ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Primary Hyperparathyroidism: A Single-Center Experience

Primer Hiperparatiroidi: Tek Merkez Sonuçları

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ABSTRACT Objective: Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia and elevated parathyroid hormone (PTH) levels. In this study, we aimed to report our clinical experience by presenting the demographic, laboratory, and clinical features of our PHPT patients. **Material and Methods:** A total of 217 patients who underwent parathyroidectomy from 2010 to 2018 at Ondokuz Mayıs University General Surgery Clinic were retrospectively reviewed, and PHPT patients who were diagnosed with parathyroid adenoma were further evaluated. **Results:** In total, 136 patients (85.3% females) with a mean age of 52.6±12.66 years were included. The prevalence of osteoporosis, nephrolithiasis, hypercalciuria, and vitamin D deficiency were 45.3%, 21.7%, 59.0%, and 63.8%, respectively. Postoperative hypocalcemia (21.3%) was only related with low preoperative calcium levels (p=0.002). Preoperative calcium was positively correlated with age (p=0.029), parathyroid adenoma weight (PAW) (p=0.009), and preoperative PTH (p<0.001) and negatively correlated with 25(OH)D3 (p=0.048). Preoperative PTH was positively correlated with PAW (p=0.002) and negatively correlated with 25(OH)D3 (p=0.009). There was no correlation between 25(OH)D3 and PAW (p=0.063). **Conclusion:** In our region, the prevalences of osteoporosis and nephrolithiasis were low, indicating moderate clinical presentation and early diagnosis of PHPT. Postoperative hypocalcemia was associated with lower preoperative calcium levels. Low 25(OH)D3 levels were associated with high calcium and PTH but not with PAW.

Keywords: Parathyroid neoplasm; hyperparathyroidism; parathyroidectomy

ÖZET Amaç: Primer hiperparatiroidizm (PHPT), hiperkalsemi ve yüksek paratiroid hormonu (PTH) seviyeleri ile karakterizedir. Bu çalışma ile PHPT hastalarımızın demografik, laboratuar ve klinik özelliklerini sunarak klinik deneyimimizi bildirmeyi amaçladık. **Gereç ve Yöntemler:** Ondokuz Mayıs Üniversitesi Genel Cerrahi Kliniği'nde 2010'dan 2018'e kadar paratiroidektomi yapılan toplam 217 hasta retrospektif olarak incelendi ve paratiroid adenomu tanısı alan PHPT hastaları ayrıntılı olarak değerlendirildi. **Bulgular:** Çalışmaya ortalama yaşı 52,6±12,66 yıl olan 136 hasta (%85,3 kadın) alındı. Osteoporoz, nefrolitiazis, hiperkalsiüri ve D vitamini eksikliği prevalansı sırasıyla %45,3, %21,7, %59,0 ve %63,8 idi. Postoperatif hipokalsemi (%21,3) sadece preoperatif düşük kalsiyum düzeyleri ile ilişkiliydi (p=0,002). Preoperatif kalsiyumun yaş (p=0,029), paratiroid adenom ağırlığı (parathyroid adenoma weight-PAW) (p=0,009) ve preoperatif PTH (p <0,001) ile pozitif, 25 (OH) D3 (p=0,048) ile negatif korelasyon gösterdiği bulundu. Preoperatif PTH, PAW (p=0,002) ile pozitif, 25 (OH) D3 (p=0,009) ile negatif korelasyon gösterdi. 25 (OH) D3 ve PAW arasında korelasyon yoktu (p=0,063). **Sonuç:** Bölgemizde orta derecede klinik prezentasyon ve erken dönemde PHPT tanısı konulmasını işaret edecek şekilde osteoporoz ve nefrolitiazis prevalansı düşüktü. Postoperatif hipokalsemi gelişimi düşük preoperatif kalsiyum düzeyi ile ilişkili olarak bulundu. Düşük 25 (OH) D3 seviyeleri yüksek kalsiyum ve PTH ile ilişkiliydi, fakat PAW ile ilişkili değildi.

Anahtar Kelimeler: Paratiroid tümörleri; hiperparatiroidizm; paratiroidektomi

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and elevated parathyroid hormone (PTH) levels. It is the most common cause of outpatient hypercalcemia.[1] The estimated prevalence of PHPT is approximately 0.25% to 0.66% of the population and the incidence of PHPT increases after 50 years of age.[2]

The most common cause of hyperparathyroidism is usually a parathyroid adenoma, but parathyroid hyperplasia can also lead to the condition.[3] Indications for surgery are based on international guidelines.[4,5] Intraoperative PTH level measurement is recommended in patients undergoing surgery.[6]

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Postoperative hypocalcemia is a well-known complication of parathyroidectomy (PTX), and it is observed in 10-30% of cases.[7] It is usually transient and improves within days to weeks. The rate of permanent hypoparathyroidism is very low (0.3-2%).[7] Several mechanisms have been proposed for the development of postoperative transient hypocalcemia. Some of these are the increase of urinary excretion of calcium (Ca) as a result of decreased PTH secretion from the remaining atrophic parathyroid glands and potential injury or devascularization of the remaining parathyroid glands during surgery.[7] Hungry bone syndrome (HBS) is also among the mechanisms that cause hypocalcemia and is characterized by severe and long-term hypocalcemia due to an increase in bone formation despite normal or high PTH levels.[8] The underlying cause is assumed to be the increased skeletal Ca requirement associated with the increased bone formation as a result of the sudden normalization of high PTH levels in the circulation after PTX.[8] HBS should be treated with Ca and vitamin D supplementation.[8]

Vitamin D plays a role in serum Ca and PTH homeostasis.[9] Vitamin D deficiency is frequently seen in the community in general screening tests as well as in patients with PHPT. Studies have reported that it can aggravate the existing hyperparathyroidism.[10,11]

Most studies about PHPT include chronic kidney disease patients and/or the patients with parathyroid hyperplasia. In this study, we aimed to report our clinical experience by presenting the demographic, laboratory, and clinical features of our PHPT patients who had normal renal functions and were diagnosed with parathyroid adenomas after PTX during the recent 8 years. In addition, the associated factors with postoperative hypocalcemia and the effects of vitamin D deficiency on PHPT were also evaluated with the aim of furthering our understanding of PHPT in Turkey.

MATERIAL AND METHODS

STUDY POPULATION

All patients (n=217) who underwent surgery for hyperparathyroidism at the Division of General Surgery of Ondokuz Mayıs University in Samsun, Turkey from 2010 to 2018 were retrospectively reviewed in this study. All patients were operated on by the same surgical team (C.P).

Patients who had a histologically proven diagnosis of parathyroid adenoma were further evaluated. These patients with diagnoses of multiple endocrine neoplasia type 1 and type 2 or any other active malignancy (including thyroid or parathyroid malignancies diagnosed during the PTX), moderate to advanced chronic renal failure, and thyroid or hepatic dysfunction were excluded. In total, 136 patients (116 female, 20 male) who were older than 17 years and had complete medical records were included. Medical records and radiologic examinations of these patients were retrospectively reviewed for age, sex, parathyroid adenoma weight (PAW), histories of hypertension, osteoporosis and nephrolithiasis, and biochemical values for total serum calcium (Ca), creatinine (Cr), phosphate (P), 24-hour urinary Ca excretion (24-h Ca), intact PTH, alkaline phosphatase (ALP), intraoperative PTH, and 25-hydroxyvitamin D_3 ($25(OH)D_3$) before PTX and Ca, P, and PTH 24 hours after PTX.

The cohort was first divided into two groups according to their postoperative Ca levels (hypocalcemia group: Ca < 8.5 mg/dl; normocalcemia group: Ca=8.5-10.2 mg/dl), and the preoperative values were evaluated between the groups.

The cohort was divided again into two groups according to their $25(OH)D_3$ levels before PTX (Group 1: $25(OH)D_3 \geq 20$; Group 2: $25(OH)D_3 < 20$), and the preoperative values were evaluated between the groups.

This study was approved by the Institutional Ethics Committee of the Ondokuz Mayıs University (OMU-KAEK 2018/303) and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. We collected demographic data, medical histories, histological examinations, laboratory studies, and imaging from the database records of our hospital.

BIOCHEMICAL EVALUATION

All results before and 24 hours post-surgery were reviewed. Serum Ca, P, Cr, and ALP were measured with colorimetric and spectrophotometric methods by

using the Roche Cobas 8000 modular analyzer (Roche Diagnostics, Mannheim, Germany). The reference ranges (RR) were 8.8-10.2 mg/dl for Ca, 2.3-4.7 mg/dl for P, 0.4-1.4 mg/dl for Cr, and 35-104 U/L for ALP. Serum intact PTH was measured with the electrochemiluminescence immunoassay method by the Roche Modular E170 Cobas analyzer (Roche Diagnostics, Mannheim, Germany). The RR was 15-65 pg/ml. The intraoperative PTH assay was routinely applied to all patients. This assay was immediately performed before the skin incision and 10 min after the gland excision. The criteria for concluding an operation was achieving a 50% decline of the preoperative levels or a final level within the normal range (15-65 pg/mL). Serum 25(OH)D_3 was measured with high-performance liquid chromatography (HPLC) by Agilent 1100 Series (Chromsystem Diagnostics, Munich, Germany). Intra-assay and inter-assay coefficients of variation were 4.8% and 6.3%, respectively (RR: 30-80 ng/mL). Ca excretion was measured after the 24-hour urine collection for Ca (RR: 50-300 mg/24 h).

DEFINITIONS

Concentrations of total Ca in normal serum generally range between 8.5 and 10.2 mg/dl. Postoperative hypocalcemia was defined as having a Ca level below 8.5 g/dl. Hypercalciuria was defined as urinary Ca levels above 300 mg/day.

The following definitions and criteria were used to evaluate the parathyroid functions of the patients in the postoperative period:

- Normal parathyroid function: 8.5-10.2 mg/dl of Ca and 15-65 ng/l of PTH

- Hypoparathyroidism: Ca<8.5 mg/dl and PTH < 15 ng/l (formal definition) or PTH < 10 ng/l

- Hyperparathyroidism (persisting disease): Ca > 10.2 mg/dl and PTH > 65 ng/l

- HBS: Ca < 8.5, PTH≥15 ng/l, and P<3 mg/dl

There are not any well-defined criteria for the diagnosis of HBS, so it is difficult to determine its true incidence. When we analyzed previous studies, we concluded that "HBS was considered as present if the serum Ca concentration was below 8.5 mg/dL, the serum P concentration was below 3.0 mg/dL and PTH level was above 15 pg/ml, between 1st and 7th postoperative days".[7,12-14] Although it was better to evaluate HBS between the 3rd and 7th postoperative days, the evaluation of HBS after the first day would not be correct for our study because patients who were hypocalcemic or symptomatic had already received vitamin D and/or oral/intravenous (IV) calcium treatments. Therefore, we evaluated postoperative hypocalcemia, hypoparathyroidism, hyperparathyroidism, normoparathyroidism, and HBS rates 24 hours after PTX.

Vitamin D deficiency was defined as 25 (OH) D_3 levels < 20 ng/mL and insufficiency was defined as 25 (OH)D_3 levels between 20-29 ng/mL. The third and fourth International Workshops on Asymptomatic PHPT recommended measuring 25(OH)D_3 in all patients and replenishing vitamin D in those with levels <20 ng/mL before medical or surgical treatment.[9,15,16] Therefore, we evaluated the impact of preoperative serum 25(OH) D_3 level above and below 20 ng/mL in our study population.

STATISTICAL ANALYSIS

The variables were tested for a normal distribution. If this was confirmed, the results were expressed as the mean ± standard deviation. Otherwise, they were expressed as the median and interquartile range. The Mann-Whitney U test was performed to compare the data with a non-parametric distribution, and Student's t-test was performed to compare the data with a parametric distribution. The categorical variables were expressed as percentages. For the comparison of the categorical variables among the groups, a chi-squared test was used. Spearman's correlation coefficient was used to assess the relationships between the continuous variables. IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. A p-value ≤ 0.05 was considered to be significant.

RESULTS

Chronic renal failure was present in 22.6% (n=49) out of 217 patients. When the pathology reports were examined, parathyroid adenoma was found in 161 (74.2%) patients, parathyroid hyperplasia was found in 50 (23%) patients, and normal parathyroid gland

was found in 6 (2.8%) patients. Parathyroid pathologies were associated with malignant thyroid nodules in 19 patients (8.8%), and 3 (1.4%) patients were diagnosed with multiple endocrine neoplasia-1 (MEN-1) syndrome.

In total, 136 patients (85.3% females) fulfilled the inclusion criteria and constituted our study group. The female-to-male (F/M) ratio was 5.8. The mean age of the patients was 52.6±12.66 years (ages 20-79). The patients were grouped according to decade as shown in Figure 1. The most common age range was the 6th decade (29.4%), and the majority of the patients (74.3%) were between the ages of 40-70. The prevalence of hypertension, osteoporosis, nephrolithiasis, and hypercalciuria were 39.7%, 45.3%, 21.7%, and 59.0%, respectively. Table 1 reports the clinical and laboratory data of the study group.

Table 2 reports the study group's rates of postoperative hypocalcemia (21.3%), hypoparathyroidism (16.2%), HBS (14.7%), normalized PTH and Ca levels (67.6%), and persistently high PTH and Ca levels (0%) on the first postoperative day. The cohort was divided into two groups according to their first postoperative day Ca levels (hypocalcemic group: Ca<8.5 g/dl; normocalcemic group: Ca≥8.5 g/dl). Preoperative biochemical values and clinical data of the two postoperative Ca groups were compared (Table 3). As shown in Table 4, there were no between-group differences in terms of age, sex, osteoporosis, nephrolithiasis, hypercalciuria, PAW, intraoperative PTH levels, preoperative levels of P, PTH, ALP, 25(OH)D_3, and 24-h Ca (p>0.05 for all). However, preoperative Ca levels were significantly higher in the normocalcemic group than in the hypocalcemic group postoperatively (p=0.002).

The study group was separated into two groups according to their serum 25(OH)D_3 levels as Group 1 (25(OH)D_3 < 20) and Group 2 (25 (OH)D_3≥ 20), and the parameters were compared as shown in Table 5. The rate of vitamin D deficiency was 63.8%. There were no between-group differences in the evaluated parameters (p > 0.05 for all) except for preoperative serum PTH. In the 25(OH)D_3-deficient group (Group 1), preoperative PTH levels were significantly high (p=0.013).

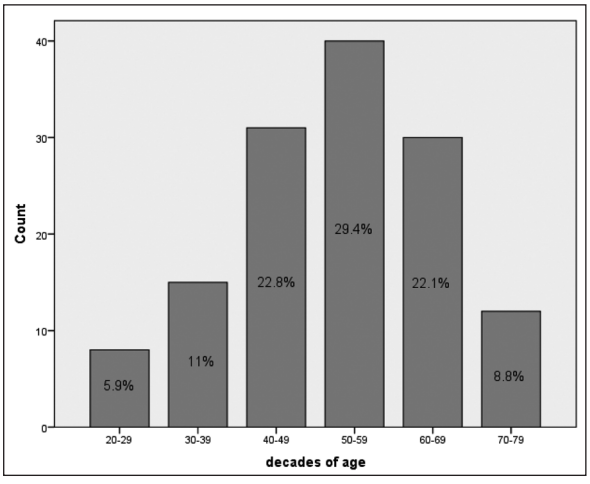

FIGURE 1: Age ranges of the patients.

TABLE 1: Clinical and laboratory data of the study group.

Parameters	Results
Age (y), Mean±SD	52.6±12.7
Female/Male (%)	85.3/14.7
Hypertension (%)	39.7
Osteoporosis (%)	45.3
Nephrolithiasis (%)	21.7
Hypercalciuria (%)	59.0
PAW (gr), Median (IQR)	0.7 (1.1)
Creatinine (mg/dL), Median (IQR)	0.68 (0.2)
Calcium (mg/dL), Median (IQR)	11.3 (1.0)
Phosphate (mg/dL), Mean±SD	2.55±0.47
PTH (pg/mL), Median (IQR)	163.4 (121.1)
ALP (U/L), Median (IQR)	98.0 (54.0)
25(OH)D_3 (µg/L), Median (IQR)	16.6 (15.4)
24-hour urinary Ca^{+2} (mg/24 h), Median (IQR)	144.6 (371.5)

PAW: Parathyroid adenoma weight; PTH: Parathyroid hormone; ALP: Alkaline phosphatase. Mean values are given as mean ± standard deviation (Mean ± SD) for normally distributed data and median (interquartile range) (IQR) non-normally distributed data.

TABLE 2: Results of postoperative day 1.

Postoperative day 1	Rate (%)
Hypocalcemia	21.3
HBS	14.7
Hypoparathyroidism	16.2
High PTH and Ca	0
Normal PTH and Ca	67.6

HBS: Hungry bone syndrome; PTH: parathyroid hormone; Ca: calcium.

TABLE 3: Comparison of the post-operative biochemical parameters between Ca groups on postoperative day 1.

Parameters	Study Group	Hypocalcemic Group	Normocalcemic Group	p
Ca (mg/dL), Median (IQR)	8.8 (0.7)	8.1 (0.7)	9.0 (0.7)	**<0.001****
Phosphate (mg/dL), Mean ± SD	2.5±0.59	2.64±0.62	2.48±0.58	0.235*
PTH (pg/mL), Median (IQR)	19.2 (17.2)	22.7 (19.8)	17.7 (16.5)	0.111**

PTH: Parathyroid hormone; Ca: Calcium. Mean values are given as mean ± standard deviation (Mean ± SD) for normally distributed data and median (interquartile range) (IQR) non-normally distributed data. In normally distributed data, Student's t-test* and in non-normally distributed data Mann-Whitney-U test** were used.

TABLE 4: Comparison of the preoperative biochemical and clinical parameters between Ca groups on postoperative day 1.

Parameters	Hypocalcemic Group (n:29)	Normocalcemic Group (n: 107)	p
Age (y)	49±13.8	53.6±12.2	0.084*
Female (%)	93.1	83.2	0.244***
Osteoporosis (%)	34.6	48.8	0.208***
Nephrolithiasis (%)	11.1	24.7	0.13***
Hypercalciuria (%)	61.1	58.5	0.84***
PAW (gr)	0.55 (0.55)	0.9 (1.1)	0.058**
Calcium (mg/dL)	11.0 (0.85)	11.4 (1.0)	0.002**
Phosphate (mg/dL)	2.3±0.4	2.54±0.49	0.567*
PTH (pg/mL)	162.3 (113.9)	164.4 (121.1)	0.513**
Intraoperative PTH (pg/mL)	27.1 (32.4)	33.9 (32.4)	0.176**
ALP (U/L)	97.0 (73.0)	99.0 (51.0)	0.982**
25(OH)D3 (µg/L)	13.2 (20.6)	16.9 (14.1)	0.458**
24 hours urinary Ca^{+2} (mg/24 h)	199.0 (375.5)	140.0 (372)	0.893**

PAW: Parathyroid adenoma weight; PTH: Parathyroid hormone; ALP: Alkaline phosphatase. In normally distributed data, Student's t-test*, in non-normally distributed data Mann-Whitney-U test** and for frequency comparisons Chi-square test*** were used.

In Table 6, the correlations between the preoperative parameters (age, PAW, Ca, PTH, and $25(OH)D_3$ levels) of the entire study group were evaluated. PTH and Ca levels showed a positive correlation ($p<0.001$), and Ca levels were positively correlated with age ($p=0.029$). PAW was positively correlated with Ca ($p=0.009$) and PTH ($p=0.002$) levels, but there was no correlation between $25(OH)D_3$ levels and PAW ($p=0.063$). Levels of $25(OH)D_3$ were negatively correlated with PTH ($p=0.009$) and Ca ($p=0.048$) levels.

DISCUSSION

PHPT is a common endocrine disorder, and it is the most common cause of outpatient hypercalcemia.[1] The incidence of PHPT increases after the age of 50, and it is observed, with a F/M ratio of 3-4:1.[2,17] Of the 136 patients included in our study, the F/M ratio was 5.8, which was higher than the ratio reported in the literature.

In our study, the mean age of the patients was 52.6 ± 12.66 years, which is consistent with the literature. The incidence of PHPT has been reported to increase in the 6th and 7th decades.[2] The patients between the ages of 50 and 70 constituted 51.5% of our study group, and approximately ¾ of the patients were between 40 and 70 years of age.

Clinical presentation of PHPT is variable. In developed countries, most PHPT patients are diagnosed early in an asymptomatic stage due to routine serum Ca measurements, but in developing countries, PHPT still manifests predominantly as a bone or renal stone disease as a consequence of late diagnosis.[18] Symptomatic nephrolithiasis is present in about 10-20% of the patients, and hypercalciuria is present in 35-40% of the patients.[19] In some regions of the world where PHPT is mostly symptomatic, reported rates of nephrolithiasis were as high as 55%.[20,21] The prevalence of osteoporosis in PHPT has varied in different studies between 39-

TABLE 5: Comparison of the preoperative biochemical and clinical parameters between Ca groups on postoperative day 1.

Parameters	Group 1 25(OH)D3 ≥20	Group 2 25(OH)D3 <20	p
Age (y)	54.26±11.74	51.64±12.86	0.291*
Female (%)	94.6	82.1	0.074***
Osteoporosis (%)	45.5	43.6	0.868***
Nephrolithiasis (%)	14.3	23.7	0.27***
Hypercalciuria (%)	70.8	59.6	0.352***
PAW (gr)	0.6 (1.13)	0.86 (1.23)	0.281**
Calcium (mg/dL)	11.2 (1.15)	11.3 (0.9)	0.186**
Phosphate (mg/dL)	2.55±0.52	2.5±0.44	0.619*
PTH (pg/mL)	137.6 (108.03)	175 (114.5)	**0.013****
ALP (U/L)	98 (41.5)	99 (55.25)	0.462**
25(OH)D_3 (µg/L)	26.25 (13.56)	11 (9.13)	**<0.001****
24 hours urinary Ca^{+2} (mg/24 h)	256.0 (421.6)	272.0 (396)	0.836**

PAW: Parathyroid adenoma weight; PTH: Parathyroid hormone; ALP: Alkaline phosphatase. In normally distributed data, Student's t-test*, in non-normally distributed data Mann-Whitney-U test** and for frequency comparisons Chi-square test*** were used.

TABLE 6: Correlation of preoperative Ca, PTH and 25(OH)D_3 with other parameters.

Spearman's rho		Calcium	PTH	25(OH)D_3
Age (y)	CC	0.214	-0.035	0.125
	p value	**0.029**	0.721	0.205
PAW (gr)	CC	0.255	0.3	-0.183
	p value	**0.009**	**0.002**	0.063
Calcium (mg/dL)	CC	*	0.451	-0.194
	p value	*	**<0.001**	**0.048**
PTH (pg/mL)	CC	0.451	*	-0.253
	p value	**<0.001**	*	**0.009**

PAW: Parathyroid adenoma weight; PTH: Parathyroid hormone; CC: Correlation coefficient.

62.9%.[11,21,22] The prevalence of osteoporosis, nephrolithiasis, and hypercalciuria in our study was 45.3%, 21.7%, and 59.0%, respectively. Although hypercalciuria was frequent in our study population, nephrolithiasis was relatively low.

PTX is the standard treatment for PHPT patients. The goal of the treatment is to achieve a normocalcemic state. None of our patients had surgical complications or persistent hypercalcemia on the first postoperative day. Normal levels of Ca and PTH were achieved in 67.6% of the patients. The rates of postoperative hypocalcemia, hypoparathyroidism, and HBS were 21.3%, 16.2%, and 14.7%, respectively. Mittendorf et al. found a 42% rate of postoperative hypocalcemia in patients with PHPT, which was almost twice the rate we found.[23]

Different studies have analyzed the effects of preoperative Ca, PTH, P, vitamin D, intraoperative PTH levels, PAW, and postoperative Ca levels on parathyroid function and the development of postope rative hypocalcemia in patients with PHPT.[7,23-31] There were different results and interpretations. The predictive value of some of these parameters remains elusive. The patients with larger PAW are more prone to develop postoperative hypocalcemia in some studies, but some studies have been unable to show this relationship similar to our findings.[7,12,32] The difference in the results of these studies may be due to the different study designs. While Brasier et al. included both parathyroid hyperplasia and adenoma patients, Strickland et al. included only parathyroid adenoma patients as we did in our study.[7,12] Their evaluation time of

postoperative hypocalcemia was also different. While Brasier et al. evaluated Ca levels on the third or fourth postoperative days, Strickland et al. evaluated Ca levels on the first postoperative day as we did in our study.[7,12] No clinical and laboratory parameters except preoperative Ca levels were found to be predictive of the development of postoperative hypocalcemia in our study. The postoperative hypocalcemia was only related with lower preoperative Ca levels.

Vitamin D deficiency is found in 30-100% of participants depending on the study population and $25(OH)D_3$ cut-off value.[19] Vitamin D deficiency in our country has been reported to be as high as 44-60% and more common in patients with PHPT than in the general population.[19,33] We also found a high prevalence of vitamin D deficiency (63.8%) in our study population, which is similar to that in other countries.[18,34]

In our study, PTH and Ca levels had a positive correlation and both were negatively correlated with $25(OH)D_3$ levels. The mechanisms of low $25(OH)D_3$ levels in patients with PHPT are not clear. It has been reported in various publications that increased PTH levels triggered the conversion of $25(OH)D_3$ to the active form by the renal 1-alpha-hydroxylase enzyme, increasing the level of $1\text{-}25(OH)D_2$ and decreasing the level of $25(OH)D_3$. In addition, it has been suggested that the half-life of $25(OH)D_3$ is shortened due to suppressed production of vitamin D precursors in the skin and liver and increased hepatic clearance.[35,36]

The clinical and laboratory features of PHPT cases are reported to be more severe in areas where vitamin D deficiency is endemic.[10,37,38] It is suggested that a low vitamin D level and hypocalcemia are the most important stimulants for parathyroid hyperplasia. Also, chronic $25\ (OH)D_3$ deficiency is suggested to cause parathyroid gland hyperplasia and subsequent adenomatous gland change.[33,36,39,40] There are also other mechanisms that are considered to stimulate parathyroid cell proliferation in vitamin D deficiency.[33,35,37,39] In some studies, high preoperative Ca and PTH levels are suggestive of larger PAW, which was consistent with our findings.[41-44] Several studies have investigated the effects of vitamin D deficiency on clinical findings and on PAW in PHPT.[10] Among these studies, while some reported a negative correlation between vitamin D level and PAW, the remaining studies reported no significant relationship.[10,15,33,40,45-49] We found lower vitamin D levels in PHPT patients associated with higher serum Ca and PTH levels in accordance with previous studies.[10,34,40,45,49] However, we found no significant relationship between PAW and $25(OH)D_3$ levels. The relationship of $25(OH)D_3$ with laboratory tests such as Ca and PTH was not detected with PAW in our study.

Our study had some limitations mainly because of its retrospective design. We evaluated the available data of our study cohort. However, this is one of the largest cohorts of PHPT from Turkey, and the sample size is more than the majority of the studies conducted in other countries. There is limited reported data about PHPT patients from our country.[44,45] We believe that the data from this study will contribute to the database of PHPT patients in our country.

CONCLUSION

In conclusion, we found PHPT is common in the 6^{th} and 7^{th} decades, and the prevalence rate was 5.8 times more in females and that is higher than that reported in the literature. The prevalence of osteoporosis and nephrolithiasis in our region is low when compared to the rates reported in the world, which is consistent with the moderate clinical presentation. This situation may indicate that we tend to diagnose PHPT patients in the early period. Normal levels of Ca and PTH were succeeded in 2/3 of the patients on the first post-PTX day, and the rates of postoperative hypocalcemia, hypoparathyroidism, and HBS were very low in our study. None of the parameters of PTH, P, $25(OH)D_3$, intraoperative PTH levels, PAW, and postoperative Ca levels were found to be predictive of the development of postoperative hypocalcemia in our study. The only parameter associated with postoperative hypocalcemia was low preoperative Ca levels. There was a high prevalence of vitamin D deficiency in our cohort. We found low $25(OH)D_3$ levels in PHPT patients associated with high serum Ca and PTH levels, but there was no significant relationship between low $25\ (OH)D_3$ levels and high PAW. The relationship of $25\ (OH)\ D_3$ with Ca and PTH was not detected with

PAW in our study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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