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Hormone and Metabolic Research

2026

10.1055/a-2812-1864

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Georg Thieme Verlag KG,
Oswald-Hesse-Straße 50,
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ISSN 0018-5043

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Original Article: Endocrine Care

The Fate of Normocalcemic Hyperparathyroidism: Insights from a 3-Year Multicenter Follow-Up

Mazhar Müslüm Tuna[1], Berçem Ayçiçek[2], İsmail Engin[1], Asena Gökçay Canpolat[3], Yusuf Kır[4], Ceren Tufan[5], Ekin Yiğit Köroğlu[6], Kenan Sakar[7], Ahmet Görgel[8], Dilek Kılınç Candemir[9], Yudum Yaprak Usda Konak[10], Mustafa Aydemir[11], Mustafa Şahin[3], Neşe Ersöz Gülçelik[4], Ersen Karakiliç[5], Bekir Çakir[6, 12], Gülhan Akbaba[7], Süleyman Baldane[8], Faruk Kilinç[9], Cüneyt Bilginer[10], Ramazan Sari[11]

Affiliation addresses are listed at the end of the article.

ABSTRACT

Normocalcemic primary hyperparathyroidism is thought to be an early form of hypercalcemic primary hyperparathyroidism. However, some studies have shown progression to hypercalcemia, hypercalciuria or kidney stones, bone loss and fractures in a proportion of patients over time, whereas other studies have not observed such outcomes. The aim of this study was to investigate the clinicopathological features and natural history of the disease in a large patient population and to provide clinicians with strong evidence-based recommendations. This is a nationwide, multicenter, observational, retrospective cohort study. Tertiary healthcare endocrinology departments were the setting for this study. Data from different regions of Turkey, including 527 patients, were included in this study. A total of 123 patients were not eligible for inclusion, and the remaining 404 patients were included in the final analysis. All laboratory assessments, dual-energy X-ray absorptiometry and renal ultrasound were performed locally at each center at baseline and several times during follow-up. The mean age was 54.63 ± 11.41 years. As expected, there was a female predominance of 362 (89.4 %). A total of 376 patients were followed up for 1 year and 252 patients for 3 years. Forty-seven out of 404 patients (11.6 %) developed hypercalcemia within 3 years. Twenty-eight patients became hypercalcemic within the 1st year, and 19 patients became hypercalcemic within 3 years. Among the 47 patients, only four patients had a calcium level above 11 mg/dL during the follow-up. Nephrolithiasis was detected in 50 patients (12.6 %). There was no significant difference in calcium, parathyroid hormone, 25-hydroxyvitamin D, or urinary calcium levels or the presence of nephrolithiasis. Bone mineral density assessments revealed that only 90 patients (28.5 %) had normal bone mineral density. A total of 135 (42.7 %) patients had osteopenia, and 91 (28.8 %) patients had osteoporosis at least one site at presentation. This study revealed that patients with normocalcemic primary hyperparathyroidism have significant adverse skeletal outcomes, a slight increase in kidney stones. Only a small proportion of patients develop hypercalcemia, and the risk of developing significant hypercalcemia that would alter the patient's treatment management is much lower.

Keywords normocalcemic primary hyperparathyroidism, primary hyperparathyroidism, bone/calcium homeostasis, hyperparathyroidism, hypercalcemia

received December 09, 2025 | **accepted after revision** February 11, 2026 | **article published online** 2026

Bibliography Horm Metab Res **DOI** 10.1055/a-2812-1864 **Art ID** HMR-2025-12-0519
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Correspondence Dr. Mazhar Müslüm Tuna, Department of Endocrinology and Metabolism, The University of Health Sciences, Umraniye Training and Research Hospital, Umraniye, Turkey, Email: mazharmuslum.tuna@sbu.edu.tr

Introduction

Normocalcemic primary hyperparathyroidism (NPHPT) was first described two decades ago in patients who had undergone extensive investigations for osteoporosis, low-trauma fractures and/or low bone mass, etc. Subsequently, NPHPT was recognized as part of the diagnostic spectrum of primary hyperparathyroidism (PHPT) at the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008.[1] Further characterizations and diagnostic recommendations were defined at the Fourth International Workshop in 2014.[2] NPHPT is characterized by persistently normal albumin-adjusted serum total and ionized calcium levels, accompanied by elevated parathyroid hormone (PTH) levels on at least two consecutive measurements over a period of 3–6 months. To make this diagnosis, all secondary causes of hyperparathyroidism must be ruled out. PHPT is often characterized by fluctuating serum calcium levels in the upper-normal and above-normal ranges; a single calcium measurement in the upper-normal range with high PTH should be interpreted as suspicious for PHPT rather than NPHPT. Many studies have relied on single measurements of serum calcium and PTH, leading to much confusion about the true prevalence and clinical impact of NPHPT. This condition appears to be relatively rare, with most studies using established criteria reporting a prevalence of 0.1–0.7 %.[3] The pathophysiology and etiology of NPHPT are still unclear. Among the various hypotheses, the most widely accepted concept is that NPHPT is an early form of hypercalcemic PHPT.[4] In addition, aging,

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menopause, low calcium intake, low free 25-hydroxyvitamin D levels, partial resistance to PTH and altered parathyroid sensing have been suggested as possible drivers of pathogenesis.[4,5] In population-based studies, the risk of bone or renal complications has not been increased compared with that in the general population. However, reports from small cohorts in referral centers have identified cases of NPHPT with a significant rate of osteoporosis, low-trauma fractures and renal complications.[4,6] This discrepancy is largely due to selection bias. This is because PTH is rarely measured in the presence of normocalcemia and is usually measured in the presence of a complication such as osteoporosis or renal stones. Some studies have shown progression to hypercalcemia, hypercalciuria or kidney stones, bone loss and fractures in a proportion of patients over time, whereas other studies have not observed such outcomes. There are no consistent data on the natural history of this disease. This is largely due to the small number of cases and the inadequate exclusion of all secondary causes of hyperparathyroidism in some studies. The fact that the studies reported in the literature were conducted with small cohorts prevents the generalization of the findings to the NPHPT cohort. Furthermore, longitudinal data on NPHPT patients to support definitive management guidelines are lacking.

Our aim was to investigate the clinicopathological features and natural history of this disease in a large population of patients in a multicenter setting and provide strong evidence-based recommendations to clinicians.

Materials and methods

This was a nationwide, multicenter, observational, retrospective cohort study.

All the endocrinology departments of tertiary healthcare institutions in our country were invited to participate in the study. The inclusion criteria for the centers were a sufficient number of patients with NPHPT, those diagnosed carefully according to guidelines and followed up for at least 1 year and regularly monitored for complications. Centers with a small number of cases or insufficient follow-up time periods were excluded. Data were collected for each patient until the patient underwent parathyroidectomy or initiation of medical treatment for osteoporosis or was lost to follow-up for any reason. Data from NPHPT patients were collected retrospectively from centers in Turkey from June 2024 to December 2024. All laboratory parameters were measured locally at each center at baseline and several times during the follow-up. Data management and albumin correction of calcium levels, the calcium/phosphorus (Ca/P) ratio, the Wisconsin index (WIN) and the parathyroid function index (PFindex) were calculated at the coordinating study center (Umraniye Training and Research Hospital). The WIN was defined as the combination of preoperative serum calcium with the preoperative PTH.[7] The PFindex was defined as multiplying the preoperative serum calcium level with the preoperative PTH level and dividing the value by the phosphate level.[8] Demographic and clinicopathological factors such as age, sex and laboratory results were obtained from the patients' medical records. Standard initial biochemical tests included simultaneous fasting serum calcium, phosphorus, PTH, 25-hydroxyvitamin D3, albumin, creatinine, and 24-hour urine calcium and creatinine levels. The PTH was measured via an intact PTH assay (chemiluminescence immunoassay using an Immulite 2000). The plasma 25-OH vitamin D concentration was measured via radioimmunoassay. Two different cutoff values for vitamin D deficiency were used in the literature to exclude secondary hyperparathyroidism. The 20 ng/mL (50 nmol/L) cutoff was supported by the Institute of Medicine (IOM) report and the guidelines of the Fourth International Workshop.[9,10] The 30 ng/mL (75 nmol/l) cutoff was supported by the European Society of Endocrinology Expert Consensus.[11] In our study, 25-OH vitamin D deficiency was defined as a 25-OH vitamin D level of ≤ 20 ng/mL, which is consistent with the IOM definition. Serum calcium was adjusted for hypoalbuminemia and hyperalbuminemia via the formula (serum calcium + 0.8 × [4 − albumin]). NPHPT was defined as persistently elevated PTH levels with normal albumin-adjusted serum calcium and excluding conditions associated with secondary hyperparathyroidism, including renal insufficiency (creatinine clearance, < 60 mL/min), vitamin D deficiency (25-hydroxyvitamin *D*, ≤ 20 ng/mL), inadequate calcium intake or calcium malabsorption, idiopathic hypercalciuria, and medications, including loop diuretics, thiazide diuretics, lithium, bisphosphonates, and denosumab.[12–14]

Renal ultrasound was performed by an experienced radiologist at each center. The determination of nefhrolitiasis was made by ultrasound examination rather than history.

Dual-energy X-ray absorptiometry was used to measure bone mineral density (BMD) at the lumbar spine (L1–L4), total hip and femoral neck. Repeat measurements were made with the same machine at each center.

End points

Parathyroidectomy

In the absence of sufficient data to support accepted surgical criteria, experts generally consider surgery if one or more of the indications used for asymptomatic PHPT are met.

The Fourth International Workshop for the Management of Asymptomatic PHPT recommended parathyroidectomy for NPHPT if the patient develops disease progression (e.g., worsening BMD) or new symptoms (e.g., fractures and kidney stones), very similar to hypercalcemic patients.[2] Similarly, the American Association of Endocrine Surgeons guidelines recommend surgery in symptomatic patients without distinguishing between hypercalcemic and NPHPT.[15] Surgical indications for NPHPT in our cohort included age < 50 years, an increase in calcium level of more than 1 mg/dL above the upper limit of normal during the follow-up, nephrolithiasis, a reduced estimated glomerular filtration rate(eGFR) of < 60 mL/minute, osteoporosis, and a history of nontraumatic fractures in accordance with the aforementioned guidelines.

Antiresorptive therapy

Patients who developed osteoporosis or new fractures during the follow-up were started on antiresorptive treatment at the discretion of the treating physician.

Ethics statement

The study protocol was reviewed and approved by the local ethics committee of Umraniye Training and Research Hospital (13.06.2024, 246507947). This study was conducted in accordance with the

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principles of the Declaration of Helsinki. Informed consent was not needed because of the retrospective nature of the study.

Statistical analyses

Group conformity to a normal distribution was analyzed via the Kolmogorov–Smirnov test and the Shapiro–Wilk test. Changes in non-normally distributed data among the three groups were analyzed via Friedman's test, and multiple comparisons were examined via Dunn's test with Bonferroni's correction. Changes in categorical data between times were investigated via the Cochran's *Q* test for three-time two-category data, the McNemar test for two-time two-category data, and the Friedman two-way analysis of variance for the ordinal variable test for three-time three-category data (MacFarland, T.W., Yates, J.M. 2016). When comparing categorical data according to the hypercalcemia status, the chi-square test was used when all expected values were greater than 5, and Fisher's exact test was used if any of the expected observations were less than 5 (Howell, 2011). Multiple comparisons of proportions were examined via the Bonferroni-corrected *Z* test. Factors influencing hypercalcemia status were examined via logistic regression analysis. Diagnostic skills for the presence of hypercalcemia were assessed by receiver operating characteristic (ROC) analysis. The results of the analyses are presented as the mean ± standard deviation, median (minimum–maximum) for quantitative data and frequency (percentage) for categorical data. The significance level was considered $p < 0.05$ in all calculations. IBM SPSS 26 software was used for all calculations and analyses (IBM Corp. Released 2019).

Results

Study population

Data from different regions of Turkey, representing the whole country, including 527 patients, were included in this study. Prior to data processing and statistical analysis, further secondary evaluation of patient eligibility was performed at the coordinating study center. A total of 123 patients were ineligible for inclusion for the following reasons. Fifty-four patients were excluded because of bisphosphonate use prior to the recruitment. Six patients had an eGFR of less than 60 mL/minute. A total of 42 patients had a 25-hydroxyvitamin D level of less than 20 ng/mL. Ten patients were normocalcemic with normal PTH at the follow-up, indicating previous secondary hyperparathyroidism. Eleven patients with a corrected calcium level between 10 and 10.2 mg/dL were excluded from the study to avoid confusion in the diagnosis of NPHPT. The remaining 404 patients were included in the final analysis. The mean age was 54.63 ± 11.41 years. As expected, there was a female predominance of 362 (89.4 %). A total of 376 patients were followed up for 1 year. After the 1st year, 49 patients underwent parathyroidectomy and 59 patients started antiresorptive treatment. A total of 252 patients were followed up for 3 years. At the time of the study, the remaining patients had not yet completed the 3-year follow-up period.

Demographics, laboratory parameters and BMD measurements at baseline and changes over time are shown in **Table 1**.

The corrected calcium levels of the patients significantly changed over time ($p < 0.001$). This change was observed between

Table 1 The change of laboratory parameters and BMD over time

	Baseline ($n = 404$)	1 y ($n = 376$)	3 y ($n = 252$)	*p*
Total calcium (8.5–10.2 mg/dl)	9.7 (8.5–10.7)[a]	9.7 (8.6–11.5)[a,b]	9.79 (8.7–11)[b]	0.016
Albumin (3.5–5.2 g/dL)	4.4 (3.6–5.3)[a]	4.4 (2.8–5.5)[b]	4.4 (2.6–5.3)[b]	< 0.001
Corrected calcium (8.5–10.2 mg/dL)	9.3 (8.0–10)[a]	9.4 (8.1–11.1)[b]	9.56 (8.2–10.9)[b]	< 0.001
Phosphorus (2.5–4.5 mg/dL)	3.1 (1.2–5.4)[a]	3.1 (1.4–7.7)[ab]	3.4 (1.3–5)[b]	0.002
Calcium/phosphorus	3 (1.8–6.9)	3 (1.2–7.3)	2.7 (1.9–8.2)	0.160
PTH (15–65 pg/mL)	103 (65–321)[a]	101 (46–351)[a]	98 (65–267)[b]	< 0.001
25-Hydroxyvitamin D (ng/mL)	31 (20–150)[a]	30 (3–115)[b]	28 (7–81)[b]	< 0.001
Creatinine (0.5–0.9 mg/dL)	0.7 (0.3–1.2)	0.7 (0.3–1.6)	0.7 (0.4–1.5)	0.358
eGFR (mL/min/1.73 m^2)	94 (60–145)[a]	90 (42–152)[b]	90 (48–118)[b]	< 0.001
Alkaline phosphatase (35–105 U/L)	83 (12–243)	81 (12–225)	80 (40–166)	0.830
Magnesium (1.6–2.6 mg/dL)	2 (0.7–2.8)	2 (0.7–2.7)	2 (0.7–2.6)	0.460
Sodium (mEq/L)	140 (132–146)	140 (130–145)	139 (130–145)	0.830
Potassium (mEq/L)	4.3 (3.2–5.7)	4.3 (3.1–5.6)	4.3 (3.2–5.5)	0.430
Chloride (mEq/L)	104 (94–117)	104 (87–116)	103 (90–109)	0.318
Urine calcium (mg/24 h)	189 (26–735)	210 (10–736)	213 (50–440)	0.839
Urine creatinine (mg/24 h)	988 (23–2184)	1010 (32–2201)	862 (55–1800)	0.588
BMD L1–L4 *T* score	−1.4 (−5.1–2.6)	−1.7 (−5–2)	−1 (−3.3–1.6)	0.624
BMD total hip *T* score	−0.7 (−3.6–3.7)	−0.85 (−4.2–2.2)	−0.6 (−2.8–2.2)	0.869
BMD femoral neck *T* score	−0.8 (−3.6–3.6)	−1 (−3.8–3)	−0.9 (−3.1–1.4)	0.050

Abbreviations: BMD, bone mineral density; eGFR, estimated glomerular filtration rate; *f*: Friedman's test; PTH, parathyroid hormone.
[a,b]There are no differences between groups with the same letter (Dunn's test with Bonferroni's correction), median (minimum–maximum).

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Table 2 Comparison of baseline clinical and demographic parameters between individuals who remained normocalcemic and those who became hypercalcemic

	Persistently normocalcemic *N*: 357 (88.4 %)	Patients who became hypercalcemic *N*: 47 (11.6 %)	Total (*n* = 404)	*p*
Age (y)	54.6 ± 11.3	54.3 ± 11.7	54.6 ± 11.4	0.854[t]
Gender				
Female	323 (90.2)	39 (83)	362 (89.4)	0.134[e]
Male	35 (9.8)	8 (17)	43 (10.6)	
Nephrolithiasis	40 (11.5)	10 (21.3)	50 (12.6)	0.064[e]
BMD				
Normal	81 (28.8)[a]	9 (25.7)[a]	90 (28.5)	0.004[e]
Osteopenia	112 (39.9)[a]	23 (65.7)[b]	135 (42.7)	
Osteoporosis	88 (31.3)[a]	3 (8.6)[b]	91 (28.8)	
Total calcium (mg/dL)	9.6 (8.5–10.7)	9.9 (8.7–10.7)	9.7 (8.5–10.7)	< 0.001[m]
Albumin (mg/dL)	4.1 (3.6–5.3)	4 (3.7–5.3)	4 (3.6–5.3)	0.342[m]
Corrected calcium (mg/dL)	9.3 (8–10)	9.4 (8.4–9.9)	9.3 (8–10)	0.004[m]
Phosphorus (mg/dL)	3.1 (1.2–5.4)	2.9 (1.7–4.2)	3.1 (1.2–5.4)	0.013[m]
Calcium/phosphorus	2.9 (1.8–6.9)	3.2 (2.1–5.4)	3 (1.8–6.9)	0.003[m]
PTH (pg/mL)	102(65–321)	107 (68–293)	103 (65–321)	0.274[m]
PFindex	311 (127–1260)	427 (183–1145)	318 (127–1260)	0.007[m]
WIN	957 (565–3152)	1046 (641–2496)	965 (565–3152)	0.100[m]
25-Hydroxyvitamin D (ng/mL)	31 (20–150)	30 (22.5–56)	31 (20–150)	0.726[m]
Creatinine (mg/dL)	0.7 (0.3–1.1)	0.7 (0.5–1.1)	0.7 (0.3–1.1)	0.145[m]
eGFR (mL/min/1.73 m^2)	94 (60–145)	94 (60–132)	94 (60–145)	0.734[m]
Alkaline phosphatase (U/L)	83 (29–243)	78 (12–192)	83 (12–243)	0.246[m]
Magnesium (mg/dL)	2 (0.7–2.8)	2 (1.3–2.4)	2 (0.7–2.8)	0.924[m]
Sodium (mEq/L)	140 (132–146)	139 (134–144)	140 (132–146)	< 0.001[m]
Potassium (mEq/L)	4.3 (3.2–5.7)	4.3 (3.5–5.3)	4.3 (3.2–5.7)	0.910[m]
Chloride (mEq/L)	104 (97–137)	105 (94–114)	104 (94–137)	0.296[m]
Urine calcium (mg/24 h)	194 (26–735)	175 (35–597)	190 (26–735)	0.403[m]
Urine creatinine (mg/24 h)	984 (23–2054)	1012 (207–2184)	987 (23–2184)	0.429[m]
BMD L1-L4 *T* score	− 1.4 (− 5.1–2.6)	− 1.05 (− 2.9–1.7)	− 1.4 (− 5.1–2.6)	0.033[m]
BMD total femur *T* score	− 0.7 (− 3.6–3.7)	− 0.8 (− 2.4–2)	− 0.7 (− 3.6–3.7)	0.926[m]
BMD Femoral Neck T Score	− 0.82 ± 1.18	− 0.57 ± 1.41	− 0.79 ± 1.21	0.356[t]

Abbreviations: BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PFindex, parathyroid function index; PTH, parathyroid hormone; WIN, Wisconsin index.
[t]Independent sample *t* test, [m]Mann–Whitney *U* test, [e]Fisher's exact test, [a,b]There are no differences between groups with the same letter (the *Z* test with Bonferroni's correction), median (minimum–maximum), mean ± standard deviation, and *n* (%).

the values obtained at baseline and the values obtained at year 3. After patients who developed hypercalcemia were excluded, the calcium levels tended to increase, although they remained within the normal range. The mean corrected calcium level was 9.3[8–10] mg/dL at baseline, increasing to 9.42 (8.06–10.18) mg/dL at year 1 and 9.42 (8.24–10.18) mg/dL at year 3 ($p = 0.004$).

In our cohort, only 47 out of 404 patients (11.6 %) developed hypercalcemia within 3 years. Twenty-eight patients became hypercalcemic within the 1st year, and 19 patients became hypercalcemic within 3 years. Among the 47 patients, only four patients had a calcium level above 11 mg/dL during the follow-up. Patients who became hypercalcemic had higher total calcium and lower phosphorus levels than patients who remained normocalcemic. The baseline clinical and demographic parameters of these patients are shown in **Table 2**. Patients were divided into three categories with regard to calcium levels. Ninety-four patients had calcium levels between 8 and 9 mg/dL. Only four of these patients (one with a calcium level of 8.4 mg/dL at baseline) progressed to hypercalcemia (4.2 %). A total of 162 patients had calcium levels between 9 and 9.5 mg/dL, and 20 of these patients progressed to hypercalcemia (12.3 %). A total of 126 patients had calcium levels

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Table 3 Investigation of some initial characteristics according to vitamin D levels

	25-Hydroxyvitamin D level		*p*
	20 to 30 ng/mL, *n* = 149 (%)	> 30 ng/mL, *n* = 242(%)	
Age (y)	54.67 ± 12.6	54.58 ± 10.74	0.941
Gender			
Female	137 (91.9)	213 (88)	0.218
Male	12 (8.1)	29 (12)	
Kidney stone	19 (13)	28 (11.9)	0.740
BMD			
Normal	28 (24.6)	59 (30.9)	0.250
Osteopenia	55 (48.2)	74 (38.7)	
Osteoporosis	31 (27.2)	58 (30.4)	
Progression to hypercalcemia			
Persistently normocalcemic	133 (89.3)	211 (87.2)	0.541
Patients who became hypercalcemic	16 (10.7)	31 (12.8)	

Abbreviation: BMD, bone mineral density.

between 9.5 and 10 mg/dL, and 21 of these patients progressed to hypercalcemia (16.6 %).

Hypophosphatemia (a phosphorus level of less than 2.4 mg/dL) was found in 67 patients (16.5 %). Among the patients, 15 patients progressed to hypercalcemic PHPT (22.3 %), whereas 11.6 % of patients progressed to hypercalcemic PHPT in the overall cohort.

Magnesium was measured at baseline in 344 patients. The magnesium levels were normal in all but one patient.

Patients were divided into four categories with respect to urinary calcium levels (patients with 24-h calcium levels of less than 100, 100–300, and 300–400 mg/d and more than 400 mg/d). No difference was found among the four groups in terms of progression to hypercalcemia.

Patients were divided into two categories with regard to PTH levels (patients with PTH levels below 100 pg/mL and patients with PTH levels above 100 pg/mL). There was no difference in the rate of progression to hypercalcemia between the two groups (10.5 % and 12 %, respectively).

As defined in the inclusion criteria, all patients had 25-hydroxyvitamin D levels above 20 ng/mL; 63.2 % of the cohort had a level of 30 ng/mL or greater. We evaluated whether there was a difference in the presence of complications and progression to hypercalcemia between patients with vitamin D levels between 20 and 30 and patients with vitamin D levels above 30. No significant difference was found between vitamin D levels and either complications or progression to hypercalcemia (**Table 3**).

Nephrolithiasis was detected in 50 patients (12.6 %). There were no significant differences in calcium, PTH, 25-hydroxyvitamin D, or urinary calcium levels or the presence of nephrolithiasis.

Table 4 Patients developing new manifestations of primary hyperparathyroidism over time

	1 y (*n* = 376)	3 y (*n* = 252)
Progression to hypercalcemia (*n* = 47)	28	17
Kidney stone (*n* = 8)	6	2
Parathyroidectomy	49	9
Medical therapy bisphosphanat/denosumab	39/20	– /2

Table 5 Results of ROC analysis of factors influencing the development of hypercalcaemia

	AUC (95 % CI)	*p*	Cut-off	Sensitivity (%)	Specificity (%)
Total calcium (mg/dL)	0.660 (0.577–0.743)	0.001	≥ 9.8	70.21	59.66
Corrected calcium (mg/dL)	0.634 (0.553–0.715)	0.004	≥ 9.44	62.22	61.47
Calcium/phosphorus	0.635 (0.554–0.715)	0.003	≥ 3.65	44.44	79.65
PTindex	0.624 (0.541–0.708)	0.007	≥ 342.7	66.67	59.59
Phosphorus (mg/dL)	0.611 (0.527–0.695)	0.013	≤ 2.5	40.43	82.54

Abbreviations: AUC, area under the curve, CI, confidence interval; ROC, receiver operating characteristic.

Using the World Health Organization criteria for the diagnosis of osteoporosis, the BMD assessment revealed that only 90 patients (28.5 %) had normal BMD. A total of 135 (42.7 %) patients had osteopenia, and 91 (28.8 %) patients had osteoporosis at least one site at presentation.

The development of new complications such as worsening BMD, nephrolithiasis and hypercalcemia during the follow-up period is shown in **Table 4**. The results of the ROC analysis of factors influencing the development of hypercalcemia are shown in **Table 5**.

Discussion

The impact of different Vitamin D thresholds on complication associations in NPHPT

Normocalcemic hyperparathyroidism is a diagnosis of exclusion. To make this diagnosis, it is necessary to rule out vitamin D deficiency, which is the most common cause of secondary hyperparathyroidism. Although both cutoff values (20 and 30 ng/mL) have been used in different studies in the literature, it is not clear at which level of vitamin D deficiency PTH levels begin to increase. It is generally known that PTH increases at levels below 20 ng/mL. However, it should be noted that there may be individual varia-

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tions. While some studies have shown that PTH does not increase in vitamin D insufficiency (a 25 OH vitamin level between 21 and 29 ng/mL), other studies have shown the opposite results. Yalla et al. reported similar upper reference limits for PTH in vitamin D categories between 20 and 30 ng/mL and above 30 ng/mL (60.4 and 58.6 pg/mL, respectively, compared with 86.4 pg/mL for vitamin D ≤ 20 ng/mL). These findings suggest that clinically significant increases in PTH are observed in vitamin D deficiency rather than vitamin D insufficiency.[16] On the other hand, many reports and meta-analyses have concluded that the serum PTH concentration may still be elevated in some individuals when their 25OHD concentration is less than 30 ng/mL, and decreases when these individuals are given vitamin D.[17–20] Our study found no significant difference in the incidence of skeletal and renal complications, or progression to hypercalcaemia, when either cut-off was used.

Skeletal and renal complications

With regard to the skeleton, bone pain, osteopenia, osteoporosis and fragility fractures may be observed. The development of bone disease in NPHPT can be attributed to several mechanisms. One such mechanism is the effect of the NPHPT on bone quality, which leads to changes in the microarchitecture and composition of the bone tissue and subsequently increases the risk of fracture.[21] In addition, imbalances in calcium and vitamin D metabolism, as well as abnormalities in other hormones involved in bone metabolism, may also contribute to the development of osteopenia in NPHPT.[14] To date, population-based studies have shown either no evidence or little evidence of significant bone or renal complications. Patients with NPHPT who have low bone density, osteoporosis or low-trauma fractures have mostly been reported in small cohorts in selected referral centers, and the number of cases of NPHPT has been limited. Most of these studies had limitations of power, such as very small sample sizes and diagnoses based on a single determination of laboratory values and a lack of eGFRs in some studies. The prevalence of osteoporosis in NPHPT patients is variable, ranging from as low as 15 % to as high as 57 %.[21] Fragility fractures appear to have similar variable rates, occurring in 11–21 % of subjects diagnosed with NPHPT.[22] The study by Siprova and colleagues assessed bone density in 137 patients with NPHPT. Among these patients, 42 % were described as having reduced bone density, without specifying whether they had osteopenia or osteoporosis.[23] Yankova et al. reported a similar prevalence of osteoporosis between hypercalcemic and NPHPT. The study included 316 patients (277 women and 39 men, mean age 58.7 ± 12.1 y) diagnosed with PHPT. The frequency of NPHPT was 15.2 %. Osteoporosis was present in 41.7 % of the patients with NPHPT and 44.7 % of the patients with hypercalcemic PHPT ($p = 0.575$). No significant difference in BMD or the frequency of low-energy fractures was found between hypercalcemic PHPTs and NPHPTs.[24] Armstrong et al. reported that 58.8 % (20 of 39 patients) of the subjects confirmed with NPHPT had osteoporosis, whereas 37.7 % (93 of 340 patients) of the hypercalcemic subgroup had osteoporosis ($p = 0.19$).[25] Voss et al. reported a prevalence of 53.8 % in NPHPT patients (7 of 13 patients) versus 57.1 % in hypercalcemic PHPT patients (4 of 7 patients; $p = 0.848$).[26] Burcak S reported that, in the NPHPT group, 40 of 101 patients had osteoporosis (T score, < − 2.5 in one of three areas), and 32 had osteopenia. In the hypercalcemic group, 102 patients had osteoporosis, and 73 patients had osteopenia out of 217 patients. There was no significant difference in the prevalence of osteoporosis between the two groups.[27] However, in this study, only patients who had at least one indication for surgery were enrolled; this bias may have led to an overestimation of the true prevalence. In our study, the prevalence of osteoporosis was 28.8 %, that of osteopenia was 42.7 %, and 59 patients developed osteoporosis during the 3 years of follow-up. Approximately one-third of patients with normal BMD and osteopenia lost more than 10 % of their BMD within the 1st year and between years 1 and 3. Taken together, these findings suggest that NPHPT is at least as important as typical PHPT with respect to bone. Notably, since PTH is not routinely measured in patients without osteoporosis, the picture we see looks worse than it is.

In contrast to adverse effects on bone health, nephrolithiasis is infrequently observed in patients diagnosed with NPHPT and is generally less common. There is a lack of consistent data on the outcomes of patients with NPHPT and nephrolithiasis. The etiology of nephrolithiasis in patients with NPHPT remains uncertain, in contrast to the established association between hypercalcemic PHPT and kidney stone formation. A study by Siprova and colleagues suggested that nephrolithiasis was more common in patients with hypercalcemic PHPT, with 22 % reported to have kidney stones, whereas only 4 % of NHPT patients had nephrolithiasis.[23] Yankova et al. reported a similar prevalence of nephrolithiasis between hypercalcemic and NPHPT patients (33.5 % vs 27.1 %, $p = 0.386$).[24] Armstrong et al reported a prevalence of nephrolithiasis in 35.9 % of patients with NPHPT and 24.6 % of patients with hypercalcemic PHPT.[25] In another study, 22 of 95 (21.7 %) patients with NPHPT and 58 of 212 (26.7 %) patients with hypercalcemic PHPT were found to have kidney stones on ultrasound. The prevalence of nephrolithiasis was similar between the two groups ($p = 0.721$).[27] In our study, the prevalence of nephrolithiasis was 12.4 %. The rates of nephrolithiasis in patients with NPHPT have varied in the literature, ranging from 4 % to 35 %.[25] An important reason for this wide range is related to the characteristics of the population studied. PTH measurements are made more frequently in patients with recurrent nephrolithiasis or osteoporosis. Therefore, the rate is higher in NPHPT cohorts when complications are investigated. There is certainly potential for selection bias in the extensive screening of patients with a history of recurrent kidney stones. Nevertheless, given that 7–10 % of the population experiences nephrolithiasis, it appears that patients with NPHPT are more prone to developing it.

Progression to hypercalcemia

Few data are available concerning the course of NPHPT; a minority of patients progress to develop overt hypercalcemia, but it is impossible to predict who will progress or when. The group from the Czech Republic followed the 187 patients with NPHPT for 1–7 years. Among these patients, 151 (81 %) patients remained normocalcemic and 36 (19 %) patients became hypercalcemic within 6 years. Twenty-four (67 %) patients became hypercalcemic within 2 years, 10 (28 %) patients within 2–4 years, and 2 (5 %) patients within 4–6 years.[23] The study by Schini and colleagues summarized the available literature on the natural history of biochemical changes in NPHPT. This review revealed highly variable rates of progres-

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sion from NPHPT to classic PHPT, ranging from 0 to 19 %, making it difficult to draw definitive conclusions. The reasons for this wide range may include misdiagnosis at baseline on the basis of single biochemical measurements, an insufficient follow-up period or selection bias.[28] Our study found that 11.6 % (n = 47) of patients developed hypercalcemia within 3 years, which is consistent with the literature. High calcium levels, calcium/phosphorus ratios, PFindices and low phosphorus levels were found to be independent predictors of progression, whereas PTH, 25-hydroxyvitamin D and urinary calcium were not.

Strengths and limitations

The strongest aspects of our work are as follows:

1. This study included the largest number of NPHPT patients to date.
2. Designed as a multicenter to represent the whole population.
3. In contrast to many studies, the diagnosis of NPHPT was made by repeated calcium and PTH measurements several times.
4. The availability of patient follow-up data over a medium period of time.
5. To the best of our knowledge, this is the first study to compare the incidence of complications and progression to hypercalcemia between the two cutoff values for vitamin D deficiency.

Our study has several limitations. First, in this retrospective study, ionized calcium values were not measured in the majority of patients. Corrected calcium values are used to diagnose NPHPT, as ionized calcium is not widely used in clinical practice. Second, idiopathic hypercalciuria was not properly excluded by a thiazid challenge test. However, the majority of patients who were initially hypercalciuric had a radiological diagnosis, and some were normocalciuric at the follow-up.

Conclusions

This study revealed that patients with NPHPT have significant adverse skeletal outcomes, a slight increase in kidney stones. Only a small proportion of patients develop hypercalcemia, and the risk of developing significant hypercalcemia that would alter the patient's treatment management is much lower.

Author Affiliations

1 Department of Endocrinology and Metabolism, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Türkiye
2 Department of Endocrinology and Metabolism, Istinye University, Faculty of Medicine, Istanbul, Türkiye
3 Department of Endocrinology and Metabolism, Ankara University, Faculty of Medicine, Ankara, Türkiye
4 Department of Endocrinology and Metabolism, University of Health Sciences, Gulhane Training and Research Hospital, Ankara, Türkiye
5 Department of Endocrinology and Metabolism, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Türkiye
6 Department of Endocrinology and Metabolism, Ankara City Hospital, Ankara, Türkiye
7 Department of Endocrinology and Metabolism, Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Türkiye
8 Department of Endocrinology and Metabolism, Selcuk University, Faculty of Medicine, Konya, Türkiye
9 Department of Endocrinology and Metabolism, Firat University, Faculty of Medicine, Elazig, Türkiye
10 Department of Endocrinology and Metabolism, Karadeniz Technical University, Faculty of Medicine, Trabzon, Türkiye
11 Department of Endocrinology and Metabolism, Akdeniz University, Faculty of Medicine, Antalya, Türkiye
12 Department of Endocrinology and Metabolism, Ankara Yildirim Beyazit University, Faculty of Medicine, Ankara, Türkiye

Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

Acknowledgement Declaration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Funding: This research did not receive any specific grant from any funding agency in the public, commercial or non-for-profit sector.

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