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ORIGINAL ARTICLE

Clinical characteristics, mid-term outcomes and management of asymptomatic primary hyperparathyroidism: A multicentre retrospective cohort study

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Abstract

Purpose The primary objective of this study was to retrospectively evaluate the demographic, biochemical, and clinical characteristics of patients with asymptomatic primary hyperparathyroidism (aPHPT), analyze their long-term outcomes, and discuss the effectiveness of current therapeutic strategies in light of the existing literature. We anticipate that our study will provide clinicians with guidance regarding surgical decision-making beyond the standard criteria for aPHPT.

Methods This was a nationwide, multicenter, observational, retrospective cohort study. All tertiary care endocrinology departments across the country were invited to participate. Center inclusion criteria required the enrollment of a sufficient number of aPHPT patients, confirmed by careful diagnostic evaluation in accordance with established guidelines, regular follow-up for at least one year, and systematic monitoring for complications.

Results Data from 27 centers representing various regions of Turkey were included in the study. A total of 829 patient records were reviewed, and after excluding 25 patients who did not meet eligibility criteria, 804 patients were included in the final analysis. The mean age was 55.59 ± 11.54 years, with a female predominance (85%, $n = 683$). The baseline prevalence of comorbidities was as follows: hypertension in 43% ($n = 346$), diabetes mellitus in 27.1% ($n = 216$), and cardiovascular disease in 10.8% ($n = 87$) of patients. Bone mineral density (BMD) measurements were available for 701 patients, among whom osteoporosis was present at 23.4% and osteopenia at 50.5%. Glomerular filtration rate (GFR) significantly declined by the third year compared to baseline ($p = 0.003$). The prevalence of cardiovascular disease significantly increased at year three compared to baseline and the first year ($p = 0.002$). A significant association was found between the presence of osteoporosis and lower baseline serum magnesium levels ($p < 0.001$), particularly among patients with magnesium levels below 1.6 mg/dL compared to those with levels within the normal range (1.6–2.5 mg/dL). Additionally, patients with osteoporosis demonstrated significantly lower serum phosphate levels compared to other groups ($p < 0.001$).

Conclusion The management of asymptomatic PHPT continues to present numerous unanswered questions. Hypertension, cardiovascular disease, and diabetes mellitus were found to be more prevalent among aPHPT patients compared to the general population. The observed increase in cardiovascular events over time suggests that cardiovascular disease could become a more prominent factor in future surgical decision-making. Furthermore, the significant decline in GFR over follow-up may necessitate revisiting the surgical threshold of GFR < 60 mL/min in future guidelines. Routine assessment of serum magnesium and phosphate levels should be considered, particularly in patients at high risk for osteoporosis. Future research may further redefine surgical indications in the management of aPHPT.

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by excessive secretion of parathyroid hormone (PTH) from the parathyroid glands, profoundly affecting bone and mineral metabolism. The clinical spectrum of this disease ranges from the classic form presenting with "bones, stones, abdominal complaints, and psychiatric

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symptoms" to the asymptomatic form detected through modern laboratory screenings. From a historical perspective, the clinical presentation of PHPT has undergone a dramatic shift over the past 50 years [1]. Before the 1970s, the majority of patients presented with severe symptoms such as nephrolithiasis, bone deformities, or hypercalcemic crisis. In contrast, today, more than 80% of cases are diagnosed asymptomatically. The term "asymptomatic PHPT" has been introduced for patients diagnosed through routine screening without apparent symptoms [2]. This epidemiological change is closely linked to the widespread adoption of routine biochemical screenings and the standardization of serum calcium measurements.

The emergence of asymptomatic primary hyperparathyroidism (aPHPT) in modern medicine has raised important clinical questions. In particular, the long-term risk of complications and the optimal management strategies for patients who appear clinically silent remain subjects of ongoing debate. Recent prospective studies have demonstrated that the subclinical skeletal and renal effects of aPHPT are far more prevalent than initially anticipated. Asymptomatic PHPT is regarded as a milder presentation of classical PHPT [3]. It can be classified into two subgroups: patients with and without target organ involvement. The natural history and optimal management of aPHPT, especially regarding the decision for surgical intervention, continue to be controversial. A balance must be struck between observation and surgery. According to guidelines established by the Asymptomatic PHPT Workshop, parathyroidectomy is recommended for patients meeting specific criteria. However, the impact of milder forms of PHPT, such as aPHPT, on overall survival remains uncertain [4]. When examining the pathophysiological mechanisms of PHPT, it is evident that PTH exerts significant effects not only on bone and kidneys but also on the cardiovascular system and metabolic parameters. In the skeletal system, excessive PTH activity leads to increased osteoclastic bone resorption, resulting in decreased bone mineral density and deterioration of bone microarchitecture. In the renal system, complications such as hypercalciuria, nephrocalcinosis, and nephrolithiasis may develop [5, 6].

In cases where surgical intervention is not indicated, regular patient monitoring is recommended. Annual laboratory evaluations and bone mineral density (BMD) assessments every 1–2 years are important for assessing disease progression. Nevertheless, further research is necessary to conclusively determine the long-term benefits and risks of surgical intervention [7].

Purpose

The primary aim was to retrospectively evaluate the demographic, biochemical, and clinical characteristics of patients with asymptomatic PHPT, analyse their long-term outcomes, and discuss the efficacy of current treatment strategies in the light of the literature. We believe that our study will guide clinicians in the decision of surgical treatment of aPHPT beyond the standard criteria.

Patients and Methods

Ethics

The study protocol was reviewed and approved by the local ethics committee of Umraniye Training and Research Hospital (13.06.2024, 246507833). The study was conducted by the principles of the Declaration of Helsinki. Due to its retrospective nature, informed consent was not required.

Materials and methods

This was a nationwide, multicenter, observational, retrospective cohort study. All endocrinology departments of tertiary healthcare institutions across Turkey were invited to participate. The inclusion criteria for centers required having an adequate number of asymptomatic PHPT patients, ensuring careful diagnosis in accordance with established guidelines, and following patients regularly for at least one year with systematic monitoring for complications. Centers with insufficient case numbers or inadequate follow-up duration were excluded from the study.

The terminology for asymptomatic PHPT was adopted as defined by Bilezikian et al. during the Fifth International Workshop. For instance, the detection of a renal stone by ultrasonography does not reclassify the patient as symptomatic; rather, it is considered an indication of target organ involvement. The recommended terminology differentiates between asymptomatic PHPT patients with and without target organ involvement, preserving the term "symptomatic PHPT" solely for patients exhibiting clinical symptoms [4].

For each patient, data were collected until parathyroidectomy was performed, medical treatment for osteoporosis was initiated, or the patient was lost to follow-up for any reason. Due to the retrospective design, the followed patient group was heterogeneous, including patients who refused surgical treatment despite having surgical indications, patients in the waiting period for surgery, and patients who preferred conservative follow-up management.

Data regarding asymptomatic PHPT cases were retrospectively gathered from Turkish centers between June 2024 and December 2024. All biochemical parameters were measured locally at each center at baseline and during follow-up. Data management and corrections for albumin-adjusted calcium levels were performed at the coordinating center (Ümraniye Training and Research Hospital).

Demographic and clinicopathological factors (such as age, sex, hypertension, diabetes, and cardiovascular disease) and laboratory results were extracted from patient records. Standard baseline biochemical assessments included fasting serum calcium, phosphate, PTH, 25-hydroxyvitamin D3, albumin, creatinine, and 24-h urinary calcium and creatinine levels.

PTH levels were measured using an intact PTH chemiluminescent immunoassay (Immulite 2000 analyzer). Plasma 25-hydroxyvitamin D was measured by radioimmunoassay. In the literature, two different threshold values are proposed to exclude secondary hyperparathyroidism:

20 ng/mL (50 nmol/L), as recommended by the Institute of Medicine (IOM) report and the Fourth International Workshop Guidelines [8, 9]. 30 ng/mL (75 nmol/L), as supported by the European Society of Endocrinology Expert Consensus [10].

In this study, vitamin D deficiency was defined as a 25-hydroxyvitamin D level ≤20 ng/mL, consistent with the IOM definition. Serum calcium levels were corrected for hypo- or hyperalbuminemia using the following formula: [serum calcium + 0.8 × (4 - albumin)].

Renal stone detection

Renal stones were assessed objectively by ultrasonography performed by an experienced radiologist at each center. It should be noted that only stones detected by imaging methods were recorded in this study; past history of stone passage was not systematically queried, which may have led to underestimation of the true prevalence of nephrolithiasis.

Bone mineral density (BMD)

BMD was measured at the lumbar spine (L1-L4), total hip, and femoral neck using dual-energy X-ray absorptiometry (DEXA), with the same device used consistently for follow-up measurements. Notably, forearm (radius) DEXA measurements were not routinely performed at all participating centers due to varying institutional practices and equipment availability, which represents a limitation of our study as forearm measurements have been shown to increase the rate of patients meeting surgical criteria.

Definitions

Hypertension

Defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or a documented history of hypertension or use of antihypertensive medication.

Diabetes mellitus

Defined as a fasting plasma glucose ≥126 mg/dL or HbA1c ≥ 6.5%, or a documented history of diabetes or use of antidiabetic medications.

Cardiovascular disease

Defined based on self-reported patient history.

Statistical Analyses

The normality of data distribution across groups was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparisons of non-normally distributed variables across three time points, the Friedman test was applied, followed by post-hoc analyses using the Bonferroni-corrected Dunn test. Changes in categorical variables across time points were evaluated using the Cochran's Q test for binary variables measured at three time points, the McNemar test for binary variables at two time points, and the Friedman two-way ANOVA for ordinal variables across three time points.

For comparisons based on osteoporosis status, the Kruskal-Wallis H test was used for non-normally distributed continuous variables, with post-hoc analyses conducted using the Bonferroni-corrected Dunn test. Categorical variables were compared using the Pearson chi-square test when all expected frequencies were greater than five; otherwise, Fisher's exact test was applied. Multiple comparisons of proportions were analyzed using the Bonferroni-corrected Z test.

Factors influencing the change in cardiovascular disease (CVD) status over time were evaluated using the Generalized Estimating Equations (GEE) model. Binary logistic link functions were used for modeling, and an autoregressive (AR-1) correlation structure was applied to account for the dependency between repeated measures.

Quantitative data were presented as mean ± standard deviation or median (minimum–maximum) as appropriate, while categorical data were summarized as frequencies and percentages. A p-value < 0.05 was considered statistically significant in all analyses. All statistical analyses were performed using IBM SPSS Statistics version 26.

Results

Data from 27 centers representing various regions of Turkey were included in this study. Prior to data processing and statistical analyses, a secondary evaluation of patient eligibility was performed at the coordinating center. Data from

Table 1 Descriptive statistics of the baseline characteristics of the patients

	n / Ort. ± SS	%
Age of diagnosis	55.59 ± 11.54	
Gender		
Female	683	85
Male	121	15
Renal Stone		
Not available	672	86.6
Available	104	13.4
BMD		
Normal	183	26.1
Osteopenia	354	50.5
Osteoporosis	164	23.4
Parathyroid adenoma		
Unidentified	232	30.2
Detected	537	69.8
Hypertension		
Not available	458	57
Available	346	43
Diabetes Mellitus		
Not available	588	73.1
Available	216	26.9
Cardiovascular Disease		
Not available	717	89.2
Available	87	10.8

a total of 829 patients were reviewed; 25 patients were deemed ineligible for inclusion, and the remaining 804 patients were included in the final analysis. The mean age of the patients was 55.59 ± 11.54 years, and as expected, there was a female predominance with 683 (85%) female patients. At baseline, the prevalence of comorbidities was as follows: hypertension in 43% (n = 346), diabetes mellitus in 27.1% (n = 216), and cardiovascular disease in 10.8% (n = 87) of patients. Bone mineral density (BMD) measurements were available for 701 patients, among whom 164 (23.4%) had osteoporosis and 354 (50.5%) had osteopenia (Table 1). A total of 722 patients were followed for one year, 300 patients for three years, and 27 patients for five years.

Among the 164 patients diagnosed with osteoporosis, a significant association was found between the presence of osteoporosis and lower baseline serum magnesium levels ($p < 0.001$). Specifically, 37.8% of patients with osteoporosis had magnesium levels ≤1.6 mg/dL compared to 19% in the normal BMD group and 17% in the osteopenia group. Furthermore, patients with osteoporosis demonstrated significantly lower serum phosphate levels (median 2.7 mg/dL) compared to those with normal BMD (median 2.8 mg/dL) and osteopenia (median 2.86 mg/dL) ($p < 0.001$).

Changes in laboratory parameters and BMD measurements over time are shown in Table 2. The mean corrected serum calcium level at baseline was 10.61 mg/dL, and there was no statistically significant change over time ($p = 0.392$). However, mean PTH levels decreased significantly over time ($p = 0.026$), which may be associated with vitamin D supplementation initiated after diagnosis. Consistently, there was a significant increase in the mean 25-hydroxyvitamin D levels over time ($p = 0.007$).

Patients' glomerular filtration rate (GFR) levels significantly declined at the third year compared to baseline ($p = 0.003$).

The prevalence of cardiovascular disease was found to significantly increase in the third year compared to baseline and the first year ($p = 0.002$), possibly reflecting the association between hypercalcemia and increased cardiovascular risk.

At the first-year follow-up, the number of patients who met the criteria for parathyroidectomy indication was 316 (41%), which was significantly higher compared to the third-year follow-up ($p < 0.001$). Changes across the three time points are presented in Table 3.

At the time of diagnosis, patients were categorized into three groups according to the World Health Organization (WHO) criteria for osteoporosis diagnosis: osteoporosis, osteopenia, and normal BMD. Analyses based on these groups are presented in Table 4. Among the 164 patients diagnosed with osteoporosis, 90.9% (n = 149) were female, with a mean age of 62 years.

A statistically significant association was found between the presence of osteoporosis and lower baseline magnesium levels ($p < 0.001$); specifically, patients with magnesium levels ≤1.6 mg/dL had a significantly higher prevalence of osteoporosis compared to those within the normal range (1.6–2.5 mg/dL). The proportion of patients with magnesium levels ≤1.6 mg/dL was significantly higher in the osteoporosis group compared to the other groups.

Patients with osteoporosis also exhibited significantly higher levels of serum calcium, corrected calcium, and PTH compared to the other groups ($p = 0.026$, $p < 0.001$, and $p = 0.003$, respectively).

Serum vitamin D levels were significantly lower in patients with osteoporosis ($p < 0.001$).

Similarly, serum phosphate and magnesium levels were significantly lower in the osteoporosis group compared to the other two groups ($p < 0.001$).

There were significant differences in GFR values among the groups ($p < 0.001$), with patients diagnosed with osteopenia or osteoporosis having lower GFR levels.

Patients who received antiresorptive therapy demonstrated significant improvement in L1-L4 T-scores at the third year compared to baseline ($p = 0.002$) (Table 5).

Table 2 Analysis of changes between quantitative data from three different time points

	At first (n = 804)	1st year (n = 722)	3rd year (n = 300)	Test is.	p[f]
Calcium(Ca)	10.9 (10.1–12.98)	10.9 (8.3–13.4)	10.8 (8.7–13.9)	3.697	0.157
Corrected Calcium	10.61 (9.39–12.42)	10.6 (7.81–13.24)	10.48 (8.2–13.51)	1.875	0.392
İonised Calcium	1.33 (0.9–4.76)[a]	1.3 (1–1.61)[ab]	1.26 (1–1.54)[b]	16.262	<0.001
Albuumin	44 (27–57)	44 (22–54.2)	44 (4–53)	0.136	0.934
Parathormone (PTH)	123 (65.2–1169)[a]	127 (5.5–837)[a]	112 (2–1554)[b]	7.265	0.026
Phosphor	2.8 (1.28–5.2)	2.8 (1.2–4.7)	2.9 (0.78–5.59)	6.511	0.050
Magnesium (Mg)	2 (0.57–4.7)	1.97 (0.47–217)	2 (0.68–3.4)	1.231	0.545
Sodium	140 (130–147)	140 (129–148)	140 (133–146)	0.936	0.626
Potassium	4.5 (2.3–5.53)	4.5 (3–5.9)	4.5 (3.2–5.96)	0.234	0.889
Alkalene Phosphataz (ALP)	89.5 (20–491)	92 (33–790)	90 (27–834)	4.887	0.087
25 OH vitamin D	22.53 (3–96)[a]	24 (4–66.9)[b]	23.48 (1.05–71.19)[b]	9.886	0.007
Creatinine (Cr)	0.71 (0.36–2)	0.72 (0.3–1.9)	0.73 (0.4–1.9)	1.390	0.499
GFR	93 (31–143)[a]	91 (33–155)[b]	92.24 (32–139)[b]	11.315	0.003
Urine Ca (24 h)	258 (39–1530)	275.5 (10.49–1794)	236.5 (28–894)	2.976	0.226
Urine Cr (24 h)	984 (30.41–3272)	1012 (39–4268)	867 (17–1977)	0.021	0.989
L1-L4 T Score	−1.5 (−5–3.8)[a]	−1.5 (−4.6–3.7)[ab]	−0.6 (−4.3–2.3)[b]	10.501	0.005
Femur Total T Score	−0.9 (−4.3–2.5)	−0.9 (−4.4–2)	−0.5 (−4.2–2.9)	6.495	0.051
Femur Neck T Score	−1 (−4.6–2.5)	−1 (−3.8–1.2)	−0.6 (−3.9–2.1)	0.942	0.624

f friedman test

[a-b]no difference between groups with the same letter, median (min.-max.)

Table 3 Examination of changes in three separate follow-ups

	At First (n = 797)	1st year (n = 771)	3rd year (n = 285)	Test ist.	p
Renal Stone					
Not available	672 (86.6)	570 (83.7)	213 (83.5)	5.474	0.065[Q]
Available	104 (13.4)	111 (16.3)	42 (16.5)		
Hypertension					
Not available	458 (57)	395 (54.9)	145 (54.3)	4.667	0.097[Q]
Available	346 (43)	324 (45.1)	122 (45.7)		
Diabetes Mellitus (DM)					
Not available	588 (73.1)	520 (71.8)	206 (73)	1.125	0.570[Q]
Available	216 (26.9)	204 (28.2)	76 (27)		
Cardiovascular Disease (CVD)					
Not available	717 (89.2)	636 (88.1)	247 (87.3)	12.600	0.002[Q]
Available	87 (10.8)[a]	86 (11.9)[ab]	36 (12.7)[b]		
Parathyroidectomy					
None	-	455 (59)	197 (69.1)	34.286	<0.001[mc]
Positive İndication	-	316 (41)	88 (30.9)		
Anti-resorbtive Medication					
Not available	-	605 (84)	216 (78)	7.259	0.007[mc]
Available	-	115 (16)	61 (22)		

Q cochran's Q test, *mc* mcnemar test, *f* friedman two-way variance test, n (%)

[a-b]no difference between times with the same letter

In contrast, patients who did not receive antiresorptive therapy showed no statistically significant change over time in L1-L4 T-score, total femur, or femoral neck T-scores (Table 6).

Discussion

Asymptomatic PHPT is a disease affecting mostly middle-aged women. The disease is most common in the first

Table 4 Examination of the relationship between baseline demographic and clinical characteristics of the patients and osteoporosis

	BMD			Test is.	p
	Normal (n = 138)	Osteopenia(n = 354)	Osteoporosis (n = 164)		
Age of diagnosis	51 (19–76)[a]	56 (19–88)[b]	62 (25–90)[c]	84.484	<0.001[h]
Gender					
Female	142 (77.6)	306 (86.4)	149 (90.9)	12.955	0.002[x]
Male	41 (22.4)[a]	48 (13.6)[b]	15 (9.1)[b]		
Mg					
≤1.6	30 (19)[a]	53 (17)[a]	59 (37.8)[b]	25.488	<0.001[e]
1.6–2.5	125 (79.1)[a]	250 (80.4)[a]	95 (60.9)[b]		
≥2.5	3 (1.9)[a]	8 (2.6)[a]	2 (1.3)[a]		
Renal Stone					
Not available	150 (84.7)	304 (87.9)	132 (83.5)	2.023	0.364[x]
Available	27 (15.3)	42 (12.1)	26 (16.5)		
Hypertension					
Not available	116 (63.4)	197 (55.6)	83 (50.6)	5.952	0.051[x]
Available	67 (36.6)	157 (44.4)	81 (49.4)		
DM					
Not available	132 (72.1)	257 (72.6)	116 (70.7)	0.195	0.907[x]
Available	51 (27.9)	97 (27.4)	48 (29.3)		
CVD					
Not available	168 (91.8)	313 (88.4)	141 (86)	3.007	0.222[x]
Available	15 (8.2)	41 (11.6)	23 (14)		
Ca	10.9 (10.1–12.5)[ab]	10.9 (10.1–12.7)[a]	11 (10.2–12.98)[b]	7.288	0.026[h]
Corrected Ca	10.53 (9.72–12.18)[a]	10.58 (9.39–12.22)[a]	10.72 (9.66–12.36)[b]	16.771	<0.001[h]
PTH	116 (65.6–453)[a]	123.2 (65.8–780)[ab]	140 (65.4–1169)[b]	11.387	0.003[h]
Phosphor	2.8 (1.28–4.5)[a]	2.86 (1.5–4.32)[a]	2.7 (1.6–5.2)[b]	15.313	<0.001[h]
Mg	2 (0.7–2.9)[a]	2 (0.63–2.8)[a]	1.89 (0.57–2.6)[b]	19.005	<0.001[h]
ALP	86 (39–217)	90 (33–283)	94 (31–491)	5.561	0.062[h]
25 OH vitamin D	24.45 (3–96)[a]	25 (3–69)[a]	18.75 (3–54)[b]	19.503	<0.001[h]
Cr	0.7 (0.42–1.82)	0.72 (0.4–2)	0.71 (0.36–1.8)	0.260	0.878[h]
GFR	99 (36–133)[a]	93 (31–140)[b]	89.9 (37–143)[c]	36.499	<0.001[h]
Urine Ca (24 h)	294 (59–1086)	256.85 (55–1383)	256.34 (63–1530)	3.099	0.212[h]
Urine Cr (24 h)	1082 (59.42–2593)[a]	977 (33–2317)[b]	896 (34–3272)[b]	16.308	<0.001[h]
L1-L4 T Score	0.1 (−0.9–3.8)[a]	−1.6 (−2.4–2.2)[b]	−2.9 (−5–0.8)[c]	411.720	<0.001[h]
Femur Total T Score	0.1 (−0.9–2.5)[a]	−1 (−2.4–1.8)[b]	−2.1 (−4.3–1)[c]	277.121	<0.001[h]
Femur Neck T Score	0 (−0.9–2.5)[a]	−1.2 (−2.4–1.8)[b]	−2 (−4.6–0.7)[c]	192.136	<0.001[h]

h: Kruskal-Wallis H test, x: Pearson chi-square test, e: Fisher's exact test, median (min.-max.), n (%), a-c: No difference between groups with the same letter

Table 5 Examination of the changes between DEXA scores obtained at three different times in patients receiving antiresorptive therapy

	At First (n = 119)	1st year (n = 97)	3rd year (n = 57)	Test ist.	pf
L1-L4 T Score	−2.6 (−5–0.8)[a]	−2.4 (−4.2–0)[ab]	−2 (−3.7–1.6)[b]	12.984	0.002
Femur Total T Score	−1.8 (−4.3–0.3)[a]	−1.9 (−4.4–0.5)[ab]	−1.3 (−4.2–0)[b]	10.500	0.005
Femur Neck T Score	−1.7 (−4.6–1)	−1.7 (−3.8–0.3)	−1.05 (−3.9–0.2)	1.265	0.531

f: Friedman test, a-b: No difference between groups with the same letter, median (min.-max.)

Table 6 Examination of the changes between DEXA scores obtained at three different times in patients without antiresorptive therapy

	At First (n = 152)	1st year (n = 126)	3rd year (n = 142)	Test ist.	p[f]
L1-L4 T Score	−1.1 (−3.6–2.2)	−0.25 (−3.4–1.7)	−0.25 (−4.3–2.3)	3.219	0.200
Femur Total T Score	−0.6 (−2.8–2)	0 (−3.3–2)	0 (−3.1–2.9)	2.172	0.338
Femur Neck T Score	−0.4 (−3–2.5)	−0.08 (−3.6–1.2)	−0.45 (−3.5–2.1)	1.523	0.467

f friedman test

[a-b]No difference between groups with the same letter, median (min.-max.)

decade of menopause. The female-to-male ratio is more than 3:1 [11]. The mean age of the study population was 55.5 years, and the proportion of women was 85%, similar to the literature.

Biochemistry and Skeletal System

In our study, osteoporosis was detected in 23.4% and osteopenia in 50.5% of patients with asymptomatic PHPT. However, this relatively low prevalence of osteoporosis should be interpreted cautiously, as it may be attributed to the absence of routine forearm DEXA measurements in our study. Recent studies have demonstrated that forearm BMD evaluation significantly increases the rate of patients meeting surgical criteria. Castellano et al. reported that the inclusion of forearm DEXA measurements increased the detection of osteoporosis from 15.8% to 31.6% in patients with primary hyperparathyroidism, suggesting that our reported prevalence may be an underestimate of the true skeletal involvement [8]. Piskinpasa et al. reported that the inclusion of forearm DEXA measurements increased the detection of osteoporosis from 15.8% to 31.6% in patients with primary hyperparathyroidism, suggesting that our reported prevalence may be an underestimate of the true skeletal involvement [9]. These rates suggest that bone health may be more seriously compromised in asymptomatic cases than previously anticipated. It is well-established in the literature that asymptomatic PHPT adversely affects bone mineral density (BMD) [4]. In baseline evaluations, patients diagnosed with osteoporosis had significantly higher corrected calcium and PTH levels, supporting the deleterious skeletal effects of hyperparathyroidism. Additionally, significantly lower serum phosphorus and magnesium levels were observed in the osteoporosis group ($p < 0.001$), highlighting the importance of these often-overlooked parameters in PHPT management.

The significant association between hypomagnesemia and osteoporosis in our study ($p < 0.001$) warrants particular attention. Patients with magnesium levels ≤1.6 mg/dL had a significantly higher prevalence of osteoporosis (37.8%) compared to those with normal magnesium levels (19–17%). This finding suggests that routine measurement of serum magnesium in PHPT patients may be valuable for clinical risk stratification and identification of patients at higher risk for skeletal complications.

Similarly, the significantly lower serum phosphate levels in the osteoporosis group emphasize the potential clinical significance of hypophosphatemia in PHPT patients. Serum phosphate appears to be an underappreciated parameter in routine PHPT management, despite its potential implications for bone health and surgical decision-making. Castellano et al. demonstrated that serum phosphate levels are negatively correlated with disease severity in PHPT, with patients showing more severe bone density impairment at cortical sites having significantly lower phosphate levels [10]. Furthermore, Düğer et al. showed that hypophosphatemia is associated with higher rates of osteoporosis and renal stones in PHPT patients, and that even moderate hypophosphatemia may be predictive of surgical indication regardless of hypercalcemia severity [12]. More recent evidence from Columbu et al. confirms that PHPT patients with lower serum phosphate levels have a worse biochemical and clinical phenotype, including higher prevalence of kidney stones [13]. These findings support the need for routine phosphate monitoring and its potential consideration in surgical decision-making algorithms. Recent evidence suggests that moderate hypophosphatemia may represent a new indication for surgery in asymptomatic primary hyperparathyroidism, as proposed by Clarke et al. [14]. Furthermore, Bhadada et al. have highlighted phosphate as an underrated component of primary hyperparathyroidism, emphasizing its importance in the comprehensive evaluation of these patients [15]. The significant association between hypophosphatemia and osteoporosis in our cohort supports the need for routine phosphate monitoring and its potential consideration in surgical decision-making algorithms.

The study by Düğer et al. demonstrated that hypomagnesemia in PHPT patients could be associated with an increased risk of osteoporosis and nephrolithiasis [16]. Similarly, Na et al. found that PHPT patients with hypomagnesemia exhibited more severe hyperparathyroidism compared to those without hypomagnesemia, and that the prevalence of osteoporosis, anemia, and hypercalcemic crises was higher among PHPT patients with hypomagnesemia [17]. Routine measurement of serum magnesium in PHPT patients may therefore be valuable for clinical risk stratification.

Moreover, the risk of bone loss appears particularly pronounced among postmenopausal women, who constituted 90.9% of the osteoporosis group in our study. Since both osteoporosis and PHPT are more frequently observed in postmenopausal women, it is important to consider additional fracture risk factors, such as age, using tools like the Fracture Risk Assessment Tool (FRAX®), alongside dual-energy X-ray absorptiometry (DXA) measurements. Although FRAX can help estimate absolute fracture risk, the lack of PHPT-specific data incorporated into FRAX calculations remains a notable limitation. Furthermore, a study by Bisceglia et al. suggested that the Trabecular Bone Score (TBS) could reveal new indications for surgery in patients with aPHPT, by better capturing trabecular bone microarchitecture deterioration not evident on BMD alone [18].

In our cohort, patients receiving antiresorptive therapy demonstrated a significant improvement in L1--L4 T-scores ($p = 0.002$), supporting current guidelines recommending medical therapy in the presence of osteoporosis. Numerous studies have shown that bisphosphonates, particularly alendronate, improve BMD and reduce bone turnover markers in PHPT patients, although they do not consistently lower serum calcium concentrations [19–21]. However, the absence of significant bone loss progression in the untreated group ($p > 0.05$) may reflect the heterogeneous natural course of the disease.

Cardiovascular/Metabolic

In our study, the prevalence of hypertension, diabetes mellitus, and cardiovascular disease (CVD) among patients with asymptomatic PHPT was found to be 43%, 27.1%, and 10.8%, respectively. The Turkish Society of Cardiology (TKD) has conducted meta-analyses incorporating epidemiological studies from the last 15 years with low bias and strong representativeness of the national population distribution. These analyses reported an overall hypertension prevalence of 31.2% and a diabetes prevalence of 14.6% in the general population [22]. The age-standardized prevalence of cardiovascular disease was found to be 7.9% in men and 7.3% in women [23].

The prevalence of hypertension in our cohort (43%) was significantly higher than that reported in the general Turkish population (~ 31.2%) [22]. This finding may be explained by the direct effects of PHPT on the cardiovascular system. Elevated PTH levels may promote calcium accumulation within vascular smooth muscle cells, leading to endothelial dysfunction and hypertension [24]. Increased PTH concentrations have been proposed as potential markers of elevated cardiovascular risk, even in the presence of normal serum calcium levels [25].

Similarly, the prevalence of diabetes mellitus was found to be notably higher among our patients (27.1%) compared to the general population (14.6%) [22]. Elevated PTH levels have

been associated with insulin resistance and hyperglycemia [26, 27]. Although evidence suggests an association between PHPT and type 2 diabetes mellitus (T2DM), the exact nature of this relationship remains incompletely understood, and further research is needed to elucidate the underlying mechanisms. Some studies have indicated that individuals with PHPT may have an increased risk of developing insulin resistance and consequently T2DM [28]. In a study by Iglesias et al., the prevalence of T2DM was found to be 3.4 times higher in PHPT patients compared to controls without PHPT [29].

The negative impact of elevated PTH levels on glucose metabolism and insulin homeostasis is likely mediated by both intracellular hypercalcemia and hypophosphatemia, which may impair insulin receptor expression and responsiveness. One proposed mechanism is that increased intracellular calcium levels, resulting from elevated PTH, reduce insulin-stimulated glucose uptake in peripheral tissues, leading to insulin resistance, subsequent glucose intolerance, and eventually diabetes mellitus [30].

In our cohort, the prevalence of cardiovascular disease was 10.8%, which is notably higher than that observed in the general population. The association between PHPT and cardiovascular disease has yielded conflicting results in previous studies. The Fifth International Workshop on the Evaluation and Management of Primary Hyperparathyroidism, chaired by Bilezikian et al., concluded that the relationship between PHPT and CVD remains unclear and recommended that CVD should not be used as an indication for surgery at this time [4]. However, the high baseline prevalence of CVD and the significant increase observed at the third year of follow-up in our study (Table 3) should not be overlooked. Future larger-scale studies may further clarify the relationship between elevated PTH levels and cardiovascular morbidity. It is conceivable that, over time, the presence of CVD could emerge as an indication for surgical intervention in patients with aPHPT.

Renal

In the study by Cassibba et al., the prevalence of silent nephrolithiasis in PHPT patients was found to be 11.35%, significantly higher compared to controls [31]. Similarly, in our patient cohort, the prevalence of renal stones was identified as 13.5%. However, this prevalence should be interpreted with caution, as our study methodology only captured stones detected by imaging methods and did not systematically query patients' past history of stone passage. This methodological limitation may have resulted in underestimation of the true prevalence of nephrolithiasis in our cohort. These findings support the recommendation

proposed by Bilezikian et al. during the Fifth International Workshop, emphasizing the necessity of routine renal imaging in patients with asymptomatic PHPT [4].

According to our findings, a significant decline in glomerular filtration rate (GFR) was observed throughout follow-up ($p = 0.003$). This suggests that asymptomatic PHPT may lead to a gradual deterioration in renal function over time.

In a study conducted by Tay et al., a progressive decline in GFR was similarly reported among PHPT patients who did not undergo parathyroidectomy [32]. However, the threshold GFR value at which PHPT begins to significantly impair renal function remains uncertain. It is also unclear whether the observed decline in renal function in PHPT patients is directly attributable to the disease itself or to concomitant comorbidities. Nevertheless, a widely accepted threshold value for considering surgical intervention remains at 60 mL/min [4].

Given the evidence of progressive GFR decline and potential nephron loss over time, it is important to recognize that subclinical renal damage in aPHPT should not be overlooked, and closer monitoring may be warranted.

Strengths and limitations

The strongest aspects of our work are

1. A sufficient number of aPHPT patients were included in the study
2. Designed as a multi-centre to represent the whole population
3. The availability of patient follow-up data over a medium period of time

The limitations of our study include its retrospective design**,** the absence of routine forearm DEXA measurements which may have led to underestimation of osteoporosis prevalence, the systematic exclusion of past stone passage history in nephrolithiasis assessment, the heterogeneous nature of the followed patient group including patients who refused surgery despite indications, and the lack of FRAX score calculations due to retrospective data collection limitations.

Conclusions

There are still many unanswered questions about how to manage patients with asymptomatic PHPT. Hypertension, diabetes mellitus, and cardiovascular disease were found to be more prevalent in this patient population compared to the general population in this study of 804 patients from 27 centres across Turkey. The significant associations between hypomagnesemia and hypophosphatemia with osteoporosis suggest that routine measurement of these parameters should be considered in PHPT management, particularly in patients at high risk for skeletal complications. The pronounced increase in cardiovascular disease observed during the follow-up period may have implications for future surgical indication criteria. Similarly, the notable decline in GFR over time may require future guidelines to reconsider the current surgical threshold of <60 mL/min. Future studies incorporating comprehensive BMD evaluation including forearm measurements and detailed assessment of mineral metabolism parameters may lead to a revision of the surgical indications in the management of aPHPT.

Data availability

No datasets were generated or analysed during the current study.

Author contributions İ.E., M.M.T., data collection, data analysis, writing of original draft, supervision, writing-review and editing. All authors data collection, and editing. All authors approved the final version of the paper.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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