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Normocalcemic Primary Hyperparathyroidism: Further Characterization of a New Clinical Phenotype

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Context: Patients with elevated PTH and consistently normal serum calcium levels, in whom secondary causes of hyperparathyroidism have been excluded, may represent the earliest presentation of primary hyperparathyroidism (PHPT).

Objective: The objective of the study was to characterize patients with normocalcemic PHPT referred to a bone disease unit.

Design: This was a longitudinal cohort study.

Setting: Ambulatory patients were referred to the metabolic bone disease unit.

Patients: The study population included 37 patients [aged 58 yr, range 32–78; 95% female; serum calcium, 9.4 ± 0.1 (SEM) mg/dl (2.3 ± 0.02 mmol/liter), reference range, 8.5–10.4 (2.1–2.6 mmol/liter); PTH, 93 ± 5 pg/ml].

Interventions: Interventions included yearly (median 3 yr; range 1–8 yr) physical examination, biochemical indices, and bone mineral density (BMD).

Main Outcome Measures: We measured the development of features of PHPT.

Results: Evaluation for classical features of PHPT revealed a history of kidney stones in five (14%), fragility fractures in four (11%), and osteoporosis in 57% [spine (34%), hip (38%), and/or distal one third radius (28%)]. BMD did not show preferential bone loss at the distal one third radius (T scores: spine, −2.00 ± 0.25; hip, −1.84 ± 0.18; one third radius, −1.74 ± 0.22). Further signs of PHPT developed in 40% (seven hypercalcemia; one kidney stone; one fracture; two marked hypercalciuria; six had >10% BMD loss at one or more site(s) including four patients developing World Health Organization criteria for osteoporosis). Seven patients (three hypercalcemic, four persistently normocalcemic) underwent successful parathyroidectomy.

Conclusions: Patients seen in a referral center with normocalcemic hyperparathyroidism have more substantial skeletal involvement than is typical in PHPT and develop more features and complications over time. These patients may represent the earliest form of symptomatic, rather than asymptomatic, PHPT. **(*J Clin Endocrinol Metab* 92: 3001–3005, 2007)**

PRIMARY HYPERPARATHYROIDISM (PHPT) commonly presents as a disorder of mild, asymptomatic hypercalcemia in which biochemical indices and bone mineral density (BMD) remain stable over time in most patients (1–3). Because both hypercalcemia and the typical pattern on bone densitometry are generally present at the time the diagnosis is made, it has been hypothesized that PHPT has a biphasic disease course (1). During the first phase, when the PTH concentration is initially elevated in the circulation, hypercalcemia is not yet present. The elevated PTH concentration in this early phase is postulated to cause reduced cortical bone density. The second phase of PHPT, the clinically apparent presentation, is defined by the development of hypercalcemia. The natural history of PHPT in most patients is consistent with this theoretical construct, in that progression of the disease after the diagnosis is made is seen in only a minority of patients (4).

As awareness of the importance of skeletal health has increased, some community physicians and bone specialists have begun to measure PTH in the context of an evaluation for low bone density. In this setting, we and others have described individuals with elevated PTH levels in the absence of hypercalcemia, in whom secondary causes for increased PTH concentration have been carefully investigated and ruled out. We hypothesized that these patients represent that first phase of PHPT, in which patients have not yet become hypercalcemic, and predicted that some of them would go on to develop hypercalcemia. In this report, we document our growing experience with normocalcemic PHPT, an experience that has led to new hypotheses about the nature and significance of this clinical finding.

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Abbreviations: BMD, Bone mineral density; IRMA, immunoradiometric assay; PHPT, primary hyperparathyroidism.

Patients and Methods

Patient selection and study design

Patients were recruited from the clinical facilities of the Metabolic Bone Disease Unit at Columbia University Medical Center (New York, NY) between 1998 and 2005. All patients had concomitantly elevated serum PTH concentration by the intact immunoradiometric assay (IRMA) (reference range, 10–65 pg/ml) and normal total serum calcium concentration (reference range, 8.5–10.4 mg/dl; 2.1–2.6 mmol/liter) when corrected for serum albumin using the formula: corrected calcium = (4-serum albumin) * 0.8 + serum calcium. All patients had 25-hydroxyvitamin D concentrations within the physiologically normal range [≥20 ng/ml (50 nmol/liter), assay reference range 9–54 ng/ml (23–135 nmol/liter)]. Other secondary causes of hyperparathyroidism were also excluded, including renal insufficiency [glomerular filtration rate < 40 ml/min per 1.73 m^2 by the equation of the Modification of Diet in Renal Disease Study (5)]; liver disease; significant hypercalciuria [urinary calcium > 350 mg per 24 h (88 mmol per 24 h)]; thiazide diuretic or lithium use; and other metabolic bone diseases (*e.g.* Paget's disease). Nephrolithiasis and fractures were documented by history and review of medical records.

All patients were evaluated yearly. Medical history was obtained and

physical examination was done. Biochemical studies included serum total calcium, phosphorus, and alkaline phosphatase activity (measured by automated techniques; Technicon Instruments, Tarrytown, NY); serum 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; urinary calcium; and N-telopeptide excretion [measured as previously described (3)]. BMD was assessed by dual-energy x-ray absorptiometry (Hologic, Inc., Waltham, MA) at the lumbar spine (L1-L4), hip, and distal one third of the nondominant radius, and follow-up bone density was always measured on the same dual-energy x-ray absorptiometry instrument. Data are reported for both absolute BMD and T-scores (SD values from the mean for a sex-matched young reference population).

Statistical analysis

Student's unpaired *t* tests were used to compare patients who developed hypercalcemia with those who remained normocalcemic. All data are presented as mean ± SEM, median, and range.

The study was approved by the Institutional Review Board of Columbia University Medical Center, and all patients gave written informed consent.

Results

Characteristics at time of presentation

Thirty-seven patients (aged 58 ± 2 yr, median 58, range 32–78) were identified who met criteria for normocalcemic hyperparathyroidism. The cohort consisted of 29 postmenopausal women, six premenopausal women, and two men. The reasons for referral to our unit included hyperparathyroidism discovered during the evaluation of low bone mass (n = 27; 73%); recent fragility fracture (n = 4; 11%) or kidney stone (n = 2; 5%); and hyperparathyroidism found during the evaluation of other complaints (n = 4; 10%). Five patients (14%) had a history of nephrolithiasis. As expected by the referral characteristics, 46% of the cohort had a history of fracture in adulthood. Because PTH levels are not routinely measured, all subjects were discovered with a specific indication for a PTH measurement.

Baseline biochemical and densitometric characteristics of the cohort are outlined in Table 1. In addition to normal levels of serum calcium [9.4 ± 0.1 mg/dl (2.3 ± 0.02 nmol/liter), corrected for albumin], the serum phosphorus, alkaline phosphatase activity, urinary calcium, and N-telopeptide were also in the middle of the normal range. As defined in the inclusion criteria, all patients had 25-hydroxyvitamin D levels above 20 ng/ml (50 nmol/liter); 65% of the cohort had a level of 30 ng/ml or greater (75 nmol/liter). The only finding typical of hypercalcemic PHPT was a serum 1,25-dihydroxyvitamin D [62 ± 4 pg/ml (161 ± 10 pmol/liter)] that was in the top quintile of the normal range with nine patients (24%) having frankly elevated levels.

Using World Health Organization (WHO) criteria for the diagnosis of osteoporosis, BMD assessment showed that 21 of the 37 subjects (57%) had osteoporosis in at least one site at presentation. Nineteen percent (n = 7) had a T-score in the osteoporotic range at two of three sites, and 8% (n = 3) were osteoporotic at all three sites. Osteoporosis tended to be more common at the lumbar spine (34%) and hip (38%) than it was at the distal one third radius (28%), and BMD T-scores revealed no preferential bone loss at the distal one third radius site (Fig. 1). This contrasts with the findings in our cohort of 139 hypercalcemic patients originally enrolled in our natural history of primary hyperparathyroidism study, in whom initial evaluation was undertaken because of hypercalcemia. In contrast to our normocalcemic cohort, whose evaluation was mostly triggered by low bone mass, our hypercalcemic cohort had a preponderance of osteoporosis by WHO criteria at the more highly cortical radius site (42%), with fewer having osteoporosis at the lumbar spine and total hip (25 and 29%, respectively).

Longitudinal follow-up

Patients were followed up for 3.1 ± 0.3 yr (maximum 8 yr; median 3.0; follow-up: 1 yr, n = 7; 2 yr, n = 9; 3 yr, n = 7;

TABLE 1. Baseline biochemical and bone densitometric parameters

	Mean (SE)	Median	Range	Reference range
Serum corrected calcium (mg/dl)[a]	9.4 (0.1)	9.3	8.5–10.2	8.5–10.4
Serum uncorrected calcium (mg/dl)	9.6 (0.1)	9.5	9.0–10.4	8.5–10.4
PTH IRMA (pg/ml)	93 (5)	79	65–182	10–65
Serum phosphorus (mg/dl)[b]	3.3 (0.1)	3.2	2.4–4.8	2.1–4.3
Urinary calcium (mg per 24 h)[a]	193 (12)	192	71–350	50–300
25-hydroxyvitamin D (ng/ml)[c]	33 (1)	32	20–54	9–54
1,25-dihydroxyvitamin D (pg/ml)[d]	62 (4)	55	31–109	19–67
BUN (mg/dl)[e]	16 (1)	15	10–27	7–30
Serum creatinine (mg/dl)[f]	0.9 (0.03)	0.9	0.6–1.2	0.5–1.2
Creatinine clearance (ml/min per 1.73 m^2)	74 (2)	75	52–106	
Alkaline phosphatase (U/liter)	72 (5)	73	39–134	20–125
Urinary N-telopeptide (nM BCE per mM creatinine)	38 (5)	34	7–69	10–110
BMD lumbar spine (g/cm^2)	0.857 (0.029)	0.873	0.567–1.163	
BMD lumbar spine T-score	−2.00 (0.253)	−1.80	−4.4 to +1.1	
BMD femoral neck (g/cm^2)	0.697 (0.025)	0.705	0.397–1.069	
BMD femoral neck T-score	−1.84 (0.184)	−2.00	−4.1 to +0.7	
BMD distal one third radius (g/cm^2)	0.582 (0.028)	0.571	0.473–0.695	
BMD distal one third radius T-score	−1.74 (0.22)	−1.80	−3.6 to +0.02	

BUN, Blood urea nitrogen; BCE, bone collagen equivalent.

[a] To convert calcium from milligrams per deciliter to millimoles per liter, multiply by 0.25.

[b] To convert phosphorus from milligrams per deciliter to millimoles per liter, multiply by 0.323.

[c] To convert 25-hydroxyvitamin D from nanograms per milliliter to nanomoles per liter, multiply by 2.496.

[d] To convert 1,25-dihydroxyvitamin D from picograms per milliliter to picomoles per liter, multiply by 2.6.

[e] To convert BUN from milligrams per deciliter to millimoles per liter, multiply by 0.357.

[f] To convert creatinine from milligrams per deciliter to micromoles per liter, multiply by 88.4.

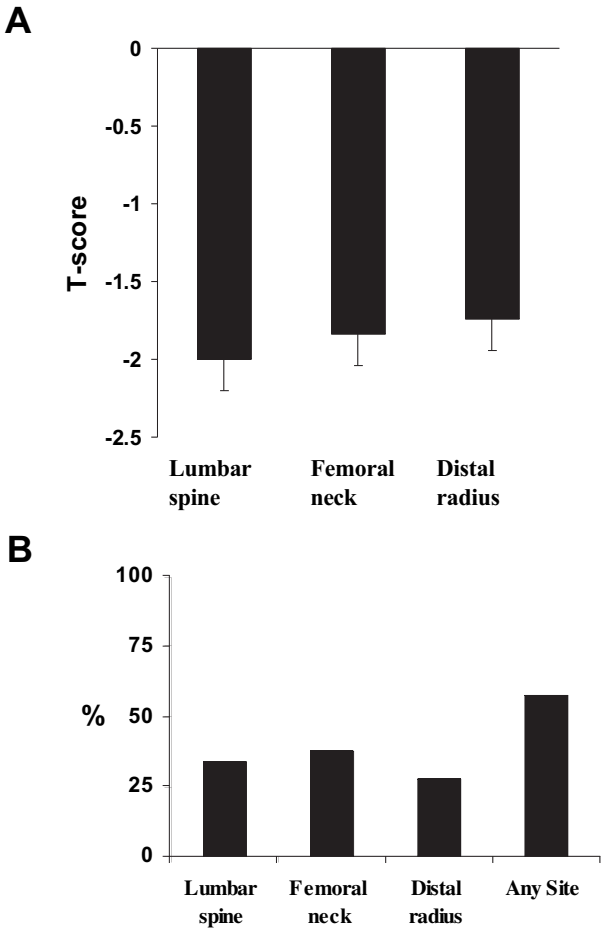

FIG. 1. BMD in patients with normocalcemic PHPT. A, T-Score by site. B, Percentage of patients with osteoporosis by site.

4 yr, n = 7; ≥ 5 yr, n = 7). Seven patients (19%) became hypercalcemic, all within the first 3 yr of observation. None of the remaining 17 individuals who have been followed for 3 yr or longer developed hypercalcemia. Among the 30 patients who remained normocalcemic, serum ionized calcium levels were normal in the 20 patients in whom these data were available. Patients who became hypercalcemic had higher baseline serum calcium levels than those who did not [9.7 ± 0.2 *vs.* 9.3 ± 0.09 mg/dl, $P < 0.01$ (2.4 ± 0.05 *vs.* 2.3 ± 0.02 mmol/liter); Table 2]. They also tended to be older and had higher baseline urinary calcium excretion. There was no significant difference in baseline serum PTH levels between those who became hypercalcemic and those whose serum calcium remained within the normal range. Patients who became hypercalcemic did not have lower baseline BMD at any site than those who had stable serum calcium levels over time, nor did they lose bone more substantially under observation.

In addition to monitoring for the emergence of hypercalcemia, patients were assessed for other indicators of progressive PHPT. In all, 41% of patients (15 of 37) developed evidence for progressive hyperparathyroid disease (Table 3). Two persistently normocalcemic patients developed overt signs of classical PHPT (one fracture, one kidney stone). Patients were also followed up for emergence of National Institutes of Health (NIH) guidelines for parathyroidectomy (6). None of the seven patients who became hypercalcemic met surgical criteria by that parameter alone because their serum calcium was within 1 mg/dl of normal. Marked hypercalciuria (≥400 mg/d) developed in two patients (one who became hypercalcemic and one who did not). Four patients who did not meet WHO criteria for osteoporosis at baseline had sufficient bone loss over time that they met this surgical guideline during follow-up; only one of the individuals who became osteoporotic also developed hypercalcemia. Bone density declined by at least 5% at one or more skeletal site in 43% of patients, with similar rates of decline seen at all skeletal sites (Table 4). A more significant rate of decline (>10%) was observed in six of the 30 subjects with repeated BMD measurements. In this group, significant bone loss tended to be more frequent at the hip and forearm than at the spine (4% at the spine, 10% at the hip, and 13% at the radius). The magnitude of BMD loss did not correlate with the degree of PTH excess. Patients who had osteoporosis at baseline evaluation did not lose more BMD than did those with higher bone density.

TABLE 2. Comparison of baseline parameters between individuals who remained normocalcemic and those who became hypercalcemic

Baseline parameter	Patients who became hypercalcemic (n = 7)	Persistently normocalcemic patients (n = 30)	*P* value
Age (yr)	64 (2)	57 (2)	0.028
Years of follow-up	3.1 (0.6)	3.0 (0.3)	NS
Baseline serum Ca (mg/dl)[a]	9.7 (0.2)	9.3 (0.09)	0.003
PTH IRMA (pg/ml)	96 (15)	93 (5)	NS
Serum phosphorus (mg/dl)[b]	3.4 (0.2)	3.3 (0.1)	NS
Urinary calcium (mg per 24 h)[a]	230 (13)	183 (15)	0.024
25-Hydroxyvitamin D (ng/ml)[c]	29 (3)	33 (2)	0.037
1,25-Dihydroxyvitamin (pg/ml)[d]	62 (11)	62 (4)	NS
Urinary NTX (nM BCE per mM creatinine)	41 (11)	38 (5)	NS
Lumbar spine T-score	−1.47 (0.59)	−2.17 (0.28)	NS
Femoral neck T-score	−1.78 (0.29)	−1.85 (0.22)	NS
Distal one third radius T-score	−1.81 (0.45)	−1.71 (0.25)	NS

NTX, N-telopeptide; BCE, bone collagen equivalent; NS, not significant.
[a] To convert calcium from milligrams per deciliter to millimoles per liter, multiply by 0.25.
[b] To convert phosphorus from milligrams per deciliter to millimoles per liter, multiply by 0.323.
[c] To convert 25-hydroxyvitamin D from nanograms per milliliter to nanomoles per liter, multiply by 2.496.
[d] To convert 1,25-dihydroxyvitamin D from picograms per milliliter to picomoles per liter, multiply by 2.6.

TABLE 3. Patients developing new manifestations of primary hyperparathyroidism over time

Any	15
Hypercalcemia	7
Kidney stone	1
Fracture	1
New osteoporosis	4
Urinary calcium greater than 400 mg per 24 h	2
Greater than 10% decline in BMD	6

Parathyroid surgery

Of the 16 patients tested, ^{99m}technetium-labeled sestamibi scans suggested the presence of a parathyroid adenoma in eight. Three of the hypercalcemic patients underwent parathyroid exploration with removal of one or more adenomas. Four additional patients with normal serum calcium levels also had successful parathyroidectomy. They had surgery because they developed skeletal criteria (osteoporosis, n = 3) for parathyroidectomy (6) or, in one case, because of patient choice. Pathological examination revealed findings similar to those found in typical PHPT. In the hypercalcemic patients, a single parathyroid adenoma was removed from two patients (weights 500 mg each), whereas two hyperplastic glands were removed from one patient (glands weighed 100 mg each). In the normocalcemic patients, a single adenoma was removed in one patient (weight 200 mg), one hyperplastic gland was removed in two patients (gland weights 200 and 140 mg), and two hyperplastic glands were removed from one patient (gland weight 700 and 200 mg). Serum calcium normalized in the hypercalcemic patients after surgery. In the normocalcemic patients who underwent parathyroid surgery, serum calcium levels did not change (preoperative median 9.6, range 9.4–10.3 mg/dl; postoperative median 9.6, range 8.9–10.3 mg/dl), despite a significant fall in PTH levels (preoperative median 103, range 79–164 pg/ml; postoperative median 50, range 21–57 pg/ml).

Discussion

In this report, we describe the clinical course of 37 patients with normocalcemic PHPT who were followed for up to 8 yr (median 3.0). Our diagnostic criteria excluded those with elevated serum or urinary calcium levels (the latter because they could lead to a secondary rise in PTH concentration). We did not find these patients to have the clinical phenotype typical of mild asymptomatic PHPT. Confirming our preliminary observations (4), we also did not find evidence of preferential cortical bone loss by BMD (3). Indeed, the only finding suggestive of typical mild PHPT was an elevated 1,25-dihydroxyvitamin D concentration in 24% of patients. Instead the majority of patients had clinical features of classical PHPT: nephrolithiasis (14%), osteoporosis (57%), and/or fragility fracture (11%). Although many were initially discovered as part of an evaluation for low bone density, some did develop further features of PHPT during the course of follow-up (hypercalcemia in 19%, marked hypercalciuria in 5%, or progressive cortical bone loss in 29%). Progressive bone loss in these patients was not confined to the more highly cortical distal radius, instead occurring at all sites.

TABLE 4. Bone loss over time by site

	>5% decline in BMD[a]	>10% decline in BMD
Any site	7/30 (23%)	6/30 (20%)
Lumbar spine	3/27 (11%)	1/27 (4%)
Femoral neck	5/29 (17%)	3/29 (10%)
Distal one third radius	4/24 (17%)	3/24 (13%)

[a] Percentage loss from baseline BMD.

This is the largest study of normocalcemic PHPT in which there are longitudinal clinical, biochemical, and bone densitometric data on a cohort in whom secondary causes of hyperparathyroidism have been rigorously ruled out. The phenomenon of normocalcemic primary hyperparathyroidism has been debated in the literature for more than 30 yr. Earlier reports of normocalcemic hyperparathyroidism were limited by methodological limitations in PTH measurement and issues related to the possible coexistence of secondary causes for elevated PTH levels (7–13). In one such study, patients were clearly vitamin D deficient (mean 25-hydroxyvitamin D level 13 ng/ml or 33 nmol/liter), suggesting that secondary hyperparathyroidism could have accounted for the normal calcium levels in this population (14). Another study did not assess BMD at the distal one third radius site, the key site for bone loss in hypercalcemic PHPT, nor was BMD measured over time (15). The idea that normocalcemic PHPT represents the earliest manifestation of the disorder (4, 15–17), however, remains a credible hypothesis and one that is supported by the current study. In our cohort, hypercalcemia did develop in a small subset of patients. They had higher serum calcium levels at baseline than those who did not develop hypercalcemia. The fact that some of those followed for the longest time did not show evidence of disease progression suggests that there is no uniform time course for the emergence of hypercalcemia in normocalcemic PHPT and in fact raises the possibility that some of these patients may never develop the more typical hypercalcemic phenotype of the disease. These individuals may have reached a new steady state with regard to serum calcium and PTH levels and may therefore never become hypercalcemic. One could postulate, in such cases, that these patients had serum calcium levels before developing hyperparathyroidism that were lower and that they increased but stayed within the reference range for serum calcium. In these patients we observed that the emergence of clinical features of PHPT is similarly unpredictable. Extended follow-up of patients with normocalcemic PHPT will allow for a more complete picture of this unfolding clinical scenario.

Although it was our hypothesis that patients with normocalcemic PHPT represent the earliest clinical manifestation of typical mild asymptomatic PHPT, the data in this report support a more complex picture. Indeed, although many of these patients were initially evaluated because of low bone density, there is no evidence of the preponderance of cortical bone loss seen in typical hypercalcemic patients with mild PHPT. Furthermore, fragility fractures are much more frequent in this cohort than is seen in typical mild PHPT (3). This finding is most likely due to selection bias because more than half of these patients were discovered during evaluation for osteoporosis, fragility fracture, or low BMD.

The data in this report suggest that these patients are not the forerunners of mild asymptomatic PHPT. What we and others are describing now is likely to be another presentation of PHPT in which patients have already developed signs and symptoms of the disease but in whom the serum calcium concentrations remain normal. Rather than representing the earliest form of asymptomatic PHPT, the data suggest that these individuals may represent the earliest form of symptomatic PHPT.

The marked selection and referral bias inherent in this study makes it impossible to use these data to predict the prevalence of these laboratory abnormalities (normal serum calcium and elevated PTH levels). However, this characterization may have descriptive importance that is helpful in two ways. First, it may help in the management of the increasing number of such patients seen in subspecialty metabolic bone practices. Second, it may be important as we consider the various phenotypes of a disease once thought to have a unidimensional clinical picture.

Thus, these patients are likely to be only part of the description of the earliest stage of primary hyperparathyroidism. The discovery of the modern clinical phenotype of PHPT was due primarily to the introduction of the multichannel biochemical screening test that became available in the early 1970s. Asymptomatic PHPT as a clinical disorder is thus the product of an epidemiological screening experience in which large populations had serum calcium measurements without regard to symptoms or signs of hypercalcemia or PHPT. In contrast to the case of the multichannel autoanalyzer, it would be inappropriate for clinicians to consider widespread measurement of PTH to screen for normocalcemic PHPT. However, these data do suggest that only such a large-scale evaluation of PTH levels in healthy normocalcemic but asymptomatic individuals would succeed in identifying those with the earliest forms of truly asymptomatic primary hyperparathyroidism.

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