Primary Hyperparathyroidism

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Background: Primary hyperparathyroidism (PHPT), the most common cause of hypercalcemia, is most often identified in postmenopausal women. The clinical presentation of PHPT has evolved over the past 40 years to include three distinct clinical phenotypes, each of which has been studied in detail and has led to evolving concepts about target organ involvement, natural history, and management.

Methods: In the present review, I provide an evidence-based summary of this disorder as it has been studied worldwide, citing key concepts and data that have helped to shape our concepts about this disease.

Results: PHPT is now recognized to include three clinical phenotypes: overt target organ involvement, mild asymptomatic hypercalcemia, and high PTH levels with persistently normal albumin-corrected and ionized serum calcium values. The factors that determine which of these clinical presentations is more likely to predominate in a given country include the extent to which biochemical screening is used, vitamin D deficiency is present, and whether parathyroid hormone levels are routinely measured in the evaluation of low bone density or frank osteoporosis. Guidelines for parathyroidectomy apply to all three clinical forms of the disease. If surgical guidelines are not met, parathyroidectomy can also be an appropriate option if no medical contraindications are present. If either the serum calcium or bone mineral density is of concern and surgery is not an option, pharmacological approaches are available and effective.

Conclusions: Advances in our knowledge of PHPT have guided new concepts in diagnosis and management. **(*J Clin Endocrinol Metab* 103: 3993–4004, 2018)**

Within the lifetimes of many of us, primary hyperparathyroidism (PHPT), the most common cause of hypercalcemia, has appeared to change in its clinical presentation regarding the involvement of classic and nonclassic target organs. Progress in understanding this disease has also been marked by the application of technologies, not available previously, leading to recognition of a disease that has the potential to be pervasive even when discovered incidentally. However, this devastating potential to be pervasive, a feature that was realized by the famous aphorism coined by Fuller Albright as a disease of bones, stones, moans, and groans (1), has a variable natural history that can remain as asymptomatic as it was when it was first discovered or progress to clinical symptoms. The decades have also given new insights into the surgical and medical management of PHPT, along with guidelines that have been periodically updated since 1991 (2–5). A disease that was worthy of case reports in the 1930s (6), now has seen >6000 published reports in the past 20 years. Moreover, it has spawned interest in the PTH molecule itself and its pleotropic cellular and molecular mechanisms of actions (7, 8). The disease has also catalyzed interest and new insights into its counterpart but much more uncommon disorder of parathyroid function, namely hypoparathyroidism (9). The disease has given us a greater appreciation of bone, as controlled by PTH and other molecular regulators that work in concert with

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 6 June 2018. Accepted 24 July 2018.
First Published Online 27 July 2018

Abbreviations: BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; FHH, familial hypocalciuric hypercalcemia; HRpQCT, high-resolution peripheral quantitative computed tomography; NPHPT, normocalcemic primary hyperparathyroidism; PHPT, primary hyperparathyroidism; TBS, trabecular bone score.

each other to keep our skeleton and circulating elements under exquisite control under normal circumstances. With this perspective, I provide an update on PHPT based, in part, on my investigative experience with this disease that has extended for over four decades.

Diagnosis

PHPT is due to abnormal, incompletely-regulated secretion of PTH from one or more of the four parathyroid glands (10, 11). In virtually all cases, the disorder will be benign with either a single adenoma (80%) or multiple gland, generally hyperplastic, disease (20%) responsible. PHPT is characterized by hypercalcemia and levels of PTH that are inappropriately high for the hypercalcemic state. Typically, the PTH level is frankly elevated, but it can also be within the normal range. In both situations, detectable or elevated levels of PTH are clearly inappropriate when the serum calcium is elevated. Well-documented PHPT has been reported with PTH levels as low as 20 to 25 pg/mL, given a normal range of ~10 to 65 pg/mL (12). In virtually all other etiologies of hypercalcemia, the PTH level will be frankly suppressed (12). Interfering substances such as biotin can cause the PTH to read low with certain assays (13). When biotin is discontinued, the repeated PTH measurement level will be more compatible with the diagnosis of PHPT if the patient has the disease.

The differential diagnosis of PTH-dependent hypercalcemia includes the use of thiazide diuretics or lithium (14, 15). If possible, these medications should be discontinued. Although the serum calcium will return to normal in some patients, most will demonstrate persistence of the biochemical hallmarks of PHPT, namely hypercalcemia and elevated levels of PTH. More perplexing to some has been the distinction between familial hypocalciuric hypercalcemia (FHH), a rare disorder of the *CASR* (calcium-sensing receptor gene) and PHPT (16). It is important to recognize that FHH is a rare disorder. In addition, FHH has such high penetrance that virtually all patients will be shown to have hypercalcemia in their young adult years, by the age of 30. A family history is also usually present. The typical postmenopausal woman who develops biochemical signs of PHPT in the first decade after the menopause is highly unlikely statistically to have FHH. In FHH, the 24-hour urinary calcium excretion will be very low (<100 mg) and the calcium clearance/creatinine clearance ratio will be <0.01. Because of PTH's calcium-conserving renal actions, low urinary calcium excretion (*i.e.,* calcium clearance/creatinine clearance ratio <0.01) can also be compatible with PHPT, especially for patients whose dietary calcium has been restricted. Genetic testing for the most common form of FHH (*i.e.,* mutations in the CaSR), is readily available if FHH is considered to be a plausible diagnosis.

Normocalcemic PHPT

Approximately 15 years ago, our group recognized a form of PHPT that was characterized by an elevated PTH level with persistently normal concentrations of albumin-adjusted total and ionized calcium (17). The explanation for why this biochemical phenotype was discovered and is now rather common relates to our proactive approach to the evaluation of osteoporosis or low bone mass syndromes. In these clinical settings, the PTH measurement, in some centers, has become a routine part of the evaluation. In hypercalcemic PHPT, the serum calcium can occasionally be normal; however, in normocalcemic PHPT (NPHPT), the albumin-adjusted and ionized serum calcium levels will be consistently normal. The differential diagnosis of NPHPT requires exclusion of secondary causes of increased PTH. Vitamin D deficiency is one of the most important secondary causes to be ruled out. Although this point inevitably leads to a discussion of the normal range of 25-hydroxyvitamin D and immediately recalls the Institute of Medicine's definition of vitamin D deficiency (18) as a level <20 ng/mL (50 nmol/L), it is important to appreciate that the Institute of Medicine's cutpoint was directed primarily toward a normal population with no known metabolic bone disease. In the context of NPHPT, it seems reasonable to set the low threshold at 30 ng/mL (75 nmol/L), because some epidemiology studies have associated levels <30 ng/mL with progressive increases in PTH (19, 20). It is also reasonable in some situations to aim for an even higher level of 25-hydroxyvitmain D (*e.g.,* 40 ng/mL) to see whether the PTH level would become normal. Other disorders associated with a secondary increase in PTH such as renal insufficiency (estimated glomerular filtration rate <60 mL/min) and malabsorption syndromes and medications such as diuretics, lithium, bisphosphonates, and denosumab should all be ruled out before invoking the diagnosis of NPHPT. Even after known causes of secondary elevations of PTH have been ruled out, the possibility of some unrecognized secondary stimulus to account for this presentation will remain in some situations. It is also possible that those whose PTH levels are minimally elevated represent the outer fringe of the normal distribution curve for PTH. Approximately 2.5% of the normal population is likely to have PTH levels in this outer, higher fringe zone. A further consideration of NPHPT addresses the observation that an analyte such as the serum calcium will have much narrower day-to-day excursions in an individual than the normal population range. It is

possible, therefore, that some patients with NPHPT actually have hypercalcemia relative to their historically lower serum calcium values. An individual, for example, whose serum calcium was typically ~9.0 mg/dL, can be considered to have become relatively hypercalcemic but still technically normocalcemic if the calcium has increased to 10 mg/dL. The 1-mg/dL increase in serum calcium would still be within the normal population range but for that given patient decidedly higher. The patient would present ostensibly with NPHPT.

Although not the subject of the present discussion, it is noteworthy that the existence of a form of PHPT with a normal serum calcium and PTH concentration that was found only by pathological examination of abnormal parathyroid tissue has been proposed (21, 22).

Epidemiology

PHPT predominates among women, usually in their postmenopausal years, with a female/male ratio of 3 to 4:1. The prevalence varies by country and race. In the United States, for example, the prevalence of PHPT has been 0.86% (23), with a racial predilection that seems to favor blacks (24). Much wider prevalence estimates have been reported for NPHPT, 0.4% to 11% (25–27). Another determinant of the epidemiology of this disease is the extent to which routine biochemical screening is used in a country. In North American and Western European countries, where biochemical screening has been used since the early 1970s, PHPT became and continues to be a relatively common disease (28). In countries such as India, where screening is not routine, PHPT is seen much less frequently. Overall, however, the incidence and prevalence of PHPT have increased during the past several decades, even in countries that had established biochemical screening decades before (24). This could have resulted from the greater recognition and diagnostic pursuit of mild hypercalcemia and the likelihood that biochemical screening is even more widespread than previously (24, 29, 30). In countries where serum calcium has become routinely measured, the incidence of PHPT has increased. A good recent example is China, where the incidence has increased in concert with the greater use of biochemical screening (10, 28, 31). In Latin America, the disease has also seen a change in incidence as screening has become routine (32, 33).

Etiology and Risk Factors

Most patients with PHPT have single adenomatous (80%) or multiply hyperplastic (15% to 20%) parathyroid tissue. Multiglandular disease can also be manifest as two and, very rarely, three adenomas. Parathyroid carcinoma is rare, accounting for <1% of all cases of PHPT (11). Suspicion for parathyroid cancer should be increased when patients, who are typically younger by about one decade, present with much higher serum calcium and PTH levels. Invariably, renal and skeletal involvement will be readily apparent. The incidence of parathyroid cancer appears to be increasing in the United States and in China (28, 34).

Most often, PHPT is a sporadic disease, with no family history and no evidence for other endocrine gland involvement. Genetic forms of PHPT, constituting no more than 10% of the hyperparathyroid population, can be limited to the parathyroid glands or be part of a multigland endocrine syndrome (10). The germline mutations that have been associated with hereditary forms of PHPT are numerous. At least six somatic mutations have also been described (35, 36).

Environmental and modifiable risk factors that have been associated with PHPT include chronically low calcium intake, reduced physical activity, higher body weight, furosemide, and hypertension (37–40). External neck radiation (41, 42) and lithium and thiazide therapy (14, 15) are also classic risk factors. More recent experience with thiazide diuretics has suggested that hypercalcemia in this setting is most likely unmasking the underlying state of PHPT and is not likely to be reversed when the diuretic is stopped (14).

Specific Aspects of PHPT

The signs and symptoms of PHPT can be due to hypercalcemia itself, especially when the serum calcium is >12 mg/dL and/or if it has increased rapidly. Symptoms include polyuria, polydipsia, constipation, anorexia, vomiting, dehydration, arrhythmias, and altered mental status. More likely, however, the symptoms of PHPT are related not to the hypercalcemia itself but to its key target organs. Renal involvement can take the forms of hypercalciuria, nephrolithiasis, nephrocalcinosis, and/or reduced renal function (43). Although the incidence of these overt renal manifestations has declined, in the context of appreciating in many countries a milder biochemical form of the disease, more recent systematic evaluation of the kidneys among these asymptomatic patients has revealed that stones and/or nephrocalcinosis is actually present in 21% to 55% of patients with asymptomatic PHPT (44, 45).

Skeletal symptoms can take the form of any combination of fragility fractures, skeletal deformities, and bone pain. In the classic setting, o*steitis fibrosa cystica* describes the radiograph features of this presentation in which brown tumors, lytic lesions, subperiosteal bone resorption of the

phalanges, and bone cysts are seen (46, 47). When patients were first described with asymptomatic PHPT, in the early 1970s, the absence of these radiographic manifestations was assumed to mean that the skeleton was spared or not yet involved. It took the advent of bone densitometry in the mid-1980s for us to appreciate the extent to which this mild form of the disease did not spare the skeleton. Using dual energy X-ray absorptiometry (DXA), the distal one-third radius, a site of cortical bone, was shown to be low (48). The lumbar spine, a skeletal site in which trabecular bone predominates, showed lesser degrees of involvement. The hip regions, a more even admixture of trabecular and cortical bone, showed densitometric values that were midway between the relatively well-preserved lumbar spine and the affected distal one-third radius sites. This pattern, first described in the 1980s, is still the most typical densitometric profile and reinforces the need to measure the distal forearm in all patients with PHPT. The opposite pattern, however, can also be seen in which the lumbar spine is preferentially reduced (49). The early effects of estrogen deficiency, before the onset of PHPT in postmenopausal women, can explain the reduced lumbar spine bone mineral density (BMD) in at least some of these patients. However, any pattern of bone loss can be seen in PHPT, ranging from a uniformly low BMD to a uniformly normal BMD.

The preferential involvement of the distal one-third radius in PHPT was consistent with the notion that the catabolic effects of excessive PTH would be seen first at a cortical site. Because DXA is a strong predictor of fracture risk, it was thought that in PHPT, fractures would be more often seen in the nonvertebral (*i.e.*, cortical) skeleton. Two reports by Khosla *et al.* (50) and Vignali *et al.* (51), however, showed that vertebral fractures were seen with a significantly greater incidence than in the control populations. A more incisive imaging technology, with resolving power that permitted direct assessment of the trabecular compartment of bone (52), was needed to address this apparent paradox, namely that fracture risk is increased at a site that the DXA results predicted would be relatively protected. Even histomorphometry of the iliac crest bone biopsy did not help to resolve this issue (53). The technology that did, high-resolution peripheral quantitative computed tomography (HRpQCT) (54), showed that both the cortical and the trabecular compartments of bone are adversely affected in PHPT (55–57). In the study by Stein *et al.* (55), trabecular microstructure was further analyzed using individual trabecular segmentation analysis. The topology of the trabecular indexes favored the vertically oriented rods, a spatial disposition that is suboptimal for bone strength.

Although HRpQCT is available only in research centers and, thus, not assessable to most clinicians, the trabecular bone score (TBS), which can identify some aspects of bone quality from the lumbar spine DXA image, is available to anyone whose DXA instrument is installed with TBS software (58, 59). The concept of the TBS is a comparative one [*i.e.*, the extent to which the textural microstructural patterns of the lumbar spine fit more comfortably as better (homogeneous) or worse (heterogeneous) bone quality]. Using TBS, Silva *et al.* (60) showed that lower mean TBS scores were much more evident in PHPT than in reduced BMD by DXA. Similar data were reported by Romagnoli *et al.* (61). Such studies reinforced the concept, documented with greater precision by HRpQCT, that the trabecular compartment is often involved in PHPT. Applying these new imaging technologies, it is now clear that in PHPT, the skeletal microstructure in both cortical and trabecular compartments is compromised, observations that are now concordant with epidemiology studies that have shown an increased fracture risk at vertebral and nonvertebral sites with this disease. These observations have decision-making implications because vertebral fracture assessment and TBS are accessible to many clinicians and can supplement the information available from DXA alone.

Some of the most vexing clinical aspects of PHPT are neurocognitive features that have been well described but not clearly directly attributable to the "modern" form of the disease. Fatigue, anxiety, poor concentration, cognitive decline, and reduced quality of life have all been reported with varying frequency, leading some to question whether the terminology "asymptomatic" PHPT is an accurate descriptor of these patients. If these complaints can be directly attributed to the disease, the patients so afflicted are not asymptomatic. However, the attribution is uncertain. Each of these features can be seen in literally any chronic disease. They lack specificity. Even more problematic, the demonstration of reversibility after successful parathyroid surgery in rigorously conducted clinical trials has been inconclusive (62–66).

The neuromuscular, cardiovascular, rheumatologic, and gastrointestinal systems are additional putative targets of PHPT. When the disease was typically symptomatic, all these systems were described as common manifestations of the disease; however, now they are not appreciated as a clinical problem, except in "classic" PHPT or in specialized settings (11, 12, 43).

A Summary of the Variable Clinical Expressions of PHPT

The symptomatic disorder

In the era described between 1930 and 1970, PHPT was generally considered a symptomatic disorder with overt skeletal and renal complications (67). Radiologically, salt

and pepper degranulation of the skull, distal tapering of the clavicles, bone resorption of the phalanges, bone cysts, and brown tumors were common. Stones and nephrocalcinosis constituted the renal manifestations. Proximal muscle weakness was due to impaired function of type 2 muscle fibers (68).

The asymptomatic disorder

In the 1970s, with widespread biochemical screening, asymptomatic PHPT emerged as the predominant clinical form. Because PHPT was being discovered incidentally, the overt radiological features of PHPT essentially disappeared and the incidence of kidney stones plummeted. Proximal muscle weakness was no longer seen (69). It was reasonable, with the tools at our disposable in the 1970s, to describe these subjects with PHPT as asymptomatic, because they did not have any classic organ signs or symptoms of the disease.

The normocalcemic disorder

It took another four decades before the normocalcemic variant of PHPT was described in the first decade of the 21st century (17). It was discovered in patients being evaluated for low bone mass or frank osteoporosis (17, 70–75). However, when NPHPT was first described, it was not asymptomatic but rather associated with overt bone loss, an observation that spoke to the proactive approach to bone loss syndromes in which the PTH became a standard part of the evaluation. Since the early descriptions of NPHPT, an asymptomatic variant has been described when unsuspecting populations are screened with serum calcium and PTH levels (76). Thus, NPHPT can be asymptomatic or symptomatic (63). These two forms of NPHPT, symptomatic and asymptomatic, match the two forms of the more traditional hypercalcemic variant of the disease.

A World View of How PHPT Can Present

These three different presentations of PHPT have followed a timeline with the symptomatic form described first, followed by asymptomatic PHPT, and, most recently, NPHPT. Although this historical perspective is valuable, it is important to recognize that these three forms of PHPT exist concurrently in the world today. One could state that these three forms of PHPT have always coexisted. The preponderance of one variant over another will depend on several factors that tend to vary by country. In countries where biochemical screening is still not a regular part of the health care system, symptomatic PHPT is likely to be the most common form of the disease. Because hypercalcemia will be discovered only in the context of symptoms, PHPT will be considered in those countries to be an uncommon disease. India might be the best example of this form of PHPT (77). In countries where biochemical screening is routine, such as in Western Europe, North America, and many other parts of the world, asymptomatic PHPT is likely, and it will be appreciated as a rather common disease. Parenthetically, as noted already, the use of the term asymptomatic probably requires some adjustment, if only semantically, because with greater imaging tools applied to this population, it is apparent that such patients can often be shown to have involvement of the skeleton and/or kidneys. Finally, if PTH is routinely measured when patients with low BMD are being evaluated, even in normocalcemic individuals, NPHPT will emerge as an entity. Thus, all three forms of PHPT coexist with a relative incidence that is defined by country- and practice-specific variables.

Evaluation

The current recommendations for evaluation of a patient with PHPT are summarized in Table 1 (5). In contrast to the approaches for many disorders of bone and mineral metabolism, in which only the lumbar spine and hip regions are measured, DXA measurements should include the distal one-third radius (78). In addition to DXA, further evaluation of the skeleton is now recommended because of the recent evidence that many patients with asymptomatic PHPT have vertebral involvement. Thus, in addition to DXA, X-rays, vertebral fracture assessment, or TBS should be part of the skeletal evaluation. In those centers in which HRpQCT is available, its use also should be seriously considered. Additional imaging should extend also to the kidneys, because of the

Table 1. Evaluation of Patients With Primary Hyperparathyroidism

Recommended
Serum PTH, calcium, phosphate, alkaline phosphatase activity, renal function tests, 25-hydroxyvitamin D
24-Hour urine for calcium and creatinine
BMD by DXA (lumbar spine, hip, distal one-third radius)
Vertebral spine assessment (radiography, CT or VFA by DXA)
Stone risk profile (if urinary calcium >400 mg/day)
Abdominal imaging by radiography, ultrasonography, or CT scan
Optional
HRpQCT
TBS by DXA
Bone turnover markers

[Adapted with permission from Bilezikian JP, Brandi ML, Eastell R, et al. Consensus Statement: Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary Statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99:3561–3569.]

Abbreviation: VFA, vertebral fracture assessment.

recent evidence that stones and/or nephrocalcinosis are often present among those with PHPT discovered incidentally. The recommendations include abdominal X-ray, ultrasonography, or CT (44). The 24-hour test for calcium is also strongly recommended, with guidelines for more complete biochemical urinary stone risk profiling if marked hypercalciuria is present.

Treatment of PHPT

Surgical management

Surgery in PHPT offers the promise of definitive cure and should be recommended to those who meet any one of the criteria for surgery: hypercalcemia consistently >1 mg/dL above normal; fracture; renal stones, hypercalciuria, and other stone risk factors; T-score <−2.5 at any site; and age <50 years (Table 2). Surgery can also be pursued for those who do not meet any of these indications as long as no medical contraindications are present and unanimity has been reached among the endocrinologist, surgeon, and patient about this course of action.

Preoperative parathyroid localization

It is an axiom in our field that the most important aspect of parathyroid localization is locating the expert parathyroid surgeon. Although this is clearly true, virtually all parathyroid surgeons depend on successful preoperative localization of the abnormal parathyroid tissue. Ultrasonography and technetium-99m–labeled sestamibi have been the most popular approaches for preoperative localization; however, more recently, high-resolution CT and four-dimensional CT have received positive attention. Centers vary by what modality or combination of modalities are preferred (77). As is true for most procedural endeavors, surgeons who frequently perform parathyroidectomy and centers that are highly experienced in preoperative localization are most likely to have positive outcomes. The success rates among these surgeons and centers exceed 95% (79). The use of intraoperative PTH measurements with a rapid throughput assay has given assurance regarding the likelihood of cure after removal of the single or multiply involved parathyroid tissue. The intraoperative reduction in PTH should exceed 50% of the immediate preoperative PTH concentration and should be in the normal range within 15 to 30 minutes after the procedure.

Table 2. Indications for Surgery in Asymptomatic Primary Hyperparathyroidism

Parameter	Criteria for Parathyroidectomy
Age	<50 years
Serum calcium	>1 mg/dL above upper limit of normal
Skeletal manifestations	Reduced BMD by DXA to a T-score of <−2.5 at any site (lumbar spine, hip, or distal one-third radius) Vertebral fracture by X-ray, CT, magnetic resonance or VFA
Renal manifestations	Creatinine clearance <60 mL/min Kidney stone or nephrocalcinosis by abdominal imaging Hypercalciuria (>400 mg/day) accompanied by biochemical stone risk profile placing patient at risk of kidney stones

[Adapted with permission from Bilezikian JP, Brandi ML, Eastell R, et al. Consensus Statement: Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary Statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99:3561–3569.]

Abbreviation: VFA, vertebral fracture assessment.

Nonsurgical management

Given the surgical guidelines, it is obvious that those who do not meet such guidelines will not necessarily be encouraged to undergo parathyroidectomy. In these patients who are not to undergo surgery, a reasonable monitoring protocol includes semiannual testing of the serum calcium and PTH; annual or biannual DXA testing (I prefer annual testing); annual urinary calcium measurements as clinically indicated; and further skeletal and renal imaging testing as clinically indicated (Table 3) (5). If the patient develops a surgical guideline, surgery should be seriously considered.

Nutritional guidelines

Calcium intake. The intrinsic logic among many patients and some physicians is to restrict calcium intake. Dietary calcium restriction, however, can be perceived by the abnormal parathyroid tissue, which still maintains some responsiveness to fluctuations in the serum calcium—albeit at a higher level—to further increase PTH levels

Table 3. Guidelines for Medical Monitoring in Patients With Asymptomatic Primary Hyperparathyroidism Managed Conservatively

Parameter	Frequency of Evaluation
Serum calcium	Annually
Skeletal	Three-site DXA every 1-2 years Imaging of spine to access vertebral fracture if clinically suspected (*e.g.*, height loss, back pain)
Renal	Serum creatinine and eGFR annually If renal stones are clinically suspected: 24-hour biochemical stone profile, abdominal imaging by X-ray, ultrasonography, or CT

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Abbreviation: eGFR, estimated glomerular filtration rate.

(80). This does not mean that the serum calcium level fluctuates perceptively as a function of calcium intake, but that the parathyroid tissue could well perceive a deficient calcium diet and be further stimulated to synthesize and secrete PTH. For these reasons, a normal calcium intake, in accordance with the Institute of Medicine's general recommendations for calcium intake (18) should be adopted by patients with PHPT.

Vitamin D. Much evidence has suggested that vitamin D deficiency in PHPT is an inciting factor to further increases in PTH (29, 80–82) and greater expression of disease activity (82–84). Moreover, in countries where symptomatic PHPT has been well described, severe vitamin D deficiency is common (85, 86). In PHPT, vitamin D deficiency is more likely because PTH stimulates the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Although this might seem paradoxical, namely that vitamin D deficiency is a clinical problem when the 25-hydroxyvitamin D level is low and active vitamin D is normal or high, it is the case. Early cohorts of patients with PHPT typically described vitamin D deficiency. However, more recent observations have shown that 25-hydroxyvitamin D levels are more likely to be normal. This is undoubtedly because the general population much more commonly uses vitamin D supplements (83, 87). Some studies have even equated seasonal variability in the biochemical indexes of PHPT as a function of the seasonal variability in 25-hydroxyvitamin D levels (88). Although the clinical observations that related greater biochemical indexes of PHPT to low 25-hydroxyvitamin D levels, the structural skeletal indexes as measured by TBS (89, 90), quantitative CT (90), or HRpQCT (91) are not as clearly related. To restore vitamin D adequacy, vitamin D3 or D2 should be used in modest amounts, starting with 1000 IU daily (5). In a randomized clinical trial, Rolighed *et al.* (92) showed that vitamin D at 2800 IU daily for 6 months led to an increase in 25-hydroxyvitamin D from 20 ng/mL to 38 ng/mL. The restoration of vitamin D to normal was associated with lower serum PTH and C-telopeptide levels and improved lumbar spine BMD. Vitamin D supplementation was not associated with any changes in serum or urinary calcium (92).

Pharmacological guidelines

The reasons to consider a pharmacological agent for PHPT relate virtually always to patients who meet the criteria for surgery but who choose not to undergo parathyroid surgery. The reasons for not undergoing parathyroid surgery when the guidelines have been met include medical contraindications, previous and/or multiple previous neck operations, an inability to locate abnormal parathyroid tissue, and patient preference.

Low bone density. The bisphosphonate, alendronate, improves the lumbar spine BMD without any changes in the serum calcium (93–97). Alendronate has also been shown to increase BMD in NPHPT (98). Very few data are available for other bisphosphonates in PHPT (99). Although an increase in bone density would be welcome in these patients, alendronate was associated with an increase in fracture risk in a large retrospective cohort study using an insurance database. The comparison was among those who underwent parathyroidectomy, those who were treated with alendronate, and those who were simply observed without any intervention (100). The retrospective nature of that nonrandomized survey in which major differences in age, baseline BMD, comorbidities, median T-score, and incidence of osteoporosis were present among these three groups render the conclusion uncertain. Selection bias could well have predetermined who would receive parathyroid surgery or alendronate, or neither, and, thus, have influenced the results.

Very recently, denosumab has been evaluated in a comparative study of older postmenopausal women with PHPT or osteoporosis. After 2 years, the group with PHPT showed greater increases in BMD at the lumbar spine, total hip, and femoral neck than did the group with osteoporosis (101).

Hypercalcemia. In patients who are not going to have parathyroid surgery but in whom the serum calcium is >1 mg/dL above normal or symptomatic hypercalcemia is present, control by pharmacological means could be indicated. Cinacalcet is a calcimimetic agent that can accomplish this goal by virtue of its property to bind to the calcium-sensing receptor. Its calcimimetic properties lead to an intracellular effect to reduce PTH synthesis and secretion. The serum calcium level will become normal in >70% of patients (102). Although the primary effect of cinacalcet is to affect PTH synthesis, circulating levels of PTH levels will decrease but only modestly. In a wide range of clinical presentations of PHPT from mild to severe disease, cinacalcet has been shown to be effective as a calcium-lowering agent (80, 103–105). The 5-year data have not shown any change in BMD (105).

Hypercalcemia and reduced BMD. Because medications in PHPT appear to increase BMD or reduce the serum calcium level, but not both, it seems reasonable to consider combination therapy with alendronate or denosumab and cinacalcet for these patients. With the limited experience available to date, this approach has shown promise (106, 107).

Natural History of PHPT With and Without Surgery

The long-term outcomes of those who do or do not undergo parathyroid surgery are available for ≤15 years of prospective monitoring (5, 64, 65, 78, 108, 109). Among those who do not undergo parathyroid surgery (108), all relevant biochemical indexes remained stable, with only an upward trend between years 13 and 15 in the serum calcium. The BMD was stable at all three sites until year 8 when the femoral neck and distal one-third radius began to decline. These small declines became more evident and were markedly evident between years 10 and 15.

Among those who undergo successful parathyroid surgery, the biochemical indexes will promptly normalize and the BMD will improve at all sites. BMD increases first in the lumbar spine, followed chronologically by improvements in the hip and distal one-third radius sites. Parathyroidectomy also leads to improvements in skeletal microstructure and bone strength as determined by HRpQCT and finite element analysis (110–112). However, within a relatively short follow-up period, during which high-resolution imaging showed improvements, no changes were found in the TBS (110). In the setting of a randomized clinical trial (113), successful parathyroidectomy was associated, not only with improvements in BMD, but also with a reduction in fracture incidence (100, 109, 113). Even in NPHPT, when the surgical guidelines are applied, as recommended, parathyroidectomy has been associated often, but not always, with beneficial outcomes such as an increase in BMD (114–116).

The renal system appears to be stable over time among those who have not undergone parathyroidectomy, at least regarding serum creatinine and urinary calcium excretion. However, the recurrence of kidney stones was common (108). Surgery has been associated with a reduction in urinary calcium excretion and kidney stones (117). Clinically, the risk of kidney stones appears to be substantially reduced after surgery (64, 65, 100, 108, 109).

The improvements in skeletal and renal parameters in patients who demonstrate compromise in these two target organs give direct evidence for the guidelines that recommend surgery for these patients. However, it has not been possible to show with any consistency that neurocognitive and cardiovascular features, should they be present, improve with surgery (43). Summarizing the experience in this regard, a recent meta-analysis of both randomized clinical trials and observational studies of asymptomatic patients with PHPT did not show any improvements in quality of life, neuropsychiatric symptoms, or cardiovascular events (118). The lack of evidence for substantial improvements in these areas after parathyroidectomy helps to substantiate the guidelines that do not include these features among the indications for surgery.

Conclusions

During the past 40 years, we have gained progressively greater insights in presentations, involvement of target organs and the management of PHPT. New imaging technologies have helped to define involvement among those who are discovered incidentally in the course of biochemical screening. Among those who present with classic symptoms, the lack of population-based biochemical screening, along with vitamin D deficiency appear to be key determinants. NPHPT can be discovered among those who are evaluated for a reduced bone mass but can also be discovered incidentally. Although successful parathyroidectomy cures the disease, the guidelines are useful because of the benign natural history in many who do not meet the criteria for surgery. In those who do meet the surgical guidelines, but in whom surgery is not to be performed, pharmacological approaches are available to reduce the serum calcium and/or improve the BMD.

Acknowledgments

During the past 40 years, I have worked with a large number of colleagues who individually and in the aggregate have contributed much to the new knowledge we have gained and to whom I am most grateful: Sanchita Agarwal, Claude Arnaud, Andrew Arnold, Gerald Aurbach, Francisco Bandeira, Leonardo Bandeira, Victoria Borba, Joao Borges, Stephanie Boutroy, Maria Luisa Brandi, Robert Canfield, Filomena Cetani, Fred Chan, Silvia Chiavistelli, Cristiana Cipriani, Bart Clarke, Aline Costa, Serge Cremers, Natalie Cusano, Hector DeLuca, David Dempster, Richard Eastell, Ghada El Haj Fuleihan, Pierre D'Amore, Lorraine Fitzpatrick, Andrea Giustina, David Goltzman, Luiz Griz, Ed Guo, Didier Hans, Hunter Heath, Andrew Ho, Thomas Jacobs, Elias Kazam, Aliya Khan, Klaus Klaushofer, Michael Kleerekoper, Stavroula Kousteni, Henry Kronenberg, Annie Kung, Jennifer Kuo, Etah Kurland, Marise Lazaretti-Castro, James Lee, David K. Leung, Michael Levine, Michael Lewiecki, Uri Liberman, Paul LoGerfo, Marjorie Luckey, Michael McClung, Paul Miller, Jianmin Liu, Sherry Liu, Rukshana Majeed, Robert Marcus, Claudio Marcocci, Jasna Markovac, Stephen Marx, Gherardo Mazziotti, Xunwu Meng, Salvatore Minisola, Carolina Moreira, Don McMahon, Ralph Muller, Kazuhide Ogino, Beatriz Omeragic, Lefteris Pascalis, Monika Pawlowska, Munro Peacock, John Potts, Dan Rao, Paul Roschger, Clifford Rosen, Michael Rosen, Mishaela Rubin, Ego Seeman, Markus Seibel, Monica Skarulis, Elizabeth Shane, Dolores Shoback, Barbara Silva, Shonni Silverberg, Ethel Siris, Allen Spiegel, Emily Stein, Ronald Staron, Gaia Tabacco, Donovan Tay, Robert Udelsman, Marcella Walker, Nelson Watts, John Williams, Randy Yeh, and Roger Zebaze.

Financial Support: This work was supported, in part, by continuous funding since 1984 from National Institutes of Health (Grant DK 32333).

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Disclosure Summary: The author has nothing to disclose.

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