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COMMENT

"Incipient" Primary Hyperparathyroidism: A "Forme Fruste" of an Old Disease

SHONNI J. SILVERBERG AND JOHN P. BILEZIKIAN

Departments of Medicine (S.J.S., J.P.B.) and Pharmacology (J.P.B.), College of Physicians and Surgeons, Columbia University, New York, New York 10032

Although primary hyperparathyroidism today is often a relatively asymptomatic disease, it has distinct biochemical and skeletal features. These features are present at diagnosis and are generally stable over time, leading to the theory of a biphasic disease course in which alterations occur during a preclinical phase. Measurement of calciotropic hormones in individuals undergoing skeletal evaluation has led to the identification of normocalcemic individuals with elevated PTH levels. We hypothesize that these patients represent the earliest manifestations of primary hyperparathyroidism

Twenty-two patients had hyperparathyroidism (94 ± 29 pg/ml) and normal corrected serum calcium levels (2.40 ± 0.02 mmol/liter). No secondary causes of hyperparathyroidism were found. PTH levels did not correlate with urinary calcium concentration, renal function, vitamin D concentrations, or bone density. The relationship between PTH and serum calcium (regression slope, +0.004) was identical in normocalcemic and hypercalcemic hyperparathyroid patients. Preferential cortical bone loss, characteristic of patients with primary hyperparathyroidism, was not seen (T-score: spine, −1.6; hip, −1.8; distal one-third radius, −1.3). In up to 12 months of observation, three patients have developed hypercalcemia, and one has had two adenomas removed.

These patients with elevated PTH levels in the absence of hypercalcemia may provide a window into this previously unrecognized stage of the disease and permit investigators to track its evolution in ways that have not heretofore been possible. (*J Clin Endocrinol Metab* 88: 5348–5352, 2003)

MOST PATIENTS WITH mild or asymptomatic primary hyperparathyroidism demonstrate stable biochemical indices and bone density for at least 10 yr (1, 2). This observation raises a puzzling question. How can a disorder with such a particular biochemical, densitometric, and histomorphometric phenotype appear full blown, as it were, with little or no evidence of progression over time? For example, how did the pattern of bone loss in primary hyperparathyroidism develop? This vexing conundrum has led investigators to propose a biphasic disease course in which changes such as reduced cortical bone density develop early, over a period of time before the disease becomes clinically recognized (3).

The pathophysiological construct calls for a disorder that is not clinically recognized when it begins (phase 1), followed later by the appearance of its biochemical hallmark, hypercalcemia (phase 2). Up to now, it is only in phase 2 that the disease has been recognized. If one had insight into the putative earlier stage of the disorder, one would expect it to be characterized first by elevated PTH levels in the absence of hypercalcemia. During this clinically silent period, the patient would not come to medical attention because the serum calcium is normal. However, if these patients were to have PTH levels measured, one might expect to discover them. Such patients would represent the earliest manifestation of primary hyperparathyroidism, the elusive phase 1 of the disease.

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

The challenge has been to recognize a clinical context in which PTH levels are measured in individuals whose serum calcium is completely normal. Such a setting has now become relatively common because of a proactive approach, espoused by many endocrinologists, to evaluate the skeletal status of women at risk for osteoporosis not only with BMD determination but also with calciotropic hormone measurements. We have recently discovered a group of such individuals referred to our Metabolic Bone Diseases Unit. No secondary causes of elevated PTH were found. It is our hypothesis that the patients we describe in this report represent the earliest manifestations of PTH, a "forme fruste" of the disease.

Patients and Methods

Patients were recruited from the clinical facilities of the Metabolic Bone Diseases Unit at Columbia Presbyterian Medical Center (New York, NY). All patients simultaneously had elevated serum PTH concentration by the intact immunoradiometric assay (IRMA) (normal range, 10–65 pg/ml) and normal total serum calcium concentration (corrected for serum albumin). This was confirmed on at least two separate occasions. This PTH assay has been shown to measure not only PTH(1–84), but also large carboxy-terminal fragment(s) of PTH (see *Discussion*). All patients had 25-hydroxyvitamin D concentrations within the physiologically normal range (50–130 nmol/liter). Those with low normal values (22–49 nmol/liter) were excluded. Patients were also excluded if they had evidence of familial hypocalciuric hypercalcemia or any secondary cause for hyperparathyroidism, including liver disease, renal disease, or significant hypercalciuria (urinary calcium >87.5 mmol in 24 h), gastrointestinal disease associated with malabsorption, or other metabolic bone disease that could affect PTH levels (*e.g.* Paget's disease). Patients were not on any medication that might affect PTH

levels (lithium carbonate, thiazide diuretics) or calcium metabolism (estrogens, loop diuretics, bisphosphonates, and anticonvulsants).

All patients had a full medical history and physical examination, biochemical studies, and bone densitometry. Serum total calcium, phosphorus, and alkaline phosphatase activity were measured by automated techniques (Technicon Instruments, Tarrytown, NY). Serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D urinary calcium, and N-telopeptide were measured as previously described (2). Urinary N-telopeptide excretion was measured in 12 patients, whereas eight patients had ionized calcium levels measured in various laboratories. Bone mineral density (BMD) of the lumbar spine (L2–L4), femoral neck, and distal one-third of the nondominant radius was performed by dual x-ray absorptiometry (Hologic Inc., Waltham, MA). Data are reported for both absolute bone density and Z- and T-scores (SD values from the mean for a sex- and age-matched and young reference population, respectively).

Regression analysis was used to determine relationships among measured variables, and unpaired *t* tests assessed differences among groups of patients (*i.e.* patients with and without nephrolithiasis, patients with and without hypercalcemia). The study was approved by the Institutional Review Board of Columbia Presbyterian Medical Center, and all patients gave informed consent.

Results

Twenty-two patients (mean age, 57 ± 10 yr; Table 1) were identified with hyperparathyroidism and normal total serum calcium levels (corrected to a serum albumin concentration of 4 g/liter) and met the inclusion and exclusion criteria outlined above. Ionized calcium levels were also normal in the eight representative patients in whom they were assessed and were completely concordant with the corrected total serum calcium concentration. The group included 20 women (three premenopausal, 17 postmenopausal) and two men (Table 1). Patients were referred to the Metabolic Bone Diseases Unit for the following reasons: osteoporosis (n = 10), vertebral compression fracture (n = 1), and kidney stone (n = 3). Eight other patients referred themselves to our center because they were concerned about preserving their bone health; they did not have osteoporosis.

PTH levels did not correlate with urinary calcium concentration, renal function, vitamin D concentrations, or BMD (absolute, Z-score or T-score). We compared the relationship between PTH and serum calcium in this group of patients with values previously obtained in the cohort of patients from our ongoing natural history study (2, 4, 5), in whom the diagnosis of primary hyperparathyroidism was based on the presence of hypercalcemia and elevated serum PTH levels (Fig. 1). The slope of the regression analysis (+0.004) was identical in both normocalcemic and hypercalcemic patients. The y-intercept in those with normal serum calcium concentration [2.31 mmol/liter (9.3 mg/dl)] was lower than in those who were hypercalcemic [2.58 mmol/liter (10.4 mg/dl)]. In both groups, it should be noted that the relationship between serum calcium and PTH was a positive one. This positive relationship is a distinct pathophysiological departure from the usual relationship defined in normal individuals in whom the line is defined by an inverse relationship between the serum calcium and the PTH level. This point helps to confirm that these normocalcemic patients have abnormal PTH secretory dynamics.

Patients were assessed for the presence of other laboratory hallmarks of primary hyperparathyroidism. Mild hypercalciuria was present in four patients (urinary calcium excretion, 75–82 mmol); seven patients (32%) had frankly elevated levels of 1,25-dihydroxyvitamin D. Hypophosphatemia was noted in only one patient, and no one had bone density at the cortical site that was low for their age (distal one-third radius Z-score < -2). In fact, by BMD, these patients did not show the preferential cortical bone loss that is characteristically seen when patients with primary hyperparathyroidism are first evaluated (6). Using World Health Organization diagnostic criteria (T-score, < -2.5), more patients had osteoporosis at the spine (n = 5 or 23%; mean T-score, −1.6) and hip (n = 6 or 27%; mean T-score, −1.8) than at the distal one-third radius site (n = 3 or 14%; mean T-score, −1.3). The biochemical profile did not differ among patients with and without nephrolithiasis (serum calcium, 2.47 ± 0.12 mmol/liter with stones *vs.* 2.40 ± 0.12 mmol/liter with no stones; PTH, 85 ±

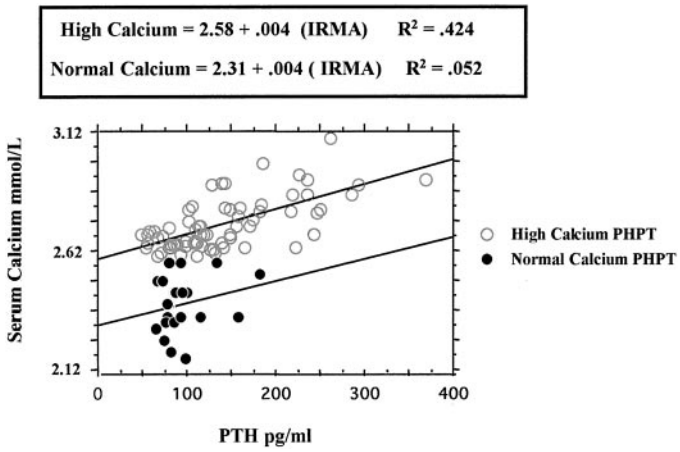

FIG. 1. Regression of serum calcium and PTH levels in patients with and without hypercalcemia. PHPT, Primary hyperparathyroidism.

TABLE 1. Biochemical characteristics of 22 patients with hyperparathyroidism and normal serum calcium levels

	Mean ± SD	Range	Normal
Serum calcium	2.40 ± 0.02	2.17–2.55	2.10–2.59 mmol/liter
Serum phosphorus	1.07 ± 0.16	0.77–1.26	0.81–1.48 mmol/liter
Urinary calcium	50 ± 21	16–82	<75 mmol/24 h
PTH IRMA	94 ± 29	66–182	10–65 pg/ml
25(OH) vitamin D	85 ± 7	50–155	22–130 nmol/liter
1,25-$(OH)_2$ vitamin D	132 ± 10	65–262	6–144 pmol/liter
BUN	19 ± 7	11–35	8–24 mg/dl
Serum creatinine	0.9 ± 0.2	0.6–1.3	0.6–1.2 mg/dl
Alkaline phosphatase	77 ± 33	39–176	<100 IU/liter
Urinary N-telopeptide	31 ± 18	7–56	<85 nmol BCE/mmol creatinine

BUN, Blood urea nitrogen.

TABLE 2. Profile of a 59-yr-old woman with two parathyroid adenomas

	Baseline	1 Yr later
Serum calcium (mmol/liter)	2.37	2.77
PTH (pg/ml)	95	99
BUN/creatinine (mg/dl)	13/1.1	22/1.0
25-hydroxyvitamin D (nmol/liter)	72	67
1,25-dihydroxyvitamin D (pmol/liter)	156	110
Urinary calcium (mmol/24 h)	65	68
Lumbar spine BMD (g/cm^2)	0.919	0.900
Total hip BMD (g/cm^2)	0.791	0.801
Distal 1/3 radius BMD (g/cm^2)	0.670	0.638

BUN, Blood urea nitrogen.

12 pg/ml with stones *vs.* 95 ± 31 pg/ml with no stones; and urinary calcium excretion, 42 ± 13 mmol/d with stones *vs.* 52 ± 22 mmol/d with no stones).

To date, patients have been followed for up to 12 months. Three have developed frank elevations of the serum calcium level. PTH levels were higher in the patients whose calcium levels became elevated (137 ± 44 *vs.* 88 ± 21 pg/ml; $P < 0.005$), but baseline calcium levels were indistinguishable (9.9 ± 0.3 *vs.* 9.6 ± 0.3 mg/dl; $P = 0.3$). ^{99}Technetium-labeled Sestamibi imaging did not reveal clear evidence of a parathyroid adenoma in the two cases in which it was performed. One of these patients was a 59-yr-old woman who initially presented because of a family history of osteoporosis. Her bone density study revealed osteopenia at the lumbar spine and hip (both sites, T-score = −1.2) and normal bone density at the radius (T-score = −0.4). One year after documenting elevated PTH levels, the patient became hypercalcemic (Table 2). Bone densitometry revealed a 5% decline at the radius. She subsequently had two adenomas surgically removed.

Discussion

The term "normocalcemic primary hyperparathyroidism" was coined in the 1960s by Wills, who described a group of patients whom he thought were different from the typical hypercalcemic patient (7). In retrospect, these patients reflected a variant of hypercalcemic primary hyperparathyroidism. **S**ome of those fitting the original description actually did have hypercalcemia. Others had marked hypercalciuria discovered in the context of nephrolithiasis. In still others, the hyperparathyroidism might have been apparent, but not real, due to the imperfect state of PTH assay development at the time (8). The midmolecule RIA for PTH then in common use measured retained hormone fragments in addition to the intact bioactive molecule. Thus, spuriously elevated PTH levels in some patients, particularly those with renal insufficiency in which clearance of hormone fragments is impaired, could have accounted for the presentation in some patients. Even using the IRMA assay for PTH, there have been reports of surgically confirmed normocalcemic primary hyperparathyroidism (9). However, it has become clear only recently that many purported cases of normocalcemic primary hyperparathyroidism can be resolved by a rigorous search for causes of secondary hyperparathyroidism. In particular, in the days of Wills *et al.* when normocalcemic primary hyperparathyroidism was first described, vitamin D metabolism, reference ranges, and physiological ranges were not well defined. Some patients undoubtedly had coexisting vitamin D deficiency, which lowered their calcium levels into the normal range. Furthermore, we now appreciate the difference between the laboratory reference range of 25-hydroxyvitamin D (22–130 nmol/liter) and the normal circulating physiological range of 25-hydroxyvitamin D (> 50 nmol/liter) (10, 11). This is the first report that takes into account these features and thus rigorously demonstrates the existence of normocalcemic primary hyperparathyroidism.

The existence of patients with normocalcemic primary hyperparathyroidism satisfies many expectations about the disease. Currently, many of the clinical manifestations of primary hyperparathyroidism are already present when the disorder is diagnosed, and the disease usually does not progress. It is difficult to explain this clinical truism without postulating a beginning to the disease that is unrecognized until hypercalcemia surfaces. In asymptomatic primary hyperparathyroidism, Rao *et al.* (1) reported stable biochemical indices over a 46-month (mean) follow-up of patients who were not considered to be surgical candidates. Forearm BMD, the only site measured, was unchanged over this period. Our study (2) monitoring both cortical and cancellous sites as well as biochemical indices confirmed that in most patients there is little evidence for disease progression once the disease has become manifest, for a period of time that is now well over a decade.

The biphasic disease course proposed by Rao *et al.* (1) to explain this conundrum suggested a subclinical phase 1 during which many of the distinctive characteristics of the disease emerge (Fig. 2, older construct). Our data help to define this phase more specifically by elevated PTH levels in the absence of hypercalcemia and without the characteristic densitometric findings in the disease. Elevated PTH levels in normocalcemic patients are likely to provide a key window into this previously unrecognized stage of primary hyperparathyroidism, expanding the scope of clinical awareness of the disease process (Fig. 2) and permitting investigators to track its evolution in ways that have not heretofore been possible.

The patients we have identified have normal corrected serum calcium concentrations, normal ionized calcium concentrations, no evidence for familial hypocalciuric hypercalcemia, and no identifiable cause for secondary hyperparathyroidism. It is important to emphasize again that normal

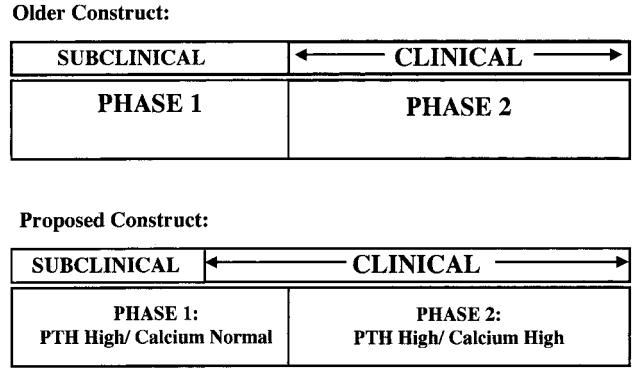

FIG. 2. Primary hyperparathyroidism: an evolving view.

physiological concentrations of 25-hydroxyvitamin D levels are a key part of this definition. Patients were not required to have a level of 1,25-dihydroxyvitamin D within the normal reference range because in primary hyperparathyroidism, levels of this metabolite are typically elevated due to PTH-stimulated conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. It is of interest that the percentage of patients with normocalcemic primary hyperparathyroidism who had elevated levels of 1,25-dihydroxyvitamin D (30%) is virtually identical to the percentage of patients with hypercalcemic primary hyperparathyroidism whose 1,25-dihydroxyvitamin D levels were elevated (12). Thus, in this respect, the biochemical profile in this earlier form of primary hyperparathyroidism was not different from patients with hypercalcemia. These patients had no evidence for preferentially decreased low bone density at the distal radius (one third site), as compared with the spine and hip. Indeed, Z-scores (age-matched comparison) ranged from −0.044 (radius) to −0.505 (hip), suggesting that these individuals had densitometric profiles quite typical for their age and sex. Despite a lack of evidence for a typical PTH effect in the skeleton, the abnormal relationship between calcium and PTH mirrored that seen in our large well-established cohort of patients with more traditional primary hyperparathyroidism.

A few words of caution in the interpretation of this data are notable. One concerns the PTH assay that was used. Although this assay is in common use, we now know that it measures, in addition to the intact PTH(1–84) molecule, a very large fragment cleaved somewhere near the extreme N-terminal end of the molecule (8, 13, 14). The abundance of this fragment in normal individuals and in patients with traditional primary hyperparathyroidism approaches 50% (15, 16). It has been proposed that some large fragments, particularly PTH(7–84), may have a biological effect to antagonize the actions of PTH(1–84) to raise the serum calcium (17, 18). Although we view this as unlikely, it is possible that in these patients with the earliest manifestations of primary hyperparathyroidism, there is a greater abundance of a circulating large fragment of PTH, which could lower serum calcium levels. This would not argue against this presentation as a very early form of primary hyperparathyroidism, but would rather help to explain why such individuals are not yet hypercalcemic. The recent availability of a newer IRMA with specificity only for PTH(1–84) should help to clarify this point, allowing a comparison of relative proportions of PTH(1–84) and fragment (14–16). Another possibility is that these patients are relatively resistant to PTH. This could explain their normal serum calcium level as well as their uncharacteristic densitometric profile. If this were the case, however, one would have to postulate that the relative resistance is transient or that these patients will not evolve into the more traditional phase of the disease. Furthermore, it is possible that they represent a completely different disorder of calcium sensing. These patients could harbor an abnormal form of the calcium receptor, analogous to, but not as severe as, patients who have been described with activating mutations of the calcium receptor. Under these circumstances, one would not expect these patients to evolve into the more traditional form of primary hyperparathyroidism. Because we already have evidence that several members of this cohort are evolving into the putative second phase of the disease, we view the possibilities of an abnormal ratio of PTH(1–84)/PTH(7–84), PTH resistance, or a primary abnormality of the calcium receptor as unlikely explanations for our observations. Finally, it must be emphasized that this report cannot be viewed as an epidemiological study, nor is it meant to imply that the finding of normocalcemic PHPT is common. The prevalence of this disorder is unknown, but it clearly does not justify widespread screening of PTH levels outside a research setting.

In summary, this report describes a group of patients who may represent the earliest manifestation of primary hyperparathyroidism. With further investigation, it is likely that they will provide new insights into the development of the disorder and fulfill some of the postulated expectations of its earliest manifestations. One major expectation is that changes will occur progressively as these patients are monitored over time, an observation that may well compare rather dramatically with the lack of change that is typical of patients with the more overt form of the disease. Information gained from further study of these patients should fill important gaps in our understanding of the development of modern primary hyperparathyroidism.

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Address all correspondence and requests for reprints to: Shonni J. Silverberg, M.D., Department of Medicine, College of Physicians and Surgeons, 630 West 168th Street, New York, New York 10032. E-mail: sjs5@columbia.edu.

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