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Research Article

Natural history and complications of normocalcemic hyperparathyroidism: a retrospective cohort study

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Abstract

Normocalcemic hyperparathyroidism (NHPT) is variably defined, and information regarding complications and natural history are scarce. We aimed to describe the phenotype of NHPT in relation to hypercalcemic hyperparathyroidism (PHPT) and controls, to determine risk of progression, and to develop a predictive model for progression to PHPT. This is a retrospective chart review of 232 patients at a tertiary medical center, comparing 75 controls, 73 patients with NHPT, and 84 with PHPT. NHPT was intermediate in biochemical profile between controls and PHPT with respect to cCa, iPTH, intraindividual coefficient of variant of cCa, phosphorus, and 25(OH)D. NHPT patients had an increased adjusted risk of urolithiasis (OR 5.34, 95%CI, 2.41-12.71, $P < .001$) and fragility fractures (OR 4.53, 95%CI, 1.63-14.84, $P = .006$) versus controls, after adjustment for age, sex, and BMI. Fewer NHPT compared with PHPTH patients achieved cure with parathyroidectomy ($P = .001$). NHPT more often had nonlocalizing imaging or polyglandular disease ($P = .005$). Parathyroidectomy improved biochemical but not BMD parameters in NHPT. Over a median follow-up of 4.23 (IQR 1.76-5.31) years, NHPT patients managed expectantly experienced no change in iPTH, and progression to PHPT occurred in 9%. An XGBoost model combining 6 factors for progression (mean index 2 iPTH, mean index 2 cCa, 24-h urinary calcium, age, 25(OH)D, and presence of urolithiasis) had an area under the curve 1.00 (95%CI, 1.00-1.00, $P < .001$) for predicting combined progression. NHPT is a mild variant of PHPT at intermediate risk of urolithiasis and fragility fractures. Cure was less often achieved with parathyroidectomy, which did not improve BMD parameters. Progression was infrequent with conservative management. Because only a minority progressed to PHPT, in addition to lower surgical success rates, we suggest conservative management for the majority of NHPT unless risk factors for progression are identified.

Keywords: NHPT, normocalcemic hyperparathyroidism, urolithiasis, parathyroidectomy, progression

Lay Summary

Normocalcemic hyperparathyroidism (NHPT) has variable definitions and its prognosis is not well-established, leading to uncertainties in management. We aimed to compare patients with NHPT with controls and patients with hypercalcemic hyperparathyroidism (PHPT). NHPT was intermediate in biochemistry between controls and PHPT and had increased odds of urinary tract stones (>5 times elevated) and fragility fractures (>4 times elevated) compared with controls. NHPT patients more often had nonlocalizing imaging studies or involvement of more than one parathyroid gland compared with PHPT, and less frequently achieved cure with parathyroid surgery. Parathyroidectomy only improved biochemistry but not bone mineral density. Over follow-up of 4.23 yr, only 9% of NHPT patients who did not undergo surgery progressed to PHPT. Factors predicting the risk of progression or requiring parathyroid surgery included baseline serum calcium and parathyroid hormone levels, urinary calcium excretion, age, vitamin D levels, and the presence of urinary tract stones. In conclusion, NHPT is a mild variant of PHPT. Cure is less often achieved with parathyroid surgery, and progression is infrequent without surgery. As such, we suggest watchful waiting for the majority of NHPT patients without risk factors for progression.

Introduction

Hypercalcemic primary hyperparathyroidism (PHPT) has well-recognized skeletal and renal complications, which may prompt diagnosis. Biochemistry panels with calcium and parathyroid hormone (PTH) levels are increasingly utilized for at-risk patients, giving rise to the detection of normocalcemic hyperparathyroidism (NHPT). This entity has a variable reported prevalence ranging from 0.18% to 8.9%.[1,2] This wide range is partly due to inconsistent diagnostic criteria for NHPT—not all studies include repeat measurements, use of ionized calcium, optimal estimated glomerular filtration rate (eGFR) or 25-hydroxyvitamin-D (25(OH)D) cut-offs, urinary calcium measurement, or considered medication use. Some studies have used an eGFR cut-off of <40 mL min^{-1} to exclude secondary hyperparathyroidism;[2,3] however, some evidence suggests that secondary PTH may occur at higher eGFR levels between 45 and 60 mL min^{-1}.[4] Studies with less stringent enrollment criteria may include patients with

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secondary hyperparathyroidism or classic PHPT, producing significant variability regarding complication and progression rates. For example, urinary stone and fracture prevalence are highly variable, ranging from 4% to 35% and 5% to 40%, respectively, according to the population selected.[5]

With the recent release of the Fifth International Workshop Guidelines, NHPT has been formally defined,[6] however detailed information on its natural history to guide management is still lacking. As skeletal and renal complications are frequently present at baseline, clinicians are faced with the uncertainty of whether these patients would benefit from surgery, as recommended in classical PHPT.[6] At least one study with long-term follow-up supports a conservative strategy given the low rate of progression.[7] To address some of these unanswered questions and conflicting evidence, we conducted a retrospective cohort study of NHPT patients with 6-yr follow-up and compared them to controls and patients with PHPT.

The aims of the study were 3-fold: (1) to establish the differences in phenotype of NHPT compared with PHPT and controls, (2) to determine the risk of progression and complications in NHPT with and without parathyroidectomy, and (3) to develop a predictive model for risk of progression in NHPT patients.

Materials and methods

Study design

This was a retrospective cohort study of patients with NHPT managed at Mayo Clinic, a tertiary medical center with 3 campuses across USA (Rochester, Florida, and Arizona). The electronic medical record was searched and patients were included if they had biochemistry for albumin-adjusted calcium (cCa) and intact PTH (iPTH) (measured within 3 d) between January 1, 2017 and January 7, 2023 with normal renal function (eGFR >60 mL min^{-1} measured within 7 d), and a BMD measurement performed within 12 mo of the index iPTH. As patients in all 3 groups including controls had cCa, iPTH, and a BMD performed at a tertiary center, this cohort represents patients at risk of skeletal and renal disease.

Patient identification and subgroup definition

NHPT was defined as normal cCa and elevated iPTH (paired measurement within 3 d of each other) on at least 2 occasions performed at least 3 mo apart, as per guidelines.[6] Patients with secondary hyperparathyroidism were excluded, including those with hypovitaminosis D (25(OH)D < 25 ng mL^{-1}), chronic kidney disease (CKD, eGFR < 60 mL min^{-1}), hypercalciuria (urinary calcium > 250 mg d^{-1} in women, >300 mg d^{-1} in men), malabsorption including celiac disease, history of bariatric surgery, thyrotoxicosis, use of diuretics and lithium, bisphosphonates within 2 yr, denosumab within 6 mo, significant glucocorticoid use within 2 yr, history of hyperparathyroidism or parathyroidectomy, organ transplant, liver disease, alcoholism, and metabolic bone diseases such as Paget's disease, osteogenesis imperfecta, or hypophosphatemic rickets. A cut-off 25(OH)D level of 25 ng mL^{-1} was chosen as intermediate between the Institute of Medicine and the Endocrine Society's definitions for Vitamin D insufficiency of 20-30 ng mL^{-1},[8,9] balancing the need for adequate sample size and significant rise in iPTH levels below a threshold of 24 ng mL^{-1}.[10] Another study found no discernable inflexion point for the rise of iPTH; hence, the intermediate threshold of 25 ng mL^{-1} acknowledges the controversies in optimal 25(OH)D levels.[11] As dietary calcium and vitamin D intake were often undocumented given the retrospective nature of the study, 24-h urinary calcium < 50 mg d^{-1} was taken to represent inadequate dietary intake[12,13] and these patients were also excluded. Patients without 24-h urine calcium studies were also excluded. While this cannot replace an accurate dietary history for calcium intake, the mandatory measurement of 24-h urine calcium as a surrogate and for the exclusion of idiopathic hypercalciuria may be considered superior to no evaluation at all in many other NHPT studies. NHPT patients were grouped into those with persistent normocalcemia and intermittent hypercalcemia,[1] defined by at least 1 elevated cCa reading.

PHPT was defined as elevated albumin-corrected calcium and elevated iPTH levels (paired measurement within 3 d of each other) on at least 2 occasions performed at least 2 wk apart.[6] For controls, only 1 set of normal albumin-adjusted calcium and normal iPTH taken within 3 d was required, and it was not compulsory to have 24-h urinary calcium studies, to avoid selection bias. Patients with intermittent hyper- or hypocalcemia, or intermittently high PTH, were excluded. For groups to be comparable, similar exclusion criteria as for NHPT were used for both PHPT and controls, such as the exclusion of secondary causes of hyperparathyroidism, secondary osteoporosis and recurrent cases after parathyroidectomy. In PHPT, the upper limit for 24-h urinary calcium was removed and a lower limit was set to <100 mg d^{-1} to exclude familial hypocalciuric hypercalcemia (FHH), which had a good negative predictive value of 95.2% for excluding FHH in one study.[14] PHPT patients were classified into 3 subgroups including symptomatic PHPT, asymptomatic PHPT with target organ involvement (TOI), and asymptomatic PHPT without TOI.[6]

Biochemical measurements

Serum total calcium, albumin, iPTH, phosphorus, 25(OH)D, creatinine, alkaline phosphatase (ALP), and 24-h urinary calcium were collected in the fasting state and measured by automated methods. cCa was calculated according to Payne's formula[15]: cCa (mg dL^{-1}) = measured total Ca (mg dL^{-1}) + 0.8 [4.25 – serum albumin (g dL^{-1})], and 4.25 g dL^{-1} was derived from the mid-point of our laboratory's reference range for serum albumin 3.5-5.0 g dL^{-1}. Up until recently, it was not routine to measure ionized calcium in outpatient clinics. In healthy ambulatory patients with normal renal function, the prevalence of abnormal pH and altered protein concentrations that significantly impact calcium homeostasis is likely to be low, hence albumin-corrected serum calcium values were deemed adequate for our study. The reference interval for serum albumin-corrected calcium is 8.8-10.2 mg dL^{-1}. iPTH was measured using a two-site chemiluminescent immunometric assay on the Roche Cobas (Roche Diagnostic) analyzer, with a reference range of 15-65 pg mL^{-1}. Intra-assay CVs are 5.3%, 2.2%, and 2.3% at 18, 199.6, and 614.25 pg mL^{-1}, respectively.

BMD

BMD was performed of the LS, TH, FN, and one-third distal radius (1/3DR) of the nondominant forearm. GE Lunar iDXA scanners were used at Rochester and Florida campuses. In Rochester, the scanner was replaced in May 2021, and least

significant change (LSC) changed from 0.028 to 0.051 g cm^{-2}, 0.033 to 0.024 g cm^{-2}, and 0.045 to 0.051 g cm^{-2} at the spine, hip, and radius, respectively. Machines were cross-calibrated at installation. In Florida, the corresponding LSCs were 0.028, 0.028, and 0.045 g cm^{-2}, respectively. The Hologic Horizon scanner was used at the Arizona campus, with LSCs of 4.9% for the LS and 6.3% for the FN. Fractured vertebrae were not measured. We used standard equations to generate standardized BMD values that were comparable across Lunar and Hologic DXA machines.[16-18]

$$\begin{aligned}&\text{Standardized FN}-\text{BMD(16)}\\&=\left[0.019+1.087^{*}\text{BMD (Hologic)}\right]\\&\quad\text{OR }\left[0.939^{*}\text{BMD (Lunar)}-0.023\right]\end{aligned}$$

$$\begin{aligned}&\text{Standardized TH}-\text{BMD(16)}\\&=\left[0.006+1.008^{*}\text{BMD (Hologic)}\right]\\&\quad\text{OR }\left[0.979^{*}\text{BMD (Lunar)}-0.031\right]\end{aligned}$$

$$\begin{aligned}&\text{Standardized LS}-\text{BMD(17)}\\&=\left[1.0755^{*}\text{BMD (Hologic)}\right]\\&\quad\text{OR }\left[0.9522^{*}\text{BMD (Lunar)}\right]\end{aligned}$$

$$\begin{aligned}&\text{Standardized DR}-\text{BMD(18)}\\&=\left[0.861^{*}\text{BMD (Hologic)}+0.020\right]\\&\quad\text{OR }\left[1.091^{*}\text{BMD (Lunar)}+0.119\right]\end{aligned}$$

Trabecular bone score (TBS), a texture-index derived from LS DXA images that provides information regarding microarchitecture independent of BMD, was measured from LS areal BMD examinations at Rochester campus using the TBS iNsight software version 3.0 (Medimaps, Merignac, France).

Data and outcome collection

Electronic health records were reviewed for past medical history to screen for exclusion criteria, treatment history, and complications including urolithiasis and fragility fractures. Imaging for localization of parathyroid adenoma was performed by scintigraphy, neck ultrasound, and/or 4D-CT as indicated. Urolithiasis was diagnosed by abdominal imaging, including radiographs, CT, MRI, and/or ultrasound. In the NHPT group, progression to hypercalcemic PHPT was defined as the mean of the last 2 cCa and mean of last 2 iPTH, both elevated above normal range. The combined progression outcome included both progression to hypercalcemic PHPT and requirement for parathyroidectomy.

Sensitivity analysis

In the primary analysis, the presence of urolithiasis was confirmed from imaging reports or the medical record. Because the proportion of patients who underwent abdominal imaging for evaluation of urolithiasis might have differed between groups, we conducted multiple sensitivity analyses that (1) excluded patients who did not have abdominal imaging performed in the preceding 10 yr prior to the index date of iPTH or during follow-up, (2) only considered the outcome of urolithiasis analysis to be positive if proven on imaging, and (3) excluded urolithiasis if diagnosed greater than 5 yr prior to the index iPTH, as the etiology of urolithiasis in the distant past may not be related to the current presentation.

Statistical analysis

Quantitative data were presented as mean (SD) for normally distributed data and median (interquartile range, IQR) for nonparametric data, and categorical data expressed as number (percentage). Numerical variables were tested for normalcy with the Shapiro–Wilk test. Missing data were assumed to be missing at random and omitted from the analysis. Between-group comparisons were made with one-way ANOVA, Kruskal–Wallis, Fisher's exact, and Chi-squared tests as appropriate. Before-after comparisons for parametric variables were analyzed with paired *t*-tests. Univariate and multivariate logistic models were fit to identify factors associated with urolithiasis and fragility fractures. Variables were inspected to ensure no significant collinearity (Variance Inflation Factors > 5). The statistical analyses utilized BlueSky Statistics software v.10.3 (Bluesky Statistics LLC, Chicago, IL, USA).

Prediction models for progression

In the NHPT group, the Cox proportional hazard model was used to estimate the hazard ratio (HRs) for progression, and a combined outcome of progression to hypercalcemic PHPT or requiring parathyroidectomy, checking for the proportional hazards assumption using Schoenfeld residuals and plotting. For the combined progression risk, the NHPT cohort was randomly split into 80% training and 20% test datasets to develop prediction models. Multivariable logistic regression was built on the training dataset, using only significant variables with $P < .1$ identified on the univariate analysis to derive the model with the best Akaike information criterion. Considering the limited dataset, only the 4 best predictors were selected to prevent overfitting, and 5-fold cross-validation was used to tune the model. Extreme gradient boosting (XGBoost), a machine-learning method available in BlueSky using the R software environment, is a gradient decision-tree boosting algorithm that successively refits a weak classifier based on errors in previous models.[19] Variables were ranked according to their relative contributions to the model. Considering both accuracy and overfitting, the initial parameters used were: number of boosting iterations = 5, max depth = 3, minimum child weight = 1, minimum delta-step = 1, learning rate = 0.1, gamma = 0, and objective = multi:softmax. Hypertuning of XGBoost parameters on the same training dataset with 5-fold cross-validation was subsequently used to optimize the accuracy of the final model. The performance of the logistic regression and XGboost models, including their area under the curve (AUC), accuracy, sensitivity, specificity, and kappa values were evaluated on both the training and test datasets.

Results

Prevalence

A total of 14 120 patients were identified on the database search as outlined in Study design section. All these patients

had a BMD measurement, normal renal function, and at least 1 set of cCa and iPTH. In the same period, there were 473 patients who fulfilled biochemical criteria for NHPT; detailed chart review identified 73 patients who met all criteria for the diagnosis of NHPT as defined above. A prevalence of 0.52% for NHPT was calculated. If vitamin D insufficiency was defined as <30 ng mL^{-1}, the prevalence would be 0.42%.

Eighty-four patients were identified on chart review with PHPT. Among them, 38 (45%), 34 (41%), and 12 (14%) had asymptomatic PHPT without TOI, asymptomatic PHPT with TOI, and symptomatic PHPT, respectively. As a large number of potential controls were identified electronically, a random sample of 500 were selected for chart review, which was performed until the required number of 75 controls was reached in order to obtain an ~1:1:1 ratio for controls, NHPT, and PHPT.

The number of PHPT patients identified being roughly equivalent to the NHPT group is not surprising considering the exclusion of a significant proportion of PHPT patients with more severe disease (eg co-existing CKD, low 25(OH)D, recurrent disease, on anti-resorptives, or no 24-h urine calcium performed due to other clear surgical indications), in an effort to make this group comparable with the NHPT group which is the focus of the study (see Patient identification and subgroup definition section). If all PHPT patients were included, including those with concomitant secondary hyperparathyroidism, the prevalence would be much higher; however, we would not know if differences in complications such as osteoporosis were due to concomitant secondary hyperparathyroidism in the PHPT group. Hence, this cohort of PHPT patients represents a subset of those with milder disease and does not imply a similar prevalence between NHPT and PHPT.

Clinical features

Table 1 describes patient demographics. In the overall cohort of 232 patients, mean age was 64.8 (SD 11.7) yr, and 73% were females; the majority (92%) of whom were postmenopausal. These factors were no different between groups. Control patients had lower BMI at baseline (Table 1).

In NHPT and PHPT groups, the first and second sets of iPTH and cCa were performed at a median of 9.9 (4.0-17.1) mo apart. The mean of 2 index iPTH, mean of all iPTH, mean of 2 index cCa, and the mean of all cCa showed a stepwise increase across controls, NHPT and PHPT groups, respectively, while phosphorus and 25(OH)D had a stepwise decrease (Table 1). Intra-individual calcium variability, determined by intra-individual coefficient of variance (CV) of cCa (calculated as intra-individual cCa SD divided by intra-individual mean cCa), was higher in the NHPT and PHPT groups compared with controls. TH-BMD and LS-BMD were significantly higher in PHPT compared with the other 2 groups. DXA and TBS parameters were similar in NHPT group and controls. Higher baseline TH-BMD and LS-BMD in the PHPT group lost significance after adjustment for age, sex, and BMI (data not shown).

End-organ complications

NHPT and PHPT groups had higher prevalence of urolithiasis both overall and within the last 5 yr (45% and 35%, respectively) compared with controls (13%) ($P < .001$) (Table 1). On logistic univariate analysis, multiple factors were associated with increased odds for urolithiasis (Table S1), including male gender, NHPT, and PHPT subgroups, higher index 2 iPTH, lower 25(OH)D, and higher creatinine. On multivariate analysis (Table S1, Model 3), only NHPT and PHPT subgroups were consistently associated with an increased odds ratio (OR) for urolithiasis.

Only the NHPT group had increased fragility fracture prevalence compared with controls (Table 1). However, after adjusting for significant confounders of gender and 25(OH)D level, both NHPT and PHPT were associated with greater OR for fragility fracture (Table S2).

By definition, asymptomatic PHPT patients without TOI have zero prevalence of urolithiasis and fractures. Excluding this subgroup revealed a stepwise increase in risk from controls to NHPT, asymptomatic PHPT with TOI, and to symptomatic PHPT for both urolithiasis and fragility fractures as compared with controls, on both unadjusted analysis and after adjustment for age, sex, and BMI (Figure 1, Table S3). With regards to urolithiasis risk, the data were consistent on sensitivity analyses, after excluding those without abdominal imaging performed, counting only those with imaging-proven urolithiasis, and only including patients with urolithiasis diagnosed within 5 yr (Table S4).

Parathyroidectomy in NHPT

Fourteen (19%) NHPT patients and 53 (63%) PHPT patients underwent parathyroidectomy, performed at a median of 1.14 (IQR 0.36-2.23) and 0.59 (IQR 0.29-1.52) yr, respectively, after the date of the index iPTH. A greater proportion of PHPT compared with NHPT patients ($P = .001$) achieved cure, as defined by a greater than 50% reduction in intraoperative iPTH postparathyroidectomy (Table 2).[20] Out of 10 NHPT patients who achieved immediate surgical cure, 2 (20%) recurred over a median of 2.34 (IQR 1.64-3.04) yr.

A significantly greater proportion of NHPT had nonlocalizing imaging studies or polyglandular disease compared with PHPT patients, and only 41% localized to 1 parathyroid gland ($P = .005$, Table 2). A similar trend was reflected in surgical histopathology of NHPT patients who underwent parathyroidectomy. Out of 14 who had nonlocalizing imaging studies, 4 underwent parathyroidectomy, of whom 2 achieved cure (these patients had 2 and 4 hyperplastic glands identified at surgery, respectively). Out of 13 NHPT patients whose imaging studies localized to 1 hyperfunctioning parathyroid gland, 9 attempted curative parathyroidectomy, and of these patients, 7 (78%) achieved cure. The majority (81%) were conservatively managed.

NHPT patients who underwent parathyroidectomy experienced improvement in biochemistry but not DXA parameters (Table 3). TBS improved significantly in 2 PHPT patients and showed a small trend toward improvement in 5 NHPT patients with available TBS data (Table 3). Postoperative BMD was measured at an interval of 2.91 (IQR 1.56-4.09) yr and 1.81 (IQR 1.17-2.83) yr after parathyroidectomy in NHPT and PHPT groups respectively. In NHPT patients, mean index 2 cCa reduced from the high-normal range to mid-normal range (Table 3). Mean index 2 iPTH declined but was still elevated above normal range. A subgroup analysis of 10 NHPT patients who achieved cure with parathyroidectomy showed a similar pattern of improved biochemistry but not DXA parameters. In contrast, PHPT patients achieved

Table 1. Clinical characteristics of controls, NHPT and PHPT.

		Controls (*N* = 75)	NHPT (*N* = 73)	PHPT (*N* = 84)	*P*-value
Demographics					
Age, yr		63.0 (12.7)	64.7 (12.2)	66.6 (10.0)	.156
Females, *n* (%)		57 (76)	54 (74)	59 (70)	.705
Menopaused, Yes, *n* (%)		54 (95)	48 (89)	55 (93)	.487
BMI, kg/m^2		26.2 (22.5-30.2)	27.4 (23.6-31.4)[c]	29.7 (26.0-34.1)[b]	**<.001**
Biochemistry					
	Normal range				
Mean of 2 Index Ca, mg/dl	8.8-10.2	9.42 (0.29)	9.66 (0.35)[ac]	10.62 (0.21)[b]	**<.001**
Mean of all Ca, mg/dl	8.8-10.2	9.41 (0.27)	9.72 (0.37)[ac]	10.59 (0.24)[b]	**<.001**
No. of Ca readings		6 (2-8)	9 (6-10)[ac]	7 (5-10)[b]	**<.001**
Intra-individual CV Ca		0.024 (0.009)	0.030 (0.011)[a]	0.028 (0.011)[b]	**.008**
Mean of 2 index iPTH, pg/ml	15-65	41 (11)	93 (23)[a,c]	102 (30)[b]	**<.001**
Mean of all iPTH, pg/ml	15-65	42 (11)	92 (24)[a,c]	107 (41)[b]	**<.001**
No. of iPTH readings		1 (1-3)	5 (3-7)[a,c]	4 (3-6)[b]	**<.001**
Intra-individual CV iPTH		0.18 (0.10)	0.20 (0.11)	0.19 (0.14)	.634
Phosphorus, mg/dl	2.5-4.5	3.6 (0.5) (*n* = 62)	3.2 (0.5)[a,c]	2.7 (0.4)[b] (*n* = 70)	**<.001**
Creatinine, mg/dl	Male 0.74-1.35 Female 0.59-1.04	0.83 (0.75-0.90)	0.90 (0.80-0.99)	0.84 (0.74-0.95)	.379
25(OH)D, ng/ml	Optimal>30	44.0 (34.0-54.0)	40.0 (33.0-48.0)[c]	34.5 (30.0-42.0)[b]	**<.001**
Urinary Ca, mg/24 h	Male <300 Female <250	212 (128-269) (*n* = 16)	150 (93-200)[c]	241 (183-324)	**<.001**
ALP, U/L	Male 40-129 Female 35-104	75 (65-91) (*n* = 68)	79 (66-91) (*n* = 68)	82 (71-96) (*n* = 76)	.155
DXA					
BMD, g/cm^2					
FN		0.765 (0.122) (*n* = 71)	0.766 (0.155) (*n* = 72)	0.810 (0.117) (*n* = 79)	.058 **<.001**
TH		0.839 (0.135) (*n* = 71)	0.846 (0.138)[c] (*n* = 72)	0.932 (0.133)[b] (*n* = 79)	**<.001** .442
LS		1.010 (0.173) (*n* = 70)	1.032 (0.193)[c] (*n* = 67)	1.149 (0.186)[b] (*n* = 76)	
1/3 DR		0.770 (0.200) (*n* = 4)	0.807 (0.215) (*n* = 25)	0.745 (0.195) (*n* = 59)	
T-scores					
FN		−1.47 (0.95) (*n* = 71)	−1.55 (0.93)[c] (*n* = 72)	−1.24 (0.91) (*n* = 79)	**.032** **<.001**
TH		−1.03 (1.02) (*n* = 71)	−0.98 (1.03)[c] (*n* = 72)	−0.33 (1.02)[b] (*n* = 79)	**<.001** .605
LS		−1.04 (1.38) (*n* = 69)	−0.87 (1.64)[c] (*n* = 66)	0.16 (1.56)[b] (*n* = 76)	
1/3 DR		−1.19 (1.37) (*n* = 4)	−0.73 (1.65) (*n* = 24)	−0.55 (1.21) (*n* = 59)	
TBS		1.337 (0.105) (*n* = 24)	1.306 (0.137) (*n* = 36)	1.323 (0.093) (*n* = 19)	.615
Complications					
Urolithiasis, *n* (%)		10 (13)	33 (45)[a]	29 (35)[b]	**<.001**
Yr 1st urolithiasis before index iPTH		16.5 (8.3-26.1)	5.5 (1.6-9.7)[a]	3.2 (0.1-11.4)	**.039**
Urolithiasis within 5 y of follow-up, *n* (%)		2 (3)	15 (21)[a]	19 (23)[b]	**<.001**
Any fracture, *n* (%)		5 (7)	17 (23)[a]	11 (13)	**.014**
Site of fracture, *n* (%)					
Vertebral		2 (3)	8 (11)	4 (5)	.122
Hip		1 (1)	2 (3)	0 (0)	.205
Distal radius		1 (1)	6 (8)	5 (6)	.131
Pelvic/ sacral		1 (1)	2 (3)	1 (1)	.693
Proximal humerus		0 (0)	0 (0)	1 (1)	1.000

Continuous data are represented by mean ± standard deviation or median (interquartile range). Number available is indicated in cells with missing data. [a]Post-hoc $P < .05$ between controls and NHPT. [b]Post-hoc $P < .05$ between controls and PHPT. [c]Post-hoc $P < .05$ between NHPT and PHPT. Abbreviations: 25(OH)D = 25-hydroxyvitamin D; ALP = alkaline phosphatase; Ca = corrected calcium; CV = intraindividual coefficient of variance; DR = distal radius; iPTH = intact parathyroid hormone; NHPT = normocalcemic hyperparathyroidism; PHPT = primary hyperparathyroidism; TBS = trabecular bone score.

mid-normal iPTH of 41 pg mL^{-1} postparathyroidectomy, a level similar to that of controls (Table 3).

Out of 52 NHPT and PHPT patients who had urolithiasis on baseline imaging, 15 had interval imaging performed postparathyroidectomy (10 PHPT, 5 NHPT) after 0.78 (IQR 0.66-1.42) yr. Twelve (80% and proportion similar in both groups) had persistent urolithiasis postparathyroidectomy, while 3 (20%) had resolution. All 3 had a urological

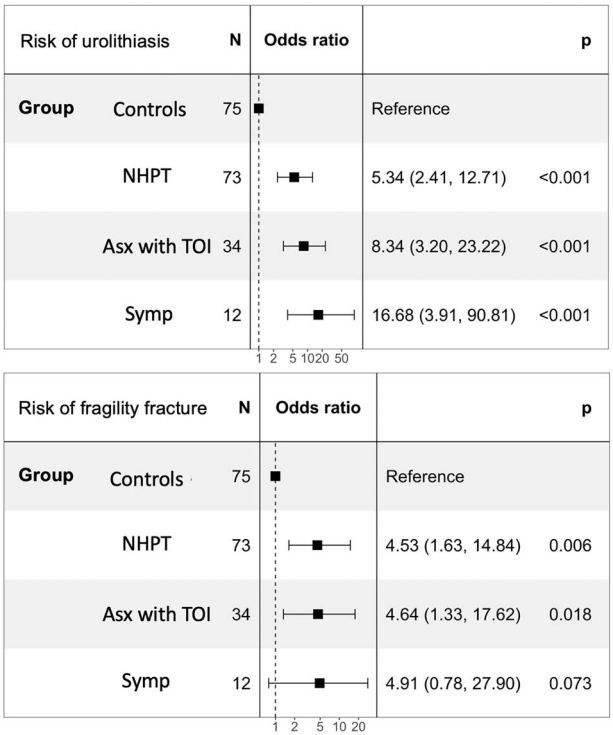

Figure 1. NHPT and PHPT groups were associated with increased risk of urolithiasis and fractures. Adjusted analysis for age, sex, and BMI shown. Abbreviations: Asx with TOI = asymptomatic primary hyperparathyroidism with target organ involvement; NHPT = normocalcemic hyperparathyroidism; Symp = symptomatic primary hyperparathyroidism.

procedure performed prior to the interval imaging, confounding the interpretation, and 31 of those with urolithiasis on baseline imaging had follow-up imaging performed without undergoing parathyroidectomy, at an interval of 1.54 (IQR 0.76-2.55) yr, and 18 (58%) had persistent urolithiasis, 7 (23%) resolved spontaneously, and 6 (19%) resolved after a urological procedure. Spontaneous resolution occurred in 4 (17%) of NHPT patients and 3 (43%) of PHPT patients.

Progression in NHPT cohort

Median follow-up for NHPT was 4.23 (IQR 1.76-5.31) yr. In NHPT patients who were managed expectantly, there was a significant, albeit nonclinically, relevant increase in a mean of 2 cCa from 9.63 to 9.73 mg dL^{-1} ($P = .006$,), still well-within the normal range, and no change in mean 2 iPTH. Interestingly, there was a 4.1% improvement ($P = .003$) in LS-BMD over an interval of 3.83 (IQR 2.49-4.35) yr. After correction for other confounders such as age and gender, BMI, NHPT was no longer associated with LS-BMD change. There was no change in BMD at other sites.

In the 59 NHPT patients who were conservatively managed, 54 had follow-up data, and 9 (17%) reverted to normal biochemistry (defined by normal mean 2 cCa and normal mean 2 iPTH), while progression to hypercalcemic PHPT occurred in 5 (9%) patients. Those who progressed did so at a median interval of 1.86 (IQR 0.19-2.82) yr. Using ROC curves, the optimal cut-off of cCa was >9.89 mg dL^{-1} (AUC 0.878, 95% CI 0.769-0.987, $P < .001$, Youden's index 0.759) and iPTH >87 pg mL^{-1} (AUC 0.819, 95% CI 0.625-1.000, $P < .001$, Youden's index 0.569) for predicting progression to hypercalcemic PHPT. No significant collinearity was identified for cCa and iPTH, and in combination, these provided an AUC of 0.900 (95% CI 0.777-1.00, $P < .001$) for predicting progression.

As only 5 NHPT patients progressed to hypercalcemic PHPT, Cox regression analyzing the HRs for the combined outcome of progression to hypercalcemic PHPT or requiring parathyroidectomy was performed. Mean index 2 cCa and mean index 2 iPTH were significantly associated with the combined outcome, on both univariate and multivariate analyses (Table 4). Every 0.1-mg dL^{-1} increase in baseline cCa was associated with 18-34% increase in combined risk, while every 10 pg mL^{-1} increase in baseline iPTH was associated with a 30-32% increased risk.

Subgroups of NHPT–persistent normocalcemia versus intermittent hypercalcemia

Forty-four (60%) NHPT patients had persistent normocalcemia over a median of 8 (IQR 6-10) readings taken over 4.24 (IQR 1.64-5.34) yr, while 29 (40%) had at least 1 elevated cCa reading over 10 (IQR 6-10) readings over 4.17 (1.99-5.30) yr. Patients with intermittent hypercalcemia had higher cCa and iPTH compared with patients with persistent normocalcemia (Table S5). There was no difference in prevalence of urolithiasis or fragility fracture. By definition, all patients with persistent normocalcemia did not progress to hypercalcemic PHPT, while this occurred in 17% of those with intermittent hypercalcemia, and 38% of patients with intermittent hypercalcemia experienced the combined outcome of progression to PHPT or required parathyroidectomy, compared with 18% of persistent normocalcemia ($P = .060$).

Predictive modeling construction and evaluation

A training dataset was used to build multivariable logistic and XGBoost modeling for the combined outcome of progression to hypercalcemic PHPT or requiring parathyroidectomy in NHPT patients. On multivariable logistic regression, which included the 4 most important risk factors (mean index 2 iPTH, mean index 2 cCa, presence of urolithiasis, and fragility fractures), only mean index 2 cCa was an important predictor for increased OR (Table S6).

On XGBoost, there were 6 most important factors identified for risk of the combined outcome. In descending order of importance, these included mean index 2 iPTH, mean index 2 cCa, 24-h urinary calcium, age, 25(OH)D, and the presence of urolithiasis (Figure 2A). After 5-fold cross-validation and hypertuning of parameters, the final XGboost model was selected based on greatest accuracy, holding gamma constant at 0, and minimum child weight held constant at 1. The final parameters selected were: nrounds = 50, maximum depth = 1, eta = 0.3, colsample_bytree = 0.6, and subsample = 0.5.

Detailed performance metrics of logistic regression and XGBoost models in both training and test datasets are described in Table S7. XGBoost consistently outperformed the logistic regression model. Using ROC analysis, the AUC for predicting combined outcome with these 6 factors on XGBoost was 1.00 (95% CI, 1.00-1.00, $P < .001$, Figure 2C). Logistic regression model was not useful in predicting risk of progression.

Discussion

Our study describes the prevalence, phenotypes, complications, and risk of progression in NHPT, a rare clinical entity

Table 2. Localization and treatment in NHPT and PHPT patients.

	NHPT	PHPT	*P*-value
Underwent Ptx	(*N* = 14)	(*N* = 53)	
Hyperplastic glands at Ptx, *n* (%)			
1	8 (57)	40 (76)	.224
2	2 (14)	4 (8)	
3	2 (14)	3 (6)	
4	1 (7)	5 (9)	
None	1 (7)	0 (0)	
Cure, *n* (%)[a]	10 (71)	53 (100)	**.001**
Localization scans done	(*N* = 32)	(*N* = 70)	
Glands identified on scan, *n* (%)			
None/ normal	14 (44)	11 (16)	**.005**
1	13 (41)	50 (71)	
Polyglandular	5 (16)	9 (13)	

[a] Cure defined as >50% reduction of intra-op PTH post-parathyroidectomy. Abbreviations: NHPT = normocalcemic hyperparathyroidism, PHPT = primary hyperparathyroidism; Ptx = parathyroidectomy.

Table 3. Before-after comparisons in patients who underwent parathyroidectomy.

	NHPT (*N* = 14)			PHPT (*N* = 53)		
	Before	**After**	***P*-value**	**Before**	**After**	***P*-value**
Mean of 2 index Ca ➔ mean of 2 last Ca, mg/dl	9.77 (0.32) (*N* = 12)	9.36 (0.34) (*N* = 12)	**<.001**	10.64 (0.22) (*N* = 50)	9.41 (0.36) (*N* = 50)	**<.001**
Mean of 2 index iPTH ➔ mean of 2 last iPTH, pg/ml	106 (31) (*N* = 12)	68 (40) (*N* = 12)	**.010**	107 (34) (*N* = 52)	41 (16) (*N* = 52)	**<.001**
BMD, g/cm^2						
FN	0.744 (0.098) (*N* = 8)	0.732 (0.090) (*N* = 8)	.326 .687	0.789 (0.129) (*N* = 17)	0.788 (0.108) (*N* = 17)	.986 .778
TH	0.804 (0.147) (*N* = 8)	0.810 (0.131) (*N* = 8)	.511 NA	0.893 (0.145) (*N* = 17)	0.904 (0.139) (*N* = 17)	.410 .304
LS	0.947 (0.119) (*N* = 6)	0.976 (0.072) (*N* = 6)		1.152 (0.225) (*N* = 13)	1.181 (0.199) (*N* = 13)	
1/3 DR	0.794 (*N* = 1)	0.786 (*N* = 1)		0.656 (0.194) (*N* = 9)	0.607 (0.099) (*N* = 9)	
T-scores						
FN	−1.61 (0.76) (*N* = 8)	−1.69 (0.70) (*N* = 8)	.345 .965	−1.28 (1.01) (*N* = 17)	−1.28 (0.84) (*N* = 17)	1.000 .799
TH	−1.23 (1.18) (*N* = 8)	−1.22 (1.98) (*N* = 8)	.574 NA	−0.51 (1.16) (*N* = 17)	−0.46 (1.10) (*N* = 17)	.538 .279
LS	−1.52 (1.03) (*N* = 6)	−1.32 (0.618) (*N* = 6)		0.27 (1.92) (*N* = 13)	0.43 (1.72) (*N* = 13)	
1/3 DR	−1.20 (*N* = 1)	−1.30 (*N* = 1)		−0.51 (1.41) (*N* = 9)	−1.08 (1.74) (*N* = 9)	
TBS	1.238 (0.138) (*N* = 5)	1.381 (0.083) (*N* = 5)	.214	1.347 (0.025) (*N* = 2)	1.493 (0.032) (*N* = 2)	**.022**

Continuous data are represented by mean ± standard deviation. Number available is indicated in cells with missing data. Abbreviations: Ca = corrected calcium; DR = distal radius; iPTH = intact parathyroid hormone; NHPT = normocalcemic hyperparathyroidism; PHPT = primary hyperparathyroidism; TBS = trabecular bone score.

Table 4. Cox regression of predictors of progression to hypercalcemic primary hyperparathyroidism or requiring parathyroidectomy in NHPT patients.

	Univariate (Model 1)			Multivariate (Model 2)		
	***P*-value**	**HR**	**95% CI HR**	***P*-value**	**HR**	**95% CI HR**
Age	.265	1.03	0.98-1.07	-	-	-
Sex: Male	.947	1.04	0.37-2.88	-	-	-
BMI	.323	0.96	0.88-1.04	-	-	-
Mean index 2 Ca∗10	**.032**	1.18	1.01-1.38	**.017**	1.34	1.05-1.71
Mean index 2 iPTH∗0.1	**<.001**	1.32	1.12-1.55	**.005**	1.30	1.08-1.56
Intermittent hypercalcemia: Yes	.191	1.84	0.74-4.57	.151	0.33	0.07-149
25(OH)D	.212	1.02	0.99-1.05	-	-	-
24 h urinary Ca	.070	1.01	1.00-1.01	.531	1.00	1.00-1.01
Phosphorus	.405	0.66	0.25-1.75	-	-	-
Hx of urolithiasis: Yes	.166	1.94	0.76-4.92	.055	3.10	0.98-9.86

Model 2: include variables with $P < .2$ in univariate analysis, $R^2 = 0.246$, $P = .002$. Abbreviations: 25(OH)D = 25-hydroxyvitamin D; Ca = corrected calcium; HR = hazard ratio; Hx = history; iPTH = intact parathyroid hormone.

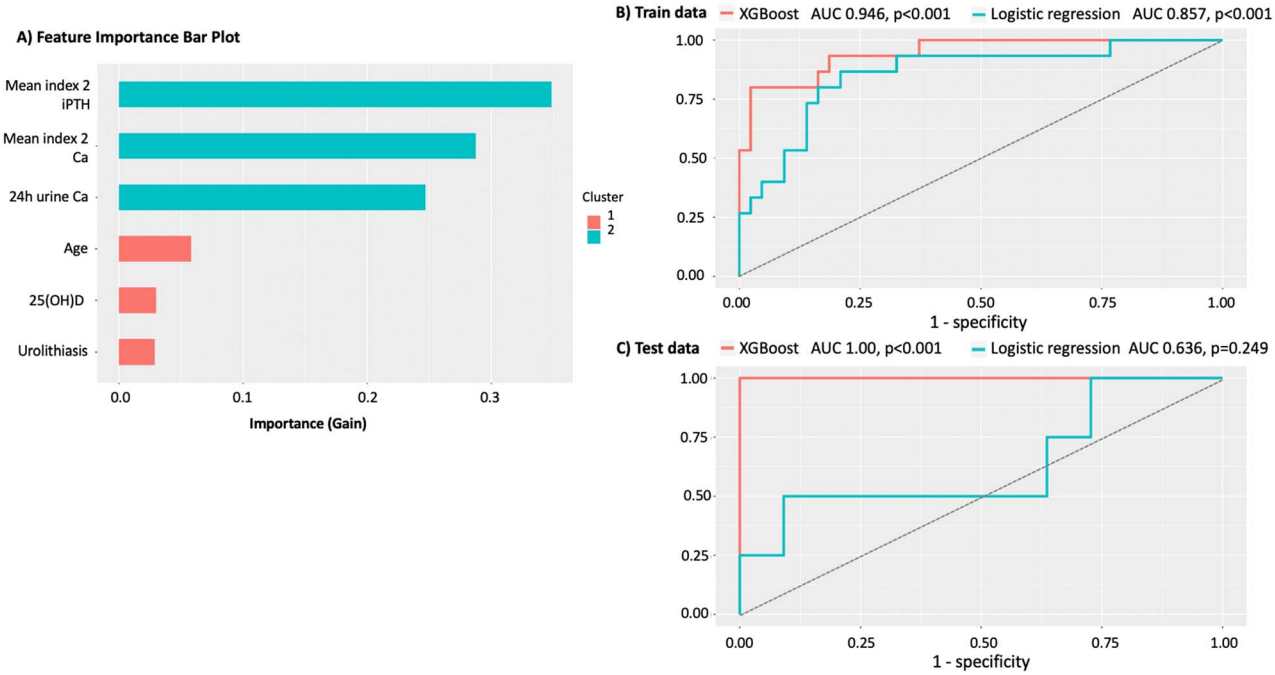

Figure 2. (A) Six most important risk factors for risk of progression to hypercalcemic primary hyperparathyroidism or requiring parathyroidectomy as identified on XGBoost, with their relative contributions to the model. (B) AUC ROCs for XGBoost and logistic regression models on training dataset. (C) AUC ROCs for XGBoost and logistic regression models on test dataset. Abbreviations: 25(OH)D = 25-hydroxyvitamin D; AUC = area under the curve; Ca = corrected calcium; iPTH = intact parathyroid hormone; ROC = receiver operating characteristic.

that remains suboptimally characterized, in part due to inconsistent clinical definitions. The low prevalence of 0.52% of NHPT found in this study is consistent with recent studies utilizing more rigorous definitions.[1] Earlier studies that failed to exclude those with mild renal insufficiency, use of anti-resorptives, or mild vitamin D insufficiency or that used only a single set of calcium and iPTH measurement may have inadvertently included those with secondary hyperparathyroidism or mild primary hyperparathyroidism, resulting in a higher reported prevalence of 3.1%-6.8%.[7,21]

The current study found NHPT to have an intermediate phenotype between controls and PHPT. Even though calcium and phosphorus were normal in our NHPT cohort, they were in the high-normal and low-normal range, respectively, with calcium being restored to the mid-normal range after parathyroidectomy. iPTH was elevated above normal range but not to the extent observed in PHPT, and 25(OH)D in NHPT patients was intermediate between controls and PHPT.

Few studies have examined intra-individual calcium variability in NHPT—our finding of increased intra-individual calcium variability observed in NHPT and PHPT over controls confirms that recently reported by Schini et al.[1] Of note, a significant proportion of NHPT patients had intermittent hypercalcemia, despite 2 normal readings at baseline. This has been proposed to be attributed to a loss of calcium homeostasis by an autonomous parathyroid tumor in the setting of PHPT.[22] Collectively, these findings point toward NHPT being a milder form of PHPT and also emphasize recent recommendations highlighting the need for more than one set of calcium and iPTH to confirm a diagnosis of NHPT,[6] and for defining progression and resolution.

With regards to end-organ complications, risk of urolithiasis in NHPT was found to be significantly elevated above that of controls. Although we cannot exclude screening bias related to fewer imaging studies performed in controls, this is less likely to be significant since the prevalence of urolithiasis in asymptomatic cohorts that uniformly underwent cross-sectional imaging was estimated at 7.8%-8.6%,[23,24] comparable, if not lower than our control prevalence of 13%. These values are also similar to the background prevalence of urolithiasis of 10.1% in epidemiological studies.[25] Other studies have also reported a high prevalence of urolithiasis in NHPT, nearly equivalent to that seen in hypercalcemic PHPT.[26]

Importantly, we demonstrated an increased urolithiasis risk despite normal urinary calcium excretion. Elsewhere, hypercalciuria as an etiology for urolithiasis has not consistently been found;[27] other factors such as polymorphisms in the calcium-sensing receptor gene may predispose to the risk of calcium-phosphate precipitation.[28] NHPT is not an indolent disease—a dose–response relationship in urolithiasis risk was shown across subgroups of PHPT, with NHPT having an intermediate risk profile between controls and asymptomatic PHPT without TOI. The sensitivity analyses showed that the strong correlation was not meaningfully altered by the change in the definition of urolithiasis formation or subgroup who underwent screening imaging, suggesting that the overall finding of increased urolithiasis risk is robust. With a significant proportion (46%-66%) of urolithiasis being detected within a recent 5-yr time frame or during follow-up, this may represent an ongoing risk of urolithiasis formation, in both NHPT and PHPT, prompting early parathyroidectomy. However, current evidence for resolution of urolithiasis post-parathyroidectomy for NHPT is scarce—only one small retrospective uncontrolled case series found resolution in 40%.[29] Data inferred from larger studies of parathyroidectomy in PHPT have shown only conservative reduction in urolithiasis risk, with benefit only materializing after yr.[30-32] Our study

also does not support the role of parathyroidectomy for urolithiasis resolution, however numbers were small and the interval of repeat imaging after parathyroidectomy was short. As such, well-conducted studies focusing on urolithiasis risk reduction with surgical or alternative medical therapy, eg cinacalcet, are needed to provide clarity.[33]

Fragility fracture risk in NHPT was also observed to be elevated above controls, equivalent to that seen PHTP with TOI and symptomatic PHPT. The high skeletal and renal complication rates were corroborated in several studies conducted in referral centers,[34,35] while population-based studies reported lower complication rates.[7,36] Although we cannot exclude referral bias for the differences reported, in the few population-based studies that reported low urolithiasis prevalence, secondary hyperparathyroidism was not adequately excluded in the definition of NHPT.[7,36] Community studies reporting on fracture prevalence in NHPT were limited by very small sample sizes and liberal definition of NHPT.[36,37] Furthermore, our control group appeared to be at a higher baseline risk of bone complications, as evidenced by a 25% prevalence of osteoporosis, lower BMI, and marginally lower BMD. This is because BMD, calcium, and iPTH in our control population were frequently measured as part of routine osteoporosis evaluation. This could have underestimated rather than overestimated fracture risk in NHPT and PHPT.

In our study, despite baseline BMD not being worse than controls, a higher prevalence of fragility fractures in NHPT, asymptomatic PHPT with TOI, and symptomatic PHPT groups was demonstrated. Interestingly, BMD has not consistently been shown to be reduced in NHPT or PHPT.[1,38] Other studies also found a higher risk of fractures, particularly vertebral, for a given LS-BMD in PHPT,[39,40] leading some authors to propose the use of TBS to evaluate bone quality and fracture risk in PHPT.[41] Few patients underwent TBS in our study; however, this should be further explored in relation to the increased fragility fractures (particularly vertebral) observed in our cohort of NHPT.

Limited TBS data in our study suggest that TBS may be more sensitive to bone changes postparathyroidectomy than BMD, showing a trend to improvement in NHPT group and a small improvement in PHPT group, while BMD did not change in both groups. In previous studies, BMD improvement with PHPT was demonstrated only for those with moderate to severe disease.[42,43] For example, in Rubin et al.'s study, baseline iPTH was 144 pg mL^{-1} in the group who experienced an improvement in BMD with parathyroidectomy, while in our study which excluded more severe forms of PHPT, mean baseline iPTH was only 107 pg mL^{-1}. Furthermore, in that study, the group which did not undergo parathyroidectomy also had milder elevation in iPTH (iPTH 116 pg mL^{-1}) and it took 8 yr for them to experience any change in BMD with conservative management.[43] Hence, this may partly explain why our patients with NHPT and mild PHPT did not experience deterioration in BMD with conservative management nor improvement with parathyroidectomy. Earlier improvement in TBS with parathyroidectomy as a more sensitive indicator of bone changes may be explored in future studies.

Surgical management is controversial in NHPT due to limited evidence of benefit. Two surgical cohorts reported BMD improvements after parathyroidectomy; however, only one calcium reading was utilized in their definition of NHPT,[35,44] leading to possible inclusion of hypercalcemic PHPT. Our study only found improvement in biochemical but not BMD parameters, though limited by few patients with interval BMD available for comparison. However, previous studies only reported small gains between 1.64% and 1.84% in TH and LS, respectively,[44] values easily attainable with medical therapy. A study reporting larger BMD improvements of 1.9%-5.7% after parathyroidectomy analyzed a subgroup of NHPT with low BMD at baseline and who achieved surgical cure,[35] characteristics not generalizable to all NHPT patients. Additionally, our study confirms the higher prevalence of nonlocalizing scans, multiglandular disease, and lower success rate of parathyroidectomy in NHPT, findings also echoed elsewhere.[29,45] Hence, one has to weigh the morbidity related to bilateral neck exploration or re-exploration after recurrence in NHPT,[29,45] against the relatively small gains in BMD with surgery. Whether this translates to reduced fracture risk as seen in hypercalcemic PHPT remains to be seen.

Natural history of NHPT remains uncertain, with few studies reporting a wide range of progression rates from 1.6% to 22%,[7,46] depending on definition of NHPT (low rates where secondary hyperparathyroidism was not excluded, and high rates where single calcium readings utilized may not have adequately excluded PHPT). In our study, a minority (9%) progressed to hypercalcemic PHPT with conservative management. More patients reverted to normal biochemistry (17%), supporting the case for watchful waiting. Importantly, those who progressed did so within 2 yr of follow-up, consistent with another study,[47] suggesting that watchful waiting need not be prolonged. In our cohort, the proportion who reverted to normal was significantly smaller than the 75% reported by Cusano et al., who either reverted to normal or were found to have secondary hyperparathyroidism,[7] again highlighting the importance of accurate classification of NHPT.

The challenge lies in identifying NHPT patients who may benefit from more intensive evaluation, to consider curative surgery. Supporting the view that NHPT is an early and mild form of classic PHPT, we observed a very small increase in calcium over time with expectant management. Although still within the normal range and clinically undetectable, this suggests that the inappropriately high iPTH has raised serum calcium, and those in the high-normal range may have a higher chance of progressing to hypercalcemic PHPT with time.[5] Indeed, a higher baseline cCa and iPTH were both strongly associated with risk of progression. Here, a combination of six predictive factors (iPTH, cCa, 24-h urinary calcium, age, 25(OH)D, and presence of urolithiasis) identified by a machine-learning approach was found to have an excellent AUC of >95% in discriminating higher risk NHPT patients. Notably, the parameters are routinely documented in clinical practice; hence, the model is easily applicable.

A recent study with well-defined inclusion and exclusion criteria illustrated the natural history of NHPT, subdividing this group into persistent normocalcemia and intermittent hypercalcemia.[1] In our study, the presence of intermittent hypercalcemia, which requires repeated measurements over time, was not found to be predictive of adverse outcome of progression by logistic regression or machine-learning approach, nor was it associated with complications of urolithiasis or fragility fractures. Despite this, this group displayed higher cCa, CV of Ca, and iPTH compared with patients with persistent normocalcemia, features associated with PHPT. Considering that the proportion who progressed to hypercalcemic PHPT or required parathyroidectomy nearly reached statistical significance, the clinical significance of this subgroup needs to be further clarified.

Controversies regarding the current definition of NHPT partly relate to whether persistence of normocalcemia is required. Given the intra-individual variability of calcium and significant proportion with intermittent hypercalcemia described in our cohort and elsewhere,[1] strict adherence to guidelines would underestimate the prevalence of NHPT and fail to adequately risk-stratify a subgroup who are at risk of morbidity from end-organ involvement. We support the use of mean calcium within the normal range instead to define NHPT proposed by Schini et al.[1] However, taking practicality into consideration, our study demonstrated the mean of all calcium and iPTH readings to be in close approximation to the mean of 2 index readings, respectively, which can serve as convenient and informative surrogates.

Our study had several strengths: (1) this represents one of the largest cohorts of NHPT followed for longer than 4 yr, with detailed information regarding prevalence, biochemical phenotype, complications, and management strategies, (2) strict inclusion and exclusion criteria were applied to define NHPT, (3) this article comes timely to address research agenda highlighted in the latest guidelines regarding natural history with and without parathyroidectomy, and controversies regarding the definition of NHPT,[6] and (4) this is the first study to employ machine-learning techniques to develop a prediction model for progression in this rare condition.

The main limitation relates to the lack of ionized calcium in our definition. This could have misclassified cases of ionized hypercalcemia as NHPT and overestimated complication rates if classical PHPT patients were included. However, the prevalence of NHPT in our study is lower or comparable to other studies with similarly stringent criteria that also utilized ionized calcium;[21] furthermore, our low rates of progression to hypercalcemic PHPT[47] also reflect that this is unlikely to be significant. Secondly, urine calcium to creatinine ratio for exclusion of FHH was not available in the PHPT group, as 24-h urine calcium was mainly performed to look for surgical indication for PHPT rather than to differentiate from FHH, and hence, 24-h urine creatinine was not routinely available. As such, this population had a high clinical suspicion for PHPT, and the chance of false negative 24-h urine calcium is less likely. Furthermore, the median 24-h urine calcium in this group was elevated at 241 mg d^{-1} and a 100% cure rate was achieved in PHPT patients who underwent parathyrodiectomy, making it unlikely that many cases of FHH were erroneously included here. In a comparative study, the calcium-creatinine ratio was only marginally and non-significantly superior to 24 h urine calcium to distinguish FHH from PHPT.[48] Third, this is a retrospective cohort study with inherent selection bias. Lastly, our study had insufficient interval BMDs performed to confirm BMD changes. A failure to demonstrate lower BMD even in the PHPT cohort may be related to the mild severity of PHPT (normal renal function, no refractory or recurrent cases in our selection criteria) or higher-risk control population (referral center bias for osteoporosis). Well-designed prospective studies with sufficiently large sample sizes are needed to clarify the benefit of parathyroidectomy in mitigating the renal and bone complications observed.

Conclusion

In conclusion, NHPT appeared to be intermediate both in biochemical phenotype and end-organ complications between controls and PHPT, supporting the opinion that it is a mild variant of PHPT.[1] In recognition of the high intra-individual calcium variability in this condition, we propose the use of normal mean 2 calcium measurements rather than an insistence on persistent normocalcemia in the diagnosis of NHPT, which may fail to identify patients at risk of complications. Timely recognition and diagnosis are necessary, as urolithiasis and fragility fractures in this cohort may occur despite normal urinary calcium excretion and BMD. At the same time, overdiagnosis should be avoided with careful exclusion of causes of secondary hyperparathyroidism, and the use of at least 2 sets of measurements. Given that only a minority progressed to hypercalcemic PHPT over 4 yr, coupled with lower surgical success rates, our study supports a strategy of watchful waiting and continued follow-up, with attention given to those with high-risk clinical features as described.

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Supplementary material

Supplementary material is available at *JBMR Plus* online.

Author contributions

Caroline Hoong (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review & editing), Stephen Broski (Data curation, Investigation, Methodology, Writing—review & editing), Jad Sfeir (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing), and Bart Clarke (Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing—review & editing)

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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