THE EFFECT OF VITAMIN D DEFICIENCY ON THE SIZE AND WEIGHT OF PARATHYROID ADENOMA IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Introduction: *To assess the effect of vitamin D deficiency on parathyroid adenoma size and weight in patients with primary hyperparathyroidism (PHPT) as well as the association between preoperative biochemical parameters.*

Material and methods*: This is a retrospective study including 286 patients (246 females/37 males) with PHPT who were operated on for a single parathyroid adenoma. Correlation analysis was performed between the size and weight of the parathyroid adenoma on the surgical pathology report with preoperative biochemical parameters. Patients with vitamin D levels < 20 ng/mL were accepted as a group 1, and the patients with vitamin D levels ≥ 20 ng/mL were accepted as a group 2, and the groups were compared in terms of all parameters.*

Results*: In correlations analysis, there were positive correlations of the adenoma size with calcium and parathormone (PTH) (r = 0.192, p = 0.001; r = 0.334, p < 0.001, respectively) and adenoma weight with calcium and PTH (r = 0.219, p = 0.011; r = 0.510, p < 0.001, respectively) but there were negative correlations between adenoma size and weight with vitamin D levels (r = -0.191, p = 0.003; r = -0,231, p = 0.015, respectively). On the other hand there were no correlations of the size and weight of adenomas with calcium and PTH levels in patients with vitamin D levels ≥ 20 ng/mL. Adenoma size, adenoma weight, and PTH were higher in the patients in group 1 than in group 2. (p = 0.02, p = 0.04 and p = 0.001 respectively).*

Conclusion*: Vitamin D affects preoperative serum PTH level, adenoma size, and adenoma weight in PHPT. So it may not be correct to predict the size and weight of adenoma with preoperative serum PTH and calcium level without considering vitamin D levels.*

Keywords: *Vitamin D deficiency, parathyroid adenoma size, parathyroid adenoma weight, primary hyperparathyroidism.*

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease characterized by hypercalcemia and elevated or inappropriately normal parathormone (PTH) secretion[(1)]. The diagnosis of the PHPT has been increasing nowadays with routine biochemical screening[(1)]. It is frequently observed in women, especially in the postmenopausal period, and the female / male ratio is 3-4/1[(2)]. A parathyroid adenoma develops on a single gland in 85% of PHPT patients, while in 15%, it develops as hyperplasia through multiglandular involvement[(1)]. There are generally four parathyroid glands in the population. The size of the parathyroid glands is often 6- 8 mm, and the weight of the glands is 0.4-0.6 gr[(3, 4)]. The relationship between the size and weight of the parathyroid adenomas with preoperative biochemical parameters is not clear. In some studies, preoperative calcium and PTH levels were found associated with the size and weight of the parathyroid adenoma, but some studies failed to show this correlation[(5-8)]. 25 OH vitamin levels and the effect of the vitamin d deficiency on these results were not specified in most of these studies about the association between the size and weight of the parathyroid adenomas and biochemical parameters[(5-7)]. Vitamin D deficiency is quite

common in our country, and vitamin D deficiency affects bone biochemical parameters[9, 10]. Intestinal calcium and phosphorus absorption decreases, and PTH levels also increase in patients with vitamin D deficiency[10]. It is also known that vitamin D deficiency often accompanies patients with PHPT[11]. We believed that the accompanying vitamin D deficiency affected the results of these studies about the association between the size and weight of adenomas with calcium and PTH levels[5-7].

Skeletal, renal, neurocognitive, and cardiovascular complications are frequently observed in patients with PHPT[1]. The complications associated with PHPT reduce with the increase of early diagnosis of PHPT nowadays[12]. Surgical treatment of the parathyroid gland or glands is recommended in patients with symptomatic PHPT, and it provides a cure[13]. Therefore, it is crucial to define surgical indications in patients with PHPT. It is recommended that all patients be evaluated in terms of osteoporosis and kidney stone, which are also among the surgical indications[13]. There is no data in the literature regarding the association between the presence of these complications in patients with PTHP and the postoperative size and weight of the adenomas.

It is crucial to predict the size and weight of the parathyroid adenoma with other data in addition to the preoperative imaging methods for surgical success. Preoperative PTH and calcium levels or complications may alert the surgeon to the possibility of small or large parathyroid adenomas. Therefore, we aimed to show the association between preoperative biochemical parameters and the complications of PHPT with the postoperative size and weight of the parathyroid adenoma in patients with primary hyperparathyroidism (PHPT), as well as the effect of vitamin D deficiency on these results in this study.

Material and methods

This was a cross-sectional and retrospective study. Two hundred eighty-three patients (246 females / 37 males) with PHPT were recruited to the study who were operated on for parathyroid adenoma between 2016 and 2020. The patients with the pathological result of single parathyroid adenoma and postoperatively cured were included in the study. The patients with chronic renal impairment estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2), thiazide- or lithium-induced hypercalcemia, and secondary/tertiary hyperparathyroidism were excluded from the study.

The diagnosis of PHPT has defined the presence of hypercalcemia with inappropriately normal and increased levels of PTH[13]. Single parathyroid adenomas were be defined from surgical pathology reports. Data of the highest diameter (mm) and weight (gr) of the parathyroid adenomas were recorded from the pathology reports.

BMI was calculated with this formula "weight in kilograms divided by height in meters squared."

Venous blood samples were drawn in following overnight fasting. Serum creatinine, eGFR alkaline phosphatase (ALP), calcium, magnesium, phosphorus were measured by the photometric method using a Beckman Coulter analyzer. The corrected serum calcium levels were calculated using this formula. "Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin (g/dL))". Corrected calcium values were used in our data (normal range, 8.6 – 10.6 mg/dL). PTH was measured by chemiluminescence method using a Beckman Coulter Analyzer (normal range, 12-88 pg/mL), and 25OH vitamin D levels were also measured by chemiluminescence method using a Beckman Coulter Analyzer (normal range, ng/mL). Hypercalciuria was accepted as 24-hour urine calcium excretion > 400 mg. Patients without renal stone history were also evaluated with abdominal ultrasonography (USG) for renal manifestations of PHPT.

Areal bone mineral density (BMD) by dual x-ray absorptiometry (DXA) (Hologic, Waltham, MA) was measured at the lumbar spine (L1–L4), total hip, femoral neck, and non-dominant distal one-third radius. BMD, T scores, and Z scores were recorded in the DXA evaluation. Osteoporosis was diagnosed with BMD T-score ≤ –2.5 at the lumbar spine, femoral neck, the total hip, or the 1/3 radius in postmenopausal women or males >50 years. Z scores of –2.0 or less are below the expected range for age was accepted osteoporosis in premenopausal women[14]. Age, gender, BMI, creatinine, eGFR, the size of the adenoma, the weight of the adenoma, ALP, calcium, magnesium, phosphorus, PTH, 25 OH vitamin D, 24-hour urine calcium levels, complications of PHPT (osteoporosis at any sites, kidney stones) were recorded.

We divided the patients into groups according to vitamin D levels. Vitamin D deficiency is defined as a 25 OH vitamin D level below 20 ng/ml according to the guideline (10). The patients with 25

OH vitamin D levels < 20 ng/mL (with vitamin D deficiency) were accepted as group 1, and the patients with vitamin D levels ≥ 20 ng/mL were accepted as group 2. Patients with vitamin D deficiency and with vitamin D levels ≥ 20 ng / mL were compared with regard to their age, gender, creatinine, eGFR, the size of the adenoma, the weight of the adenoma, ALP, calcium, magnesium, phosphorus, PTH, 25 OH vitamin D, 24-hour urine calcium levels.

Correlation analyses were performed in terms of age, gender, creatinine, eGFR, ALP, calcium, phosphorus, magnesium, PTH, 25 OH vitamin D, 24-hour urine calcium levels, complications of PHPT that may be associated with the size and weight of the adenoma in the whole study group.

Correlation analyses were also performed in terms of age, gender, creatinine, eGFR, ALP, calcium, phosphorus, magnesium, PTH, 24-hour urine calcium levels, complications of PHPT that may be associated with the size and weight of the adenoma in patients with the vitamin D levels ≥ 20 ng/mL (these patients were also in group 2).

Correlation analyses were performed between the size and weight of the adenoma with DXA parameters in the whole study group.

The study was approved by the local ethical committee and was conducted according to the Declaration of Helsinki.

Statistical analyses were performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation (SD). The Kolmogorov-Smirnov test assessed the normality of the distribution of the quantitative variables. In an independent group comparison, Student's t-test was performed for normally distributed numeric variables, and the Mann-Whitney U test was performed for non-normally distributed data. Categorical variables were compared using the Chi-square test. Pearson's correlation analysis was used for correlation analysis. Bivariate correlations were expressed by Pearson's correlation analysis or Spearman's correlation analysis when indicated.

Statistically significant results were defined with a p-value of < 0.05.

Results

Two hundred and eighty-three patients with the pathological results of a single parathyroid adenoma were included. In our study, the mean age of the patients was 55.3±11 years, and 246 of 283 patients were women, and 37 were men. The mean size of the parathyroid adenomas was 1.87 ± 0.9 cm (0.2 - 8 cm), and the mean weight of the parathyroid adenomas was 1.3±1.4 gr (0.1 - 8.4 gr). The most common preoperative clinical complication associated with hyperparathyroidism was osteoporosis in 134 (47 %) patients, followed by nephrolithiasis in 78 (28 %) patients. Characteristics of the patients in terms of clinical and laboratory findings were given in Table 1.A comparison of the patients with the groups according to 25 OH vitamin D levels with regard to clinical and laboratory findings was presented in Table 2. The size and weight of the adenomas were larger in group 1 than in the patients with group 2 (p=0.02, p=0.04, respectively). The PTH levels in group 1 were also statistically higher than group 2 (p=0.001). The age of the patients was higher in group 2 than group 1 (p = 0.01). The two groups were similar in terms of gender, creatinine, eGFR, ALP, calcium, phosphorus, magnesium, and urine calcium levels.

N=283	Value	Referange Range
Age Mean±SD	55.3±11.0	years
Female (n) / male (n)	246 / 37	
Size of the adenom Mean±SD	1.87±0.9 cm	cm
Weight of the adenom Mean±SD	1.3±1.4	gr
BMI Mean±SD	30.9±5.2	kg/m^2
Creatinine Mean±SD	0.7±0.2	0.5-0.9 mg/dL
eGFR Mean±SD	99.2±15.7	mL/min
ALP Mean±SD	109.4 ± 76.3	44–147 U/L
Calcium Mean±SD	11.4±0.8	8.6-10.6 mg/dL
Phosphorus Mean±SD	2.6±0.6	2.5-4.5 mg/dL
Magnesium Mean±SD	1.9±0.3	1.9-2.5 mg/dL
PTH Mean±SD	201.5±162.3	12-88 pg/mL
25 hydroxy-vitamin D Mean±SD	19.6±11.7	20–70 ng/mL
Urine calcium levels Mean±SD	368±187	< 400 mg/24h
Complications of PHPT		
Kidney Stones (n, %)	78 (28)	
Osteoporosis at any sites (n, %)	134 (47)	
Osteoporosis at forearm (n, %)	127 (44)	

Table 1: Characteristics of patients in terms of clinical and laboratory findings in the whole study group.
eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; PTH, parathyroid hormone; PHPT, primary hyperparathyroidism.

The correlations between the size and parathyroid adenoma weight and bone biochemical markers in all participants were given in table 3. In correlations analysis, there were positive correlations of the adenoma size with calcium and PTH (r=0.192, p=0.001; r=0.334, p < 0.001, respectively) but there were negative correlations of the adenoma size with phosphorus and 25 OH vitamin D levels (r=-0.17, p=0.028; r= -0.191, p=0.003, respectively). There were positive correlations of the adenoma weight

with calcium and PTH (r=0.219, p=0.011; r=0.510, p < 0.001, respectively). On the other hand, there was a negative correlation between adenoma weight and 25 OH vitamin D levels (r = -0,231, p = 0.015).

N:283	Patient with 25 hydroxy-vitamin D levels < 20 ng/mL (Group 1) (n=171)	Patient with 25 hydroxy-vitamin D levels ≥ 20 ng/mL (Group 2) (n= 112)	P
Age (years) Mean±SD	53.7±10.4	57.5±11.5	**0.01**
Female (n) / male (n)	151/20	95/17	*NS*
Size of the adenom (cm) Mean±SD	1.93±0.80	1.74±0.95	**0.02**
Weight of the adenom (gr) Mean±SD	1.44±1.49	0.94±0.83	**0.04**
Creatinine (mg/dL) Mean±SD	0.63±0.14	0.67±0.19	*NS*
eGFR (mL/min) Mean±SD	101.5±14.1	98.6±15.7	*NS*
ALP (U/L) Mean±SD	111.9 ± 52.3	109.5 ± 107.7	*NS*
Calcium (mg/dL) Mean±SD	11.4±0.74	11.3±0.79	*NS*
Phosphorus (mg/dL) Mean±SD	2.6±0.58	2.6±0.55	*NS*
Magnesium (mg/dL) Mean±SD	1.91±0.30	1.90±0.29	*NS*
PTH (pg/mL) Mean±SD	216.2±173.5	167.1±128.2	**0.001**
25 hydroxy-vitamin D (ng/mL) Mean±SD	12.3±5.2	30.7±9.9	**< 0.001**
Urine calcium levels (mg/24h) Mean±SD	390±191	332±173	*NS*

Table 2: Clinical and biochemical comparison of the patients grouped according to 25 hydroxy-vitamin D levels.

P < 0. 05 statistically significant, significant p values are shown in bold. eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; PTH, parathyroid hormone; hyperparathyroidism.

After the removal of five adenomas with the highest values for the weight (5 gr, 5.5 gr, 6.5 gr, 7.2 gr, and 8.4 gr), the correlation was less but still significant between weight and PTH (p < 0.001; r = 0.344). On the other hand, the correlation was lost between weight and calcium (p = 0.62; r = 0.44).

The correlations between the size and parathyroid adenoma weight and biochemical bone markers were also given in patients with vitamin D levels ≥ 20 ng/mL in table 4. In correlations analysis, there were no statistically significant correlations of the adenoma size and weight with age, gender, ALP, calcium, magnesium, phosphorus, PTH, and 24-hour urine calcium levels and complications of PHPT.

	Size of the adenom (cm)		Weight of the adenom (gr)	
N=283	r	p	r	p
Age (years)	-0.078	0.192	-0.204	**0.018**
Female gender	0.143	0.017	-0.010	0.911
Creatinine (mg/dL)	-0.017	0.817	-0.153	0.076
eGFR (mL/min)	0.129	0.075	0.203	**0.018**
ALP (U/L)	0.078	0.408	0.078	0.408
Calcium (mg/dL)	0.192	**0.001**	0.219	**0.011**
Phosphorus (mg/dL)	-0.175	**0.028**	-0.096	0.323
Magnesium (mg/dL)	-0.074	0.478	-0.163	0.181
PTH (pg/mL)	0.334	**< 0.001**	0.510	**< 0.001**
25 hydroxy-vitamin D (ng/mL)	-0.191	**0.003**	-0.231	**0.015**
Urine calcium levels (mg/24h)	0.099	0.232	0.092	0.376
Osteoporosis at any sites	-0.008	0.914	-0.024	0.802
Kidney Stones	0.077	0.277	0.150	0.094

Table 3: Correlation between the size and weight of the parathyroid adenoma and bone biochemical markers in the whole study group.

P < 0.05 statistically significant, significant p values are shown in bold.

eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; PTH, parathyroid hormone

	Size of the gland (cm)		Weight of the gland (gr)	
N=115	r	p	r	p
Age (years)	0.041	0.699	0.048	0.654
Female gender	-0.144	0.175	-0.083	0.586
Creatinine (mg/dL)	0.055	0.607	-0.247	0.098
eGFR (mL/min)	0.026	0.837	-0.441	**0.002**
ALP (U/L)	0.031	0.823	0.121	0.457
Calcium (mg/dL)	0.154	0.146	-0.124	0.411
Phosphorus (mg/dL)	-0.043	0.751	0.025	0.873
Magnesium (mg/dL)	-0.124	0.472	0.004	0.986
PTH (pg/mL)	0.179	0.091	0.118	0.428
Urine calcium levels (mg/24h)	-0.063	0.662	-0.015	0.933
Osteoporosis at any sites	0.044	0.747	0.126	0.433
Kidney Stones	-0.101	0.417	-0.11	0.943

Table 4: Correlation between the size and weight of the parathyroid adenoma with bone biochemical markers and complications of the patients with 25 oh vitamin d levels ≥ 20 ng/mL.

P < 0.05 statistically significant, significant p values are shown in bold. eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; PTH, parathyroid hormone.

The correlations between the size and weight of the parathyroid adenoma with DXA parameters in all participants were also given in table 5. There were no statistically significant correlations of the adenoma size and weight with DXA parameters.

	Size of the adenoma (cm)		Weight of the adenoma (gr)	
N=283	r	p	r	p
Distal 1/3 radius				
BMD (g/cm^2)	0.08	0.299	-0.014	0.880
Tscore	0.046	0.546	-0.026	0.781
Z score	-0.047	0.546	-0.145	0.120
Lumbar spine L1-L4				
BMD (g/cm^2)	0.088	0.274	0.078	0.418
Tscore	0.061	0.19	0.099	0.291
Z score	0.061	0.449	0.023	0.815
Femoral neck				
BMD (g/cm^2)	0.130	0.102	0.134	0.162
Tscore	0.109	0.161	0.164	0.098
Z score	-0.003	0.974	0.081	0.398

Table 5: Correlation between the size and weight of the parathyroid adenoma with DXA parameters in the whole study group.

P < 0.05 statistically significant. significant p values are shown in bold. DXA, dual energy X-ray absorptiometry; BMD, bone mineral density

Discussion

In our study, we evaluated the association between biochemical bone markers and PHPT complications with the size and weight of the parathyroid adenoma in patients operated for single parathyroid adenoma. The size and weight of adenoma positively correlated with preoperative calcium and PTH while a negative correlation with 25 OH vitamin D levels. However, when the group with only vitamin D levels ≥ 20 ng / mL were evaluated separately, no correlation was observed between the size and weight of adenomas and biochemical markers. There were no correlations between the presence of osteoporosis at any site and kidney stones with the size and weight of adenoma.

In the literature, there are studies that found a relationship between preoperative calcium and PTH levels with the size and weight of adenoma, similar to our study[6, 7, 15]. However, the size and weight of the adenoma are highly variable, especially because of the extreme values in most of these studies[8]. Williams et al. had shown that very heavy adenomas change the result of the study[8]. The correlations between adenoma weight with PTH and calcium level were lost when two heavy adenomas were excluded from the study, which was thought to be very heavy in this study[8]. In another study, the correlation between adenoma weight with PTH and calcium levels was found less when adenomas with the highest values for weight were excluded[7]. This result suggested that very heavy adenomas secrete less PTH than their weight[8].

Other explanations for this result, there were cystic cavities in most of these large and heavy adenomas and were filled with hemorrhages, so as a result, the main PTH secreting cells were relatively less[8]. In our study, the range of the adenoma weight was quite wide (0.1-8.4 gr), so we thought that it could affect our study results. Similar to other studies, when we removed the five highest heavy adenomas over 5 grams, the correlation between adenoma weight and PTH level was found less while the correlation with calcium level was lost[6-8]. In addition, there are some studies in the literature that did not show any correlation between the size and weight of the adenomas with preoperative serum calcium and PTH levels[16].

Moretz et al. explained that this situation was caused by the error size measurement during the removal of fat tissue surrounding the adenoma, especially in smaller-sized adenomas[16]. As it was known, the parathyroid glands consist of the chief and oxyphil cells[18]. Stern et al. showed that the association between the serum calcium and PTH levels with adenoma weight could change depending on the proportions of the chief cell in parathyroid adenoma[5].

There were many confounding factors that could affect the relationship between adenoma size and adenoma weight with biochemical parameters, such as daily calcium intake, renal functions, and vitamin D levels. In our study, the patients with normal creatinine levels and without renal failure were included. In the literature, most studies about adenoma size and weight had not specified the effect of vitamin D deficiency on their study results[5-7]. In our study, a negative correlation was shown between the size and weight of the adenoma with 25 OH vitamin D levels. It was found a negative correlation between vitamin D levels with the adenoma size and weight of the adenoma in studies similar to our study that also evaluated the vitamin D levels[19, 20]. Concomitant vitamin D deficiency could affect calcium and PTH levels in patients with PHPT[21]. In our study, vitamin D deficiency was found in 60% of the patients. Because the vitamin D deficiency was frequently observed in our patients, we evaluated the patients according to vitamin D levels as separate subgroups. The size and weight of adenoma and preoperative serum PTH levels were found statistically higher in patients with vitamin D levels < 20 ng / mL compared to patients with vitamin D levels ≥ 20 ng / mL. At the same time, when the patients with vitamin D levels ≥ 20 ng / mL were evaluated separately, no correlation was observed between the size and weight of the adenoma with biochemical markers and the complications of PHPT. However, when we evaluated the whole study group in correlation analysis, a positive correlation was found between the size and weight of the adenoma with serum PTH and calcium levels. These results showed that the accompanying vitamin D deficiency could affect the studies that evaluated the relationship between the size and weight of adenomas with calcium and PTH levels.

Since surgical treatment methods in PHTP are curative treatment methods, it is very important to evaluate patients' for the complications of PHPT[13]. The presence of osteoporosis and nephrolithiasis are operation criteria in patients with PHPT[13]. Therefore, it is recommended that all patients must be evaluated for the presence of osteoporosis and nephrolithiasis[13]. In our study, osteoporosis was found in 47 % of the patients and nephrolithiasis in 28% of them. In the literature, there were no studies evaluating the correlation between PHPT complications with adenoma size and weight.

In our study, there were no correlations between the presence of these frequently observed complications and DXA parameters with the size and weight of the adenoma. In this respect, the presence of complications could not predict the size and weight of the adenoma.

Our study had certain limitations. Pathological data were evaluated by different pathologists during this period because of the retrospective design. It is known that vitamin D levels can change due to season, location, exposure to sunlight, and vitamin D usage[10]. 25 OH vitamin D levels in our study may

be affected by all these conditions.

In conclusion, the association between the postoperative size and weight of adenoma with preoperative serum calcium and PTH levels was found to be related to vitamin D levels. Therefore, it may not be correct to predict adenoma size and weight in the preoperative period with PTH levels and calcium levels without considering confounding factors such as vitamin D deficiency, which often accompanies PHPT patients.

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