ORIGINAL RESEARCH

DOI: 10.4274/ejgg.galenos.2025.2024-11-8

Eur J Geriatr Gerontol 2025;7(1):1-5

Primary Hyperparathyroidism Across the Age Spectrum: A Comparative Study of Clinical and Biochemical Profiles in Older and Younger Patients

Berna Evranos Öğmen[1], Nurcan İnce[2], Oya Topaloğlu[1], Reyhan Ersoy[1], Bekir Çakır[1]

[1]Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey
[2]Artvin State Hospital, Clinic of Internal Medicine Artvin, Turkey

Abstract

Objective: Primary hyperparathyroidism (PHPT) is characterized by elevated serum calcium (Ca) levels due to excessive parathyroid hormone (PTH) secretion and is traditionally associated with skeletal and renal complications, such as osteoporosis and nephrolithiasis. With routine measurements of serum Ca, most cases are now diagnosed asymptomatically although subclinical complications like osteoporosis or hypercalciuria may still occur. This study investigated the impact of aging on the clinical and biochemical profiles of PHPT by comparing a large cohort of older and younger patients, thereby addressing the gap in understanding the disease's age-related characteristics.

Materials and Methods: This retrospective study analyzed patients diagnosed with PHPT who underwent surgical treatment. Demographic data, including age and gender, along with biochemical parameters serum Ca, corrected calcium (cCa), phosphorus, albumin, PTH, 24-hours urinary Ca, estimated glomerular filtration rate (eGFR), fractional calcium excretion (FECa), and 25-hydroxyvitamin D (25OHD) were collected. Renal imaging and dual-energy X-ray absorptiometry were used to assess nephrolithiasis and osteoporosis, respectively. Patients were stratified into two groups: those younger than 60 (Group 1) and those aged 60 and older (Group 2). The groups were compared according to the prevalence of osteoporosis, nephrolithiasis, and biochemical parameters.

Results: The cCa levels were significantly higher in Group 2, with a median of 11.1 mg/dL, compared with 10.8 mg/dL in Group 1 (p=0.002). The median serum 25OHD level was lower in Group 1 (13.2 ng/mL) than in Group 2 (17 ng/mL, p<0.001). Median 24-hours urinary Ca excretion was higher in Group 1 (375.5 mg) than in Group 2 (308 mg, p=0.003). FECa was similar between the groups, with a median of 0.02 in Group 1 and 0.02 in Group 2 (p=0.88). eGFR was significantly higher in Group 1 (median, 102 mL/min/1.73 m^2, compared to 84 mL/min/1.73 m^2 in Group 2 (p<0.001). The prevalence of nephrolithiasis was similar between the groups, affecting 33.5% of patients in Group 1 and 31.8% in Group 2 (p=0.69). Osteoporosis was significantly more common in Group 2 (62.3% of patients) than in Group 1 (40% in Group 1 (p<0.001).

Conclusion: Aging plays a pivotal role in the clinical presentation of PHPT, with distinct patterns emerging across different age groups. In particular, older adults exhibit a higher prevalence of osteoporosis.

Keywords: Primary hyperparathyroidism, aging, hypercalcemia, nephrolithiasis, osteoporosis

Introduction

Primary hyperparathyroidism (PHPT) is characterized by elevated blood calcium (Ca) levels, which is caused by the overproduction of parathyroid hormone (PTH) from one or more parathyroid glands (1). It is widely considered the most common cause of hypercalcemia. Elevated PTH leads to hypercalcemia by increasing Ca reabsorption in the kidneys, enhancing bone resorption, and stimulating renal production of 1,25-dihydroxyvitamin D (25OHD), which promotes intestinal absorption of Ca and phosphate. Most cases are sporadic and are caused by a single

Address for Correspondence: Berna Evranos Öğmen MD, Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey
E-mail: evranosberna@gmail.com **ORCID:** orcid.org/0000-0002-1848-888X
Received: 26.11.2024 **Accepted:** 02.01.2025 **Epub:** xxxxxxxxxxxxxxx **Publication Date:** xxxxxxxxxxxxxxx

Cite this article as: Öğmen BE, İnce N, Topaloğlu O, Ersoy R, Çakır B. Primary hyperparathyroidism across the age spectrum: a comparative study of clinical and biochemical profiles in older and younger patients. Eur J Geriatr Gerontol.

adenoma (80%) or multiglandular disease (10-15%). Less than 1% of cases are caused by parathyroid carcinoma (1). The incidence of PHPT varies widely, with estimates ranging from about 13 to 120 cases per 100,000 individuals (2). The incidence of PHPT increases with age and is higher in women than in men. Historically, PHPT was diagnosed based on symptomatic presentations affecting the skeletal and renal systems. Common manifestations included decreased bone mineral density, fragility fractures, kidney stones, and nephrocalcinosis. However, with the routine inclusion of serum Ca measurements in metabolic panels, many cases are identified before symptoms develop, with about 70-80% of patients presenting asymptomatically (3). Even in asymptomatic cases, patients may exhibit subclinical skeletal and renal complications, such as osteoporosis and hypercalciuria, which may remain unnoticed. Data on the impact of aging on the clinical presentation and biochemical profile of PHPT, particularly in individuals aged 60 years and older, remain limited. Although few studies have examined the relationship between patient age and PHPT characteristics (4-11), we investigated a large cohort of sporadic PHPT cases to compare clinical features and laboratory parameters between older and younger adults.

Materials and Methods

This retrospective study evaluated patients with primary PHPT who were followed up at Ankara Atatürk Research and Training Hospital between July 2007 and January 2019 and Bilkent City Hospital between February 2019 and March 2021. The study included individuals who underwent surgery for PHPT, as confirmed by histopathological analysis. The exclusion criteria included patients younger than 18 years, those diagnosed with secondary hyperparathyroidism or familial hypocalciuric hypercalcemia, and individuals without histological confirmation due to either non-surgical management or surgeries performed at external centers. Data collection included patient demographics, including age at diagnosis and sex, and comprehensive biochemical markers. These included serum Ca, corrected calcium (cCa), phosphorus (P), albumin, PTH, 24-hours urinary Ca, estimated glomerular filtration rate (eGFR), fractional excretion of calcium (FECa), creatinine (Cr), and serum 25-hydroxyvitamin D (25OHD). cCa was calculated using the formula: cCa = total Ca + [0.8 × (4.0 - albumin)], with reference ranges for the markers defined as follows: Ca (8.5-10.3 mg/dL), albumin (3.5-5.2 g/dL), P (2.5-4.5 mg/dL), PTH (18.4-80.1 ng/L), Cr (0.5-1.1 mg/dL), and 25OHD (30-100 µg/L). Nephrolithiasis was assessed using renal ultrasound or computed tomography. At the same time, osteoporosis was evaluated via dual-energy X-ray absorptiometry at the lumbar spine, femoral neck, and distal third of the radius, adhering to the World Health Organization criteria (12). Histopathological findings from the surgical specimens were also reviewed to confirm the accuracy of the surgery. The study population was stratified into two groups based on age: patients younger than 60 years (Group 1) and those 60 years or older (Group 2). Comparisons were made between the groups regarding the prevalence of osteoporosis and nephrolithiasis and serum and urinary biochemical parameters. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Ankara Bilkent City Hospital (approval number: E1-22-2425, date: 09. 03/2022).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Non-normally distributed variables are reported as medians with ranges (minimum-maximum), whereas categorical variables are expressed as absolute numbers and percentages. The chi-square test was used for comparisons of categorical variables, and the Mann-Whitney U test was used for non-parametric data. A p-value of <0.05 was considered statistically significant.

Results

Six hundred fifty-nine patients were analyzed, with 499 in group 1 and 160 in Group 2. The majority of patients in both groups were female, comprising 87.6% (437/499) in Group 1 and 79.4% (127/160) in Group 2 (p=0.01). The median age was 50 years (range 19–59) in Group 1 and 66 years (range 60–85) in Group 2.

Thyroid-stimulating hormone levels were comparable between the groups, with medians of 1.76 mU/L (range 0.008-15) in Group 1 and 1.70 mU/L (range 0.009-8.28) in Group 2 (p=0.36). Comparisons of biochemical markers in serum and urine are presented in Table 1. cCa levels were significantly higher in Group 2, with a median of 11.1 mg/dL (range 8.76-13.32) compared with 10.8 mg/dL (range 8.79-18.63) in Group 1 (p=0.002). The median serum 25OHD level was lower in Group 1 (13.2 ng/mL) than in Group 2 (17 ng/mL, p<0.001). The median 24-hour urinary Ca excretion was higher in Group 1 (375.5 mg, range 24-1438) than in Group 2 (308 mg, range 38-1038, p=0.003). FECa was similar between the groups, with a median of 0.02 (range 0.01-0.39) in Group 1 and 0.02 (range 0.01-0.18) in Group 2 (p=0.88). eGFR was significantly higher in Group 1, with a median of 102 mL/min./1.73 m^2 (range 55-202), compared with 84 mL/min/1.73 m^2 (range 24-198) in Group 2 (p<0.001). The prevalence of nephrolithiasis was similar between the groups, affecting 33.5% of patients in Group 1 and 31.8% in Group 2 (p=0.69) (Table 2). Osteoporosis was significantly more common in Group 2 (62.3% of patients) than in Group 1 (40% in Group 1 (p<0.001). The lumbar T-score was comparable between Groups 1 and 2. However, the median femoral T-score was significantly

lower in the elderly group at -1.3 (range -4.1 to 2.6) compared with 1.0 (range -5.1 to 2.7) in the younger group (p=0.028). The distal radius one-third T-score was also lower in the elderly group at -2.5 (range -6.5 to 3.0) compared with 1.5 (range -6.2 to 7.1) in the younger group (p<0.001). A higher proportion of elderly patients received osteoporosis treatment (8.8% vs. 2.2%, p<0.001). Additionally, hypertension and diabetes were significantly more prevalent in the elderly group (p<0.001). The detailed comparisons are presented in Table 2.

Discussion

In this study, we retrospectively evaluated older and younger patients with PHPT who underwent surgery. There was a clear female predominance in hyperparathyroidism, which was even more pronounced in younger patients. cCa levels were higher in the older group, whereas PTH levels were similar between the groups. Vitamin D therapy was administered more frequently in the older group; however, the difference was not statistically significant. Notably, 25OHD levels were higher in the older population. The 24-hours urinary Ca level and eGFR were higher in the younger group, whereas the incidence of nephrolithiasis was similar in both groups. Osteoporosis was more prevalent among the older group, as characterized by significantly lower femoral and distal radius T-scores, while lumbar T-scores remained comparable. The clinical presentation of PHPT according to patient age has been subject to limited investigation (4-11). Existing studies have characterized the clinical manifestations of juvenile PHPT (7,8,10,11), with findings suggesting that these younger patients may be equally (8) or even more symptomatic (7,10,11) than their adult counterparts. In contrast, there is a dearth of data on PHPT presentation among older adults (4,6,9). A notable surgical series conducted by Udén et al. (6) involving 250 patients in the 1990s highlighted that the incidence of nephrolithiasis was significantly greater in younger patients (those under 60 years). In contrast, the prevalence of osteoporosis was comparable across the age groups. Although our current study also observed a higher incidence of nephrolithiasis among younger patients, this difference was not statistically significant. Conversely, our findings indicated a substantial increase in osteoporosis

Table 1. Clinical and biochemical characteristics of patients undergoing parathyroidectomy for primary hyperparathyroidism by age group

	Group 1 (n=499)	Group 2 (n=160)	p
Age median years	50 (19-59	66 (60-85)	**<0.001**
Female n (%)	437 (87.6%)	127 (79.4%)	**0.01**
TSH mU/L	1.76 (0.008-15)	1.70 (0.009-8.28)	0.36
TPO Ab positivity (%)	20.8	18.9	0.61
Corrected calcium (mg/dL)	10.8 (8.79-18.63)	11.1 (8.76-13.32)	**0.002**
PTH (ng/L)	178 (44-2,050)	171 (48.7-1,276)	0.27
25OHD (µg/L)	13.2 (2.9-94)	17 (2.2-101)	**<0.001**
FECa	0.02 (0.01-0.39)	0.02 (0.01-0.18)	0.88
24 hours urinary Ca level (mg)	375.5 (24-1,438)	308 (38-1,038)	**0.003**
eGFR (mL/min/1.73 m^2)	102 (55-202)	84 (24-198)	**<0.001**
Phosphorus (mg/dL)	2.5 (0.7-5.7)	2.5 (1.1-3.6)	0.43

Categorical variables are expressed as absolute numbers and percentages. Non-normally distributed variables are reported as medians with ranges (minimum-maximum), eGFR: Estimated glomerular filtration rate, TPO Ab: Thyroid peroxidase antibodies, PTH: Parathyroid hormone, TSH: Thyroid-stimulating hormone, 25OHD: 25-hydroxyvitamin D, FECa: Fractional excretion of Ca

Table 2. Complications and additional conditions of patients

	Group 1 (n=499)	Group 2 (n=160)	p
Nephrolithiasis %	33.5	31.8	0.69
Osteoporosis %	40	62.3	**<0.001**
Lomber T- score	-1.8 (-5.2-3.9)	-2 (-4.9-2.4)	0.08
Femoral T-score	-1 (-5.1-2.7)	-1.3 (-4.1-2.6)	**0.028**
Distal third radius T-score	-1.5 (-6.2-7.1)	-2.5 (-6.5-3.0)	**<0.001**
Vitamin D therapy %	8.6	10.6	0.44
Osteoporosis therapy %	2.2	8.8	**0.001**
Hypertension %	28.1	66.2	**<0.001**
Diabetes mellitus %	13	33.1	**<0.001**

prevalence among older patients. It is pertinent to note that the analysis by Udén et al. (6) primarily relied on patient self-report questionnaires to assess the symptoms and signs of PHPT, thereby lacking comprehensive radiological and densitometric data regarding bone involvement. Castellano et al. (4) documented a markedly different clinical profile of PHPT between younger and older patients, wherein the older demographic exhibited a greater prevalence of bone involvement, consistent with our findings. Notably, older patients experienced a significantly lower incidence of renal stones. Recently, a study by Gasior et al. (9) involving a substantial cohort of PHPT patients corroborated the findings of elevated nephrolithiasis rates in younger individuals and a higher prevalence of osteoporosis in older patients (>40 years). Although the criteria for age stratification varied, the dominance of osteoporosis in the elderly population was consistent with the results of our study. Osteoporosis is more prevalent in older individuals, with bone loss initially affecting trabecular sites at younger ages and progressively targeting cortical bone with advancing age (13). In PHPT, structural and density deterioration predominantly involves the cortical bone (14,15). Our findings revealed a more pronounced cortical osteoporosis in older patients, highlighting the distinct impact of PTH. In the study conducted by Udén et al. (6), there were no notable differences in the biochemical profiles, such as Ca and PTH levels, between the two age groups. In contrast, our findings revealed that older patients had higher levels of 25OHD, possibly linked to vitamin D supplementation, perhaps contributing to elevated Ca levels in this older group. In a study by Castenollo et al. (4), no differences were found in the mean serum PTH, Ca, or vitamin D levels. However, urinary Ca levels were significantly lower in older patients compared with younger patients, which is consistent with our study. Gasior et al. (9) demonstrated that median 24-hours urinary Ca levels were higher in younger patients, mirroring our findings, whereas there was no difference in median serum Ca or serum PTH levels between the cohorts. Epidemiological studies have established a significant relationship between urinary Ca excretion and the risk of kidney stone formation in the general population (16) and individuals diagnosed with PHPT (17-19). In our study, we noted that younger patients exhibited significantly higher Ca excretion; however, the incidence of nephrolithiasis did not differ significantly between age groups. Although hypercalciuria is recognized as a contributing factor to renal stone development (17), it alone does not fully account for the increased risk of nephrolithiasis among all patients with PHPT. This observation implies the involvement of additional risk factors (18,20) involved, such as hyperuricosuria, hypomagnesuria, hyperoxaluria, hypocitraturia, or cystinuria (21,22), which were not examined in our study. In patients with PHPT, a reduced eGFR can significantly affect urinary Ca levels (23,24). PHPT is characterized by increased renal Ca reabsorption due to elevated PTH levels. However, as eGFR decreases and renal function declines, the kidneys' ability to filter Ca is compromised. Nevertheless, persistent hyperparathyroidism can lead to ongoing renal Ca loss because PTH stimulates Ca mobilization from bone and enhances intestinal absorption. Our study found that the older cohort had a lower glomerular filtration rate, which may have contributed to decreased urinary Ca excretion. These findings are corroborated by Black et al. (25) who identified a correlation between 24-hours urinary Ca levels and renal function and a negative correlation with age. In addition, in our study, the number of elderly patients receiving osteoporosis treatment was higher than that of younger patients, and it is known that osteoporosis treatments may reduce urinary Ca excretion (26). Despite the similar incidence of nephrolithiasis, the low urinary Ca values may also be explained by higher osteoporosis treatment in the older group. The frequency of hypertension and diabetes mellitus was higher in the older group in this study and may predispose older patients with PHPT to impaired renal function. It remains unclear whether impaired renal function is solely caused by PHPT or by traditional risk factors, such as age, diabetes mellitus, and blood pressure. Walker et al. (24) showed that traditional risk factors for renal failure in the non-hyper parathyroid population, such as age, diastolic blood pressure, and blood glucose, were associated with worse renal function in PHPT (24). Our study has some limitations. Despite the large cohort, we conducted a retrospective single-institution study, which may have been influenced by selection bias. All patients in the study indicated and underwent surgery for PHPT; therefore, the findings cannot be generalized to all patients with PHPT. Furthermore, although we included patients on bone-active medications, we could not exclude the potential effects of these drugs on bone and serum.

Conclusion

This study encompasses a substantial patient cohort. Limited research has focused on the impact of PHPT in both elderly and younger populations, underscoring the significance of this study's findings. Osteoporosis is more frequently observed in elderly individuals. Unlike osteoporosis in the general population, it predominantly affects the cortical bone. This pattern appears to reflect the influence of PTH. Thus, it can be concluded that PHPT leads to more pronounced bone deterioration in older adults than in younger individuals, highlighting the potential need for earlier intervention.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Ankara Bilkent City Hospital (approval number: E1-22-2425, date: 09.03/2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.C., R.E., O.T., Concept: B.C., R.E., Design: O.T., R.E., Data Collection or Processing: N.İ., B.E.O., Analysis or Interpretation: B.E., B.C., Literature Search: N.İ., Writing: B.E.O., N.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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