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A Significant Association between Parathyroid Adenoma Volume and Bone Mineral Loss at Distal Forearm

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Running Head: Parathyroid Adenoma Volume and Bone Mineral Loss

Abstract

Introduction: The cortical bone is the most severely affected site in patients with primary hyperparathyroidism (PHPT) and thus, a low bone mineral density (BMD) is predominantly observed in distal forearm. Several studies have investigated potential associations between the weight of the gland and bone mineral loss. In this study, we wanted to investigate the relationship between parathyroid adenoma (PTA) volume and bone mineral loss.

Methods: All patients with a diagnosis of PHPT who were operated at our hospital, and with a histologically proven single PTA were retrospectively analyzed. Z-scores were used as the main variable in our analysis to eliminate the effects of age, sex and gonadal status on BMD.

Results: Total of 153 patients who met the inclusion criteria were eligible for the study. A significant negative correlation between the PTA volume and z-score for distal third of the radius (DR) (p = 0.006, r = -0.297) was shown. The cut-off value of gland volume for predicting cortical bone mineral loss was 9043.2 mm^3. There was also a significant negative correlation between the 24-hour urine calcium and z-scores for lumbar vertebrae and total hip. A significant negative correlation was found between preoperative 25-hydroxy vitamin D levels and the PTA weight.

Conclusions: As the first study that evaluated any possible association between the volume of a parathyroid adenoma and bone mineral loss in patients with PHPT, we found a significant negative correlation between DR z-scores and resected gland volume. Since the volume of a PTA can also be determined by a preoperative US, our findings may be helpful during the preoperative evaluation of a patient with a preliminary diagnosis of PHPT.

Key Words: Primary Hyperparathyroidism, Bone Mineral Density, Radius, Parathyroid Adenoma, Organ Volume

What is new/What is important?

- A significant negative correlation was found between DR z-scores and resected gland volume in patients with PHPT.

- The cut-off value of gland volume for predicting cortical bone mineral loss was 9043.2 mm^3.

- No association was found between gland weight and DXA scan results.

- A significant negative correlation was found between the 24hr UCa and z-scores for L1-4, and Ft.

- A significant negative correlation was found between preoperative 25OH-D levels and the PTA weight.

- Significant positive correlations were found between preoperative PTH levels and PTA weight, and volume.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine condition mostly caused by a parathyroid adenoma (PTA). Although the majority of patients with PHPT are asymptomatic, bone mineral loss is not uncommon in this patient population [1–3]. An increased bone resorption and calcium release from bones induced by the increased parathormone (PTH) level is the well-known pathological mechanism underlying the bone loss in PHPT [4]. The cortical bone is the most severely affected site with relative preservation at trabecular parts and thus, a low bone mineral density (BMD) is predominantly observed in distal forearm, rather than the lumbar spine and hip [2,5,6]. Therefore, it is recommended to include a dual-energy x-ray absorptiometry (DXA) bone density scan of all 3 sites, including the lumbar spine, hip, and forearm in the workup of PHPT [5].

Several studies have focused on potential associations between parathyroid gland weight and various conditions and some of these studies have investigated potential associations between the weight of the gland and bone mineral loss. A study revealed that there was a significant negative correlation between the weight of the gland and bone loss in the second metacarpal bone, but not in the lumbar vertebrae [7]. In contrast with this study, a former study failed to demonstrate any relationships between PTH levels or parathyroid adenoma weight, and the indicators of skeletal changes, such as serum alkaline phosphatase and urinary excretion of hydroxyproline [4]. The authors stated that the direct effect of PTH was not the main determinant of the severity of bone loss in patients with PHPT. Unlike the weight of parathyroid gland, parathyroid gland volume has not been investigated for potential associations with bone mineral loss before, although it is a parameter easy to evaluate by ultrasound (US) preoperatively, in patients with PHPT. The aim of the present study was to investigate the relationship between PTA volume and distal third of the radius, lumbar vertebrae, femoral neck and total hip z-scores.

MATERIAL AND METHODS

All patients with a diagnosis of PHPT who were operated at our hospital between 2010 and 2021, and with a histologically proven single PTA were retrospectively analyzed from the electronic archives of our institution. Of these patients, those aged ≥ 18 years and who had available DXA data, and a normal thyroid/gonadal function were included in this study. A normal gonadal function was considered as the absence of any hypogonadism-related conditions. Patients with a recorded ICD-10 code of any other conditions associated with

osteoporosis, such as rheumatoid arthritis, ankylosing spondylitis, cushing's syndrome, and epilepsy were not included in the study.

Demographic (age and gender) and preoperative clinical (gonadal status, whether presence of nephrolithiasis, corrected serum calcium [Ca], phosphorus [P], parathyroid hormone [PTH], 25-hydroxy vitamin D [25OH-D], 24-hour urine calcium [24hr UCa], the weight and 3 dimensional measurements of PTA reported by the department of pathology, distal third of the radius [DR], lumbar vertebrae [L1-L4], femoral neck [Fn], and total hip [Ft] BMD z-scores) characteristics were noted. Moreover, the volume of a parathyroid adenoma was calculated using the formula for an ellipsoid (Volume = $[4/3]\ \pi\ r_1r_2r_3$, where r_1, r_2, r_3 are the lengths of the semiaxes in centimeters). A GE Lunar Prodigy® 8743 densitometer (GE Healthcare, Machelen, Belgium) was used to determine the BMD at the lumbar spine, left femur and distal forearm. Z-scores were expressed as standard deviations from the mean, calculated through comparisons with age- and sex- matched population. Z-scores were used as the main variable in our analysis to eliminate the effects of age, sex, and gonadal status on BMD. Corrected calcium was calculated by applying the following formula: serum calcium (mg/dL) + 0.8 * (4 - serum albumin [g/dL]).

All statistical analyses were performed using an IBM SPSS for Windows software package version 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to assess the normality assumption. Continuous variables were presented depending on normal distribution with either mean±standard deviation or (in the case of non-normal distribution) median (interquartile range). Comparisons between groups were performed using Mann-Whitney U test. Associations between continuous variables were determined using the Spearman's correlation analysis. A partial correlation analysis was performed to measure the strength of a correlation between two variables (z-score for DR and adenoma volume), while controlling for the effect of another variable (25OH-D). The receiver operating characteristic (ROC) curve was plotted to understand the predictive significance of gland volume for indicating bone mineral loss at distal radius. A p-value <0.05 was considered statistically significant. The ethical approval for this study was obtained from the ethics committee of Kocaeli University, Faculty of Medicine (Date:25.10.2021, No: GOKAEK 2021/18.19 - 2021/305).

RESULTS

A total of 153 patients who underwent surgery for a parathyroid adenoma and met the inclusion criteria were eligible for the study. Baseline demographic and clinical characteristics of study patients are presented in Table 1. The Spearman's rank correlation demonstrated a significant negative correlation between the PTA volume and z-score for DR ($p = 0.006$, r = -0.297). There was also a significant negative correlation between the 24hr UCa and z-scores for L1-4, and Ft ($p < 0.001$, r = -0.340, and $p = 0.016$, r = -0.229, respectively). A significant negative correlation was found between preoperative 25OH-D levels and the PTA weight ($p = 0.003$, r = -0.200). Correlations between other clinical features are presented in Table 2. A very weak positive correlation was found between preoperative corrected Ca levels and PTA weight, and volume ($p = 0.001$, r = 0.187, and $p < 0.001$, r = 0.198, respectively). Similarly, significant positive correlations were found between preoperative PTH levels and PTA weight, and volume ($p < 0.001$, r = 0.370, and $p < 0.001$, r = 0.324, respectively).

A partial correlation analysis also supported the significant negative correlation between the PTA volume and z-scores for DR ($p < 0.001$, r = -0.416), while controlling for the effect of 25OH-D. In this analysis, the degree of significance of the correlation was increased from 0.297 to 0.416. In addition, the Mann-Whitney U test revealed that patients with nephrolithiasis had lower z-scores for Ft compared to those without nephrolithiasis ($p = 0.012$). The ROC analysis of the resected gland volume revealed that the area under the curve (AUC) was 0.653 (95% CI: 0.540 to 0.755; $p = 0.0185$) (Figure 1). The cut-off value of gland volume for predicting cortical bone mineral loss was 9043.2 mm^3 with a 60.61% sensitivity and 75.51% specificity.

DISCUSSION

The present study has shown a significant negative correlation between the PTA volume and z-scores for DR, but not at the other locations, such as L1-4, Fn or Ft. To the best of our knowledge, we are the first to report a significant association between the volume of a PTA and cortical bone damage in patients with PHPT. Similarly, this study is also the first to give a significant cut-off value of the resected parathyroid adenoma volume for predicting bone mineral damage at distal forearm in patients with PHPT.

These results may have two important implications. First, BMD of the distal forearm may be used as a more valuable parameter of the severity of bone mineral loss in patients with PHPT compared to the measurements in other locations. As stated by Saleem *et al*. PHPT mostly affects the cortical bone and distal forearm, as a site rich in cortical bone, is one of the main

sites where the highest bone mineral loss occurs in patients with PHPT [2]. In another study, distal radius BMD was suggested as a better marker for bone effects of PHPT [6]. The authors reported that a routine forearm DXA led to an increase in the prevalence of diagnosed osteoporosis by 11.2% in patients with PHPT. Similarly, Wood *et al*. reported that only half of patients with PHPT who underwent parathyroid surgery had an available distal forearm DEXA bone scan and therefore, the prevalence of osteoporosis might be underestimated in this patient population [8]. Accordingly, in addition to lumbar spine and hip, it is also recommended to perform a DXA on the forearm as cortical bone loss is best shown in patients with PHPT [5].

Secondly, the volume of a PTA may indicate the severity of cortical bone damage in patients with PHPT. Previously, there have been various studies which investigated a possible correlation of PTA weight with DXA outcomes. A cross-sectional study has reported a significant negative correlation between the gland weight and bone mineral density in the second metacarpal bone, which reflects a cortical bone damage, but not in the lumbar spine [7]. Moreover, Steinl *et al*. demonstrated that the PTA weight estimated on preoperative 4D-Computerized Tomography using the size of the adenoma was associated with greater gains in lumbar spine BMD post-operatively [9]. In the same study, a significant correlation was also found between the estimated PTA weight and baseline serum calcium, which supported the hypothesized association between larger adenomas and greater impact on calcium mobilization from the bone. In line with this study, our results also showed a significant positive correlation between preoperative serum Ca levels and parathyroid gland weight.

Unlike prior studies, our study did not reveal any significant association between the PTA weight and DXA scan results, despite a significant correlation found between parathyroid gland weight and volume. Therefore, PTA volume may be a better predictor of bone mineral loss than parathyroid gland weight in patients with PHPT. One possible explanation is that the volume of a parathyroid adenoma may better reflects the disease duration than gland weight.

In this study, no correlation was found between DXA outcomes and several serum biochemical parameters, including serum Ca, P, PTH, and 25OH-D, while a significant negative correlation was shown between 24hr UCa levels and lumbar spine and total hip z-scores. Moreover, we also found that the total femur z-scores of the patients with nephrolithiasis were significantly lower than those without nephrolithiasis. In line with our results, two other studies reported that preoperative serum PTH levels did not correlate with the severity of bone mineral loss in patients with PHPT and a comprehensive review stated that bone mineral loss was more severe in patients with calcium stones and hypercalciuria compared to those with normocalciuria

[4,7,10]. In contrast, Reid *et al*. has shown a negative association of PTH and adjusted Ca levels with the hip and femoral neck z-scores [11]. Another study has demonstrated that low plasma 25OH-D levels were associated with lower BMD levels on the femoral neck and forearm, in contrast with our results in the present study [12].

A weak but significant correlation was found between preoperative 25OH-D levels and the weight of PTA in our study. In parallel with this result, two other studies also reported similar outcomes that might be explained by a possible acceleration of parathyroid adenoma growth due to chronic vitamin D deficiency [13,14]. Interestingly, this study failed to demonstrate any association between PTA volume and 25OH-D levels in this study. Despite this unexpected outcome, we also used a partial correlation analysis to control for the effect of 25OH-D levels on gland volume and this technique increased the degree of statistical significance of the negative correlation between z-scores for DR and PTA volume. The importance of PTA volume has been investigated in a study which evaluated 218 patients with PHPT. The authors have found that the volume of the resected parathyroid adenoma was the most important predictor for the development of hungry bone syndrome after surgery [15].

The main limitation of our study was the lack of body mass index data of the patients, which was an expected consequence of the retrospective nature of this study. This undesirable limitation prevented us from controlling for the effect of body mass index on bone damage, while investigating possible associations between clinical parameters and bone mineral loss in patients with PHPT. Another limitation of this study was that the conditions associated with osteoporosis have been evaluated only from the electronic archives of our institution. Any missing data on additional diagnosis or any drug usage which might alter bone mineral density, such as steroids, antiepileptics, and antiresorptive therapies would interact with the outcomes of our study.

In conclusion, we found a significant negative correlation between DR z-scores and resected gland volume in this first study that evaluated any possible association between the volume of a parathyroid adenoma and bone mineral loss in patients with PHPT. Moreover, we showed that the cut-off value of resected gland volume for predicting bone mineral loss at distal radius was 9043.2 mm^3. In contrast with this finding, no association was found between gland weight and DXA scan results. Since the volume of a PTA can also be determined by a preoperative US, we believe that our findings may be helpful during the preoperative evaluation of a patient with a preliminary diagnosis of PHPT. Our findings may suggest that a larger parathyroid

adenoma may be visualized by imaging tests preoperatively when there is a severe cortical bone damage at the distal forearm in a patient with PHPT.

Introducere: Osul cortical este afectat sever la pacienții cu hiperparatiroidism primar (PHPT) și astfel o densitate minerală osoasă minerală scăzută (BMD) este predominant observată la antebrațul distal. Mai multe studii au evaluat asocierea dintre volumul glandei paratiroide și demineralizarea osoasă. În acest studiu scopul a fost de a evalua legătura dintre volumnul adenomului paratiroidian (PTA) și demineralizarea osoasă.
Metode: Toți pacienții cu diagnosticul de PHPT operați în spital și cu PTA solitar identificat histologic au fost analizați retrospectiv. Scorurile z au fost utilizate pentru a elimina variabilitatea dată de vârstă, gen, status gonadal asupra BMD.
Rezultate: 153 de pacienți au fost incluși în analiză. S-a observat o corelație între volumul PTA și scorul z la treimea distală a radiusului (DR) (p=0.006, r=-0.297). Valoarea prag ce a prezist demineralizarea osoasă a fost de 9043.2 mm$^{3.}$ S-a observat o corelație negativă între calciuria la 24 de ore și socrurile z pentru vertebrele lombare și șold. O corelație negativă s-a observat dintr nivelurile 25-OH vitamina D înainte de operație și greutatea PTA.
Concluzii: Fiind primul studiu ce a evaluat asocierea dintre adenomul paratidoidian și demineralizarea osoasă la pacienții cu PHPT am observat o corelație negativă dintre z-scorurile DR și volumul glandei rezecate. Volumul PTA poate fi determinat și non invaziv ecografic și astfel aceste observații pot fi utile și pentru evaluarea preliminară a pacienților cu PHPT.

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Conflict of interest

The authors declare that there are not conflicts of interest.

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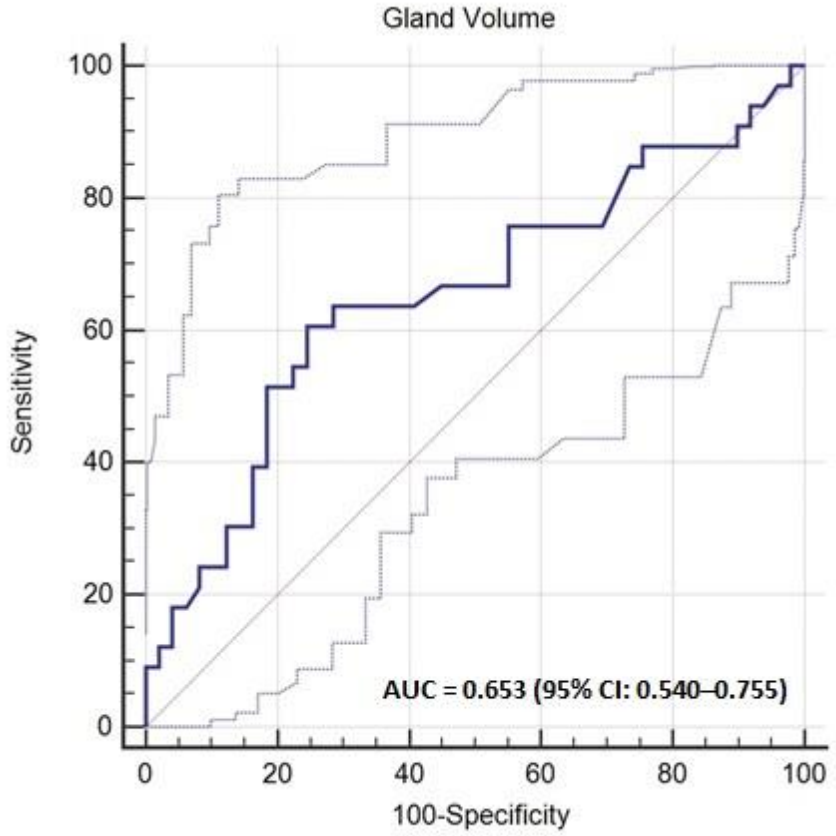


Figure 1 - Receiver operating characteristic curve of the resected parathyroid adenoma volume in predicting cortical bone mineral loss

Table 1 – Patient demographics and clinical characteristics (n=153)

Characteristic	**n (%)**
Age (years), median (min-max)	56 (18-84)
Gender	
male	24 (15.7)
female	129 (84.3)
Gonadal Status	
menopausal	69 (56.1)
eugonadal	54 (43.9)
Nephrolithiasis	
yes	28 (30.8)
no	63 (69.2)
Cortical Bone Mineral Density*	
below the expected range for age	37 (41.1)
normal	53 (58.9)
	median (25^{th}-75^{th} percentile)
Ca (mg/dL)	10.7 (10.3-11.2)
P (mg/dL)	2.5 (2.2-2.9)
PTH (pg/mL)	202 (144-300)
25OH-D (ng/mL)	18 (12-25)
Macroscopic Characteristics of Adenoma	
weight (gr)	1.02 (0.50-2.00)
volume (cm^3)	5.92 (2.51-15.7)

Ca: calcium; P: phosphorus; PTH: parathyroid hormone; 25OH-D: 25-hydroxy vitamin D

*Below the expected range for age and normal groups defined as Z-score ≤-2 and >-2, respectively.

Table 2 – Spearman correlation of z-scores at DR, L1-L4, Fn and Ft with the clinical characteristics in patients with primary hyperparathyroidism (n=153)

	z-score DR	z-score L1-L4	z-score Fn	z-score Ft	25OH-D	Ca	P	PTH	24hr UCa	Adenoma volume
z-score DR	1									
z-score L1-L4	0.425**	1								
z-score Fn	0.487**	0.593**	1							
z-score Ft	0.560**	0.644**	0.805**	1						
25OH-D	ns	ns	ns	ns	1					
Ca	ns	ns	ns	ns	ns	1				
P	ns	ns	ns	ns	ns	-0.202**	1			
PTH	ns	ns	ns	ns	-0.388**	0.127*	-0.210**	1		
24hr UCa	ns	-0.340**	ns	-0229*	ns	0.207**	ns	ns	1	
Adenoma volume	-0.297**	ns	ns	ns	ns	0.198**	-0.141**	0.324**	ns	1
Adenoma weight	ns	ns	ns	ns	-0.200**	0.187**	-0.119*	0.370**	ns	0.831**

Ca: calcium; Fn: femoral neck; Ft: total hip; L1-L4: L1–L4 lumbar spine; P: phosphorus; PTH: parathyroid hormone; ns: non-significant; DR: distal third of the radius; 24hr UCa: 24-hour urine calcium; 25OH-D: 25-hydroxy vitamin D

*Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed)