



# Review of Clinical and Laboratory Findings of Patients with Primary Hyperparathyroidism by the Literature

Primer Hiperparatiroidi'li Hastaların Klinik ve Laboratuvar Bulgularının Literatür Eşliğinde Gözden Geçirilmesi

Suat Sen<sup>1</sup>, Fettah Acibucu<sup>2</sup>, Asım Tekin<sup>3</sup>, Nese Bulbul<sup>2</sup>, Ekin Yigit Koroglu<sup>4</sup>

<sup>1</sup>Adana Health Practice and Research Center, Department of Internal Medicine, University of Health Sciences; <sup>2</sup>Department of Endocrinology, Adana Health Application and Research Center, Department of Internal Medicine, University of Health Sciences, Adana; <sup>3</sup>Provincial Health Directorate, Suruc State Hospital, Internal Diseases Clinic, Sanliurfa; <sup>4</sup>Department of Internal Medicine, Department of Endocrinology and Metabolism, Ankara City Hospital, Ankara, Turkiye

## ABSTRACT

**Introduction:** Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and a high or normal parathyroid hormone (PTH) level inconsistent with calcium. Complications caused by hypercalcemia or excess PTH in patients affect many systems. Therefore, early diagnosis of PHPT can help prevent complications and determine the treatment.

**Method:** In our study, a total of 154 patients, 122 women and 32 men, who were diagnosed with PHPT in the Endocrinology outpatient clinic were retrospectively reviewed and evaluated in the light of the literature.

**Results:** The mean age of the patients was 53.83±13.80 years. Detected mean values for calcium were 11.83±1.28 mg/dl, for phosphorus 2.47±0.57 mg/dl, for PTH 357.32±424.08 pg/ml, for vitamin 25OH D<sub>3</sub> 16.58±9.57 ng/ml, for estimated glomerular filtration rate (eGFR) was 99.03±23.84 ml/min/1.7 and for urinary calcium amount was 381.80±204.11 mg/24h. Bone mineral density (BMD) measurements were made in 64.3% (n: 99) of the patients, 38.4 % (n: 38) had osteopenia, and 42.4 % (n: 42) had osteoporosis. A history of urinary stones was found in 35.7% (n: 55) of the patients, and stone findings were found on ultrasonography in 36.1 % (n: 35). In total, 37% (n: 57) of the cases developed nephrolithiasis as a complication. In the localization study, adenoma was detected in 76.8% (n: 116) of the patients by ultrasonography, while 70.7% (n: 106) were found positive by Tc99 sestamibi scan. The lower right part was the most commonly detected adenoma localization in both imaging. In the pathology results of the operated patients, 91.5% (n: 118) were reported as adenomas. In the follow-up of the operated patients, recurrence was detected in 4.6% (n: 6).

**Conclusion:** Early diagnosis and treatment of PHPT are important to prevent serious complications. The absence of serious complications in the cases in our study shows the importance of early diagnosis.

**Keywords:** primary hyperparathyroidism; hypercalcemia; nephrolithiasis; osteoporosis

## ÖZET

**Giriş:** Primer hiperparatiroidi (PHPT), hiperkalsemi ve paratiroid hormon (PTH) seviyesinin yüksek veya kalsiyum seviyesi ile uyumsuz olarak normal olması ile karakterize yaygın bir endokrin bozukluktur. Hastalarda hiperkalsemi ya da PTH fazlalığı ile oluşan komplikasyonlar birçok sistemi etkiler. PHPT'nin erken teşhis, oluşabilecek komplikasyonları önleyebilmek ve tedavi belirlemek açısından faydalı olabilir.

**Metot:** Çalışmamızda Endokrinoloji polikliniğinde PHPT tanısı alan 122 kadın 32 erkek toplamda 154 hasta retrospektif taranarak literatür eşliğinde değerlendirildi.

**Bulgular:** Hastaların yaş ortalaması 53,83±13,80 yıl saptandı. Ortalama kalsiyum 11,83±1,28 mg/dl, fosfor 2,47±0,57 mg/dl, PTH 357,32±424,08 pg/ml, 25OH D<sub>3</sub> vitamini 16,58±9,57 ng/ml, eGFR 99,03±23,84 ml/dk/1,7, hiperkalsiüri 381,80±204,11 mg/24s saptandı. Hastaların %64,3'ünde (n: 99) kemik mineral yoğunluğu (KMD) ölçümü yapılmış ve %38,4'ünde (n: 38) osteopeni, %42,4'ünde (n: 42) osteoporoz mevcuttu. Hastaların %35,7'sinde (n: 55) taş düşürme öyküsü ve %36,1'inde (n: 35) ultrasonografide taş bulgusu saptandı. Totalde vakaların %37'sinde (n: 57) nefrolitiazis komplikasyon olarak gelişmiştir. Lokalizasyon çalışmasında hastaların %76,8'inde (n: 116) ultrasonografide adenom bulgusu tespit edilirken Tc99M sestamibide %70,7'sinde (n: 106) pozitif bulundu. Her iki görüntülemeye de adenom en sık sağ altta lokalizedi. Opere olan hastaların patolojisinde %91,5'i (n: 118) adenom olarak raporlandı. Opere olan hastaların takiplerinde %4,6'sında (n: 6) nüks tespit edildi.

**Sonuç:** PHPT'nin erken teşhis ve tedavi ciddi komplikasyonları önlemek açısından önemlidir. Çalışmamızdaki vakalarda da ciddi komplikasyonların olmaması erken tanının önemini göstermektedir.

**Anahtar Kelimeler:** primer hiperparatiroidi; hiperkalsemi; nefrolitiazis; osteoporoz

**İletişim/Contact:** Suat Şen, Adana Şehir Eğitim ve Araştırma Hastanesi, Yüreğir, Adana, Türkiye • **Tel:** 0505 504 29 09 • **E-mail:** drsuatsen@gmail.com  
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**ORCID:** Suat Şen, 0000-0003-1303-662X • Fettah Acibucu, 0000-0002-2252-2112 • Asım Tekin, 0000-0001-5131-4884 • Nese Bulbul, 0000-0002-6990-4337 • Ekin Yiğit Köroğlu: 0000-0003-3895-5817

## Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and parathormone (PTH) levels being high or normal inconsistently with the calcium level<sup>1</sup>. The current prevalence of PHPT is approximately 0.25–0.66% of the population. The incidence increases with age and rises dramatically after 50 years of age. It is reported three times more in women<sup>2</sup>. The etiology of PHPT is solitary parathyroid adenoma in 80%, parathyroid hyperplasia in 10–15%, multiple adenomas in 5%, and parathyroid cancer in <1% of cases<sup>1</sup>. Most patients are sporadic, and approximately 5% are familial. Familial syndromes with PHPT components are; multiple endocrine neoplasias (MEN) I, MEN IIA, hyperparathyroidism-jaw tumor syndrome, and severe neonatal PHPT. Primary hyperparathyroidism clinical presentation can be in 3 different ways; symptomatic PHPT, asymptomatic PHPT, and normocalcemic PHPT<sup>2</sup>. Complications affecting many systems may develop due to hypercalcemia or excess PTH in patients. Clinically, it may present as asymptomatic or complicated by affecting especially kidney, bones, gastrointestinal, cardiovascular, or nervous systems. After the diagnosis of hyperparathyroidism is made biochemically, localization studies are performed. Ultrasonography and Tc99M sestamibi method are frequently used for localization. The genetic examination should only be requested occasionally but can be performed when genetic syndromes are considered<sup>3</sup>.

Surgical treatment is recommended for all patients with laboratory-proven hyperparathyroidism and specific symptoms or signs of the disease. In asymptomatic patients, those who do not indicate surgery are followed up with medical treatment<sup>3</sup>.

Patients diagnosed with primary hyperparathyroidism should be followed up after surgery and during medical treatment. In this study, we planned to evaluate the clinical presentations, biochemical findings, treatment, and post-treatment follow-ups of patients diagnosed with PHPT in our outpatient clinic.

## Material and Methods

Patients who applied to Health Sciences University Adana City Training and Research Hospital Endocrinology and Metabolic Diseases Polyclinic between 2017–2020 and were diagnosed with PHPT were retrospectively screened. Demographic

characteristics and clinical and laboratory findings of the cases diagnosed with PHPT included in the study were recorded. The study did not include those diagnosed with familial hypocalciuric hypercalcemia and those who used drugs that affect calcium metabolism. All were analyzed using the IBM Statistical Package for Social Sciences (SPSS) program version 24.0 (Chicago, IL, USA) statistical software package. Whether the distribution of continuous variables was normal or not was evaluated with the Kolmogorov-Smirnov test. Continuous variables in group data were expressed as mean  $\pm$  standard deviation. Categorical variables were expressed as numbers and percentages. A ROC curve analysis was performed to reevaluate markers that were independent in detecting patients and to determine the breakpoint of these markers. The value of the area under the curve (AUC) was used to measure the test's accuracy. Univariate correlation analysis was performed using the Pearson-Spearman correlation method. Linear regression analysis was performed with statistically significant parameters in a multivariate model. The results were evaluated within the 95% confidence interval, and the statistical significance level was accepted as  $p < 0.05$ .

## Results

In our study, 122 of 154 patients diagnosed with PHPT were female (79.2%), and 32 were male (20.8%). The mean age was  $53.83 \pm 13.80$  years. The demographic characteristics and biochemical results of the patients are summarized in Table 1.

Neck ultrasonography was performed in 151 patients, and Tc99M sestamibi imaging was performed in 150

**Table 1.** Demographic characteristics and biochemical findings of the patients (n: 154)

	Mean $\pm$ SD
Age (years)	53.83 $\pm$ 13.80
PTH (pg/ml)	357.32 $\pm$ 424.08
Vitamin 25OH D <sub>3</sub> (ng/ml)	16.58 $\pm$ 9.57
Calcium (mg/dl)	11.83 $\pm$ 1.28
Phosphorus (mg/dl)	2.47 $\pm$ 0.57
Alkaline Phosphatase (U/L)	137.22 $\pm$ 161.23
Albumin (g/L)	4.16 $\pm$ 0.36
Creatinine (mg/dl)	0.71 $\pm$ 0.26
eGFR (ml/dk/1.7)	99.03 $\pm$ 23.84
Urinary Calcium (mg/24s)	381.80 $\pm$ 204.11

**Table 2.** Neck ultrasonography and Tc99M sestamibi imaging findings of the patients

	Neck ultrasonography		Tc99M –sestamibi	
	n	%	n	%
Negative	35	23.2	44	29.3
Lower Right	55	36.4	56	37.4
Upper Right	2	1.3	3	2
Lower Left	53	35.1	42	28
Upper Left	3	2	3	2
Lower Right + Lower Left	3	2	2	1.3
Total	151	100.0	150	100.0

patients for localization. Neck ultrasonography was negative in 23.2% (n: 35) of the patients and positive in 76.8% (n: 116). Tc99M sestamibi imaging was negative in 29.3% (n: 44) and positive in 70.7% (n: 106). Localization sites are indicated in Table 2.

Bone mineral density (BMD) was measured in 64.3% (n: 99) of the patients; 19.2% (n: 19) were detected normal, 38.4% (n: 38) were detected as with osteopenia and 42.4% (n: 42) were detected with osteoporosis. In addition, a history of stone removal was found in 35.7% (n: 55) of the patients, and stone findings were found in 36.1% (n: 35) of 97 patients who underwent renal ultrasonography.

While 83.8% (n: 129) of the patients were operated on, 16.2% (n: 25) were followed up with medical treatment. In the follow-up of the operated patients, recurrence was detected in 4.6% (n: 6). The most common pathology results were adenoma with 91.5% (n: 118), and hyperplasia was the second most common with 5.4% (n: 7). Pathology results are summarized in Table 3.

## Discussion

In the last 10–15 years, the prevalence of PHPT has increased, and new entities have been defined as a result of increased awareness and the development and widespread use of laboratory methods. Therefore, recognition and treatment of PHPT are significant for preventing complications. The most common complications are decreased BMD and subsequent development of osteoporosis and nephrolithiasis<sup>4</sup>.

In primary hyperparathyroidism, increased demineralization in bone results in decreased bone mass and the development of osteoporosis in the chronic period<sup>5</sup>. For example, Cipriani et al.<sup>6</sup> found that 62.9% of 140 PHPT

**Table 3.** Pathology results of patients who were operated on for PHPT

Pathology	n	%
Adenoma	118	91.5
Hyperplasia	7	5.4
Right adenoma + Left hyperplasia	1	0.8
Adenoma + adenoma	3	2.3
Total	129	100.0

patients, and Lowe et al.<sup>7</sup> found that 57% of the PHPT patients had osteoporosis in their study. On the contrary, our research found that 38.4% (n: 38) of the patients had osteopenia, and 42.4% (n: 42) had osteoporosis. Our study's low rate of osteoporosis may be because our patients were easily diagnosed with PHPT due to easy access to the physician, advanced laboratory methods, and routine calcium value evaluation in the daily practice.

Although parathormone directly stimulates distal tubular reabsorption of calcium<sup>8</sup>, urinary calcium excretion is increased in 35 to 40% of patients with PHPT due to the increased filtered calcium due to hypercalcemia, and kidney stones may develop due to hypercalciuria. Increased urinary calcium may result in nephrolithiasis and nephrocalcinosis<sup>9</sup>. Cipriani et al.<sup>6</sup> found kidney stones in 55% of the patients by ultrasound. Lowe et al.<sup>7</sup> stated a history of kidney stones in 14% of the patients. In their study, Anil Bhansali et al.<sup>10</sup> said that 21% of patients had recurrent kidney stones.

In our study, the mean PTH value of the patients was  $357.32 \pm 424.08$  pg/ml, the calcium value was  $11.83 \pm 1.28$  mg/dl, and the urinary calcium value was  $381.80 \pm 204.11$  mg/24h. In 38.1% (n: 35) of 92 patients whose 24-hour urine calcium was measured, hypercalciuria was present. In addition, 35.7% (n: 55) of the patients had a history of kidney stone reduction, and 36.1% (n: 35) had kidney stones on ultrasonography. In our study, it was the most common complication.

There are usually four parathyroid glands in humans, two above and two below, adjacent to the thyroid gland<sup>11</sup>. High-resolution ultrasonography and Tc99M-sestamibi imaging are the most important localization methods<sup>3</sup>. Tehseen Fatima et al.<sup>12</sup> found positive findings in the preoperative localization of PHPT in 84.1% of their patients in neck ultrasonography and 85.7% of their patients with Tc99M sestamibi. Our study found positive findings in 76.8% (n: 116) of the patients in neck ultrasonography performed for localization and

in 70.7% (n: 106) of Tc99M sestamibi. The resolution of the device used in ultrasonographic imaging and the physician's experience may affect the results if performed with a different physician and device. In Tc99M sestamibi, factors such as serum calcium, PTH, 25 hydroxy vitamin D<sub>3</sub> value, use of calcium channel blockers, average adenoma weight, and oxyphil cell content may affect the results<sup>13</sup>. These factors may be the reason why our imaging results are lower.

Berat Demir et al.<sup>14</sup> found a single parathyroid adenoma in 108 patients (78.8%) and found the most common adenoma localization in the left lower parathyroid gland (46.7%). In our study, the most frequent localization was the right lower quadrant, with 36.4% (n: 55) of the patients and 35.1% (n: 53) having adenoma in the lower left quadrant. In Tc99M sestamibi, the right lower quadrant was most frequently localized, with 37.4% (n: 56) and 28% (n: 42) of patients having adenoma in the lower left quadrant. In the pathology results of the patients, 91.5% (n: 118) adenoma and 5.4% (n: 7) hyperplasia were found.

Our study detected recurrence in 4.6% (n: 6) of the operated patients during their follow-up. CJ McIntyre et al.<sup>15</sup> found a 6.5% recurrence in their study. Surgical experience is the leading factor determining the recurrence rate. The limited number of physicians who perform parathyroid surgery in our hospital and their experience may explain the high success rate despite the low localization rate compared to other studies.

As a result, patients with PHPT may present with a high value of PTH and complications that affect many systems due to hypercalcemia. Therefore, early diagnosis and treatment of PHPT are important to prevent serious complications that affect many systems. The low complication rates in our patients also show the importance of early diagnosis.

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