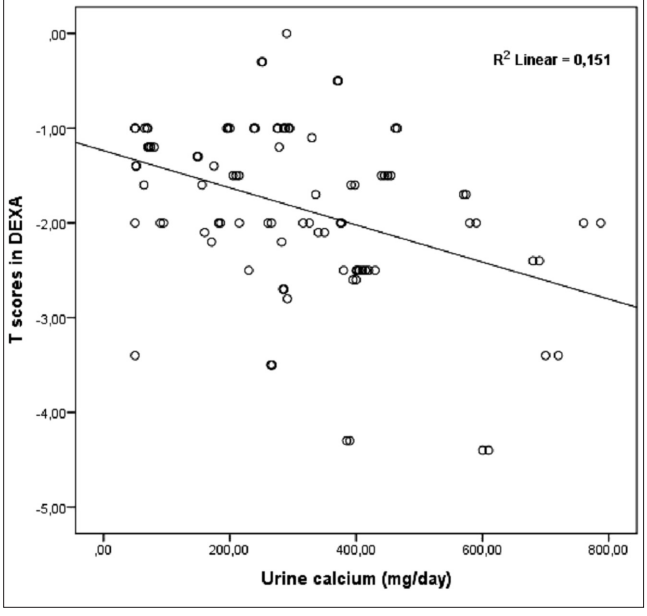
DEXA, dual x–ray absorptiometry; NT–proBNP: N terminal pro–brain natriuretic peptide.
* RAdjusted2=0.378.

Figure 2. There was a significant correlation between N-terminal-pro-brain natriuretic peptide levels and T scores in dual x-ray absorptiometry in patients with primary hyperparathyroidism.



independent relationship between urinary calcium levels and DEXA T score, and urinary calcium levels also independently identified patients with osteoporosis. As far as we investigate, a close and independent relationship between urinary calcium level and BMD has not been previously shown in patients with pHPT. However, there is no significant and independent relationship between serum calcium, PTH, and vitamin D levels and the presence of osteoporosis, but the presence of a significant and independent relationship with urinary calcium level did not make sense to us and we could not explain this relationship physio-pathologically. There is information in the literature that osteoporosis is common in patients with calcium nephrolithiasis, although it is not independently associated with urine calcium level.[22]

Figure 3. There was a significant correlation between urinary calcium levels and T scores in dual x-ray absorptiometry in patients with primary hyperparathyroidism.



In the first instance including the number of patients, there are some major limitations in our study. In conclusion, of patients' not following up there were no data on the treatment efficacy for BMD. Additionally, since the demonstration of the relationship between NT-proBNP and osteoporosis in pHPT patients is the first in the literature, there is a need to properly present data with a study involving more patients. To clarify the effect of bone density on pHPT patients in our study, the control group was not included, so studies with a control group should also be done. It has been reported that heart failure prevalence is high in patients with pHPT and high NT-proBNP.[13,14] However, in our study, we did not conduct any heart failure or cardiac evaluation.

CONCLUSION

The level of NT-proBNP is significantly increased in pHPT patients and is more useful than the other laboratory tests with the urine calcium level indicating bone involvement in patients newly diagnosed with pHPT. However, it is not a parameter to take the place of DEXA, which is a routine examination for bone involvement in pHPT patients. However, measuring a higher NT-proBNP level (>125 pg/mL) at the initial assessment and diagnostic stage of the patient may give a preliminary indication that this patient may have bone involvement or osteoporosis. Especially patients with high NT-proBNP can be followed closely for osteopenia and osteoporosis. In conclusion, NT-proBNP is an inexpensive, simple, reproducible, and objective parameter for the detection of bone involvement in addition to cardiovascular disease and cardiac involvement, in patients with newly diagnosed pHPT in early stages. However, because our study is a first in the literature, it needs to be supported by new studies and assessments.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cukurova University by the Ministry of Health (Date: May 15, 2018 / Desicion No: 59).

Informed Consent: Written informed consent was taken from all of the participants.

Peer-review: Externally peer-reviewed.

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

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