Published in final edited form as:
Endocr Pract. 2009 ; 15(5): 494–498. doi:10.4158/EP09162.CO.

ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM: A COMMENTARY ON THE REVISED GUIDELINES

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INTRODUCTION

The early 1970s marked a time point in the recognition of the natural history of primary hyperparathyroidism (PHPT) in the developed world when it became evident that the disease was no longer manifested mainly as a symptomatic disorder, but rather much more commonly as an asymptomatic one. At that time and since, routine use of the multichannel autoanalyzer, which includes the serum calcium measurement, revealed a disorder that was typically not associated with symptoms of the classic disorder, such as severe bone and overt renal disease. Even though surgical removal of the responsible abnormal parathyroid tissue is the definitive treatment of this disease, the newer clinical profile of asymptomatic PHPT raised the question: Who among the asymptomatic patients should have surgical treatment? To address this question, 3 conferences have been held on the management of asymptomatic PHPT during the past 18 years. The most recent—the Third International Workshop on Asymptomatic Primary Hyperparathyroidism—was held in Orlando, Florida, on May 13, 2008, in conjunction with the 2008 annual meeting of the American Association of Clinical Endocrinologists. This conference was supported by 10 international societies, each of which identified delegates recognized for their expertise and knowledge in the field to serve on a panel and to provide a global perspective on the key clinical questions to be addressed. The proceedings of this international conference have been published, including a list of participants, panel members, and supporting societies (1–6). Revised guidelines were offered, based on new evidence since the time of the second conference in 2002. The purpose of this commentary is to focus on selected aspects of that workshop, highlighting major issues that still confront us in this disorder, as well as to comment on the guidelines themselves.

DIAGNOSIS OF PHPT

Although the diagnosis of PHPT relies heavily on the presence of hypercalcemia and elevated parathyroid hormone (PTH) levels, it is now clear that there is another presentation in which the serum calcium concentration is consistently normal (7). In the absence of other

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DISCLOSURE

The authors have no conflicts of interest to disclose.

causes for an elevated level of PTH, such as vitamin D deficiency, the entity of normocalcemic PHPT was acknowledged at the workshop. The natural history of normocalcemic PHPT includes some, but not all, patients who become frankly hypercalcemic. That at least some of these patients have PHPT has been demonstrated by surgical removal of adenomatous or hyperplastic glands in those subjects who have undergone a parathyroid surgical procedure. Although the existence of this phenotype of PHPT was recognized, the workshop conferees thought that management guidelines for asymptomatic PHPT should not include this newly recognized form of PHPT. This is a prudent decision until we have more information about the natural history of this variant.

FEATURES OF ASYMPTOMATIC PHPT THAT LED TO CHANGES IN THE GUIDELINES

Skeletal Involvement

The workshop panel emphasized that bone densitometry is an indispensable aspect in the evaluation of asymptomatic PHPT but pointed out that skeletal x-ray examinations looking for specific radiologic features of PHPT are no longer useful. Although many patients with asymptomatic PHPT have reductions in bone mineral density (BMD), virtually no one has the specific radiographic features of PHPT. The most common densitometric pattern by dual-energy x-ray absorptiometry is a preferential reduction in cortical BMD (distal one-third of the radius) with relative preservation of cancellous BMD (lumbar spine) (8). The hip region, which represents a more even admixture of cortical and cancellous bone, typically shows a BMD that straddles the range of the density in the lumbar spine and the distal one-third of the radius. Of note, this is not the only pattern of BMD seen in asymptomatic PHPT; it is simply the most common one.

The issue of fracture incidence in asymptomatic PHPT is a vexing one because most of the literature does not give clear prospective data. Rather, the apparent increase in fracture incidence in PHPT is based mainly on cross-sectional and retrospective surveys (9). Moreover, it is not clear whether the *T* score in patients with asymptomatic PHPT carries with it the same prognostic value relative to fracture risk as it does in subjects who do not have PHPT. The reason why this is a worthy point is based on newer information, discussed at the workshop, that describes salutary features of PTH on bone geometry and microarchitecture, both of which appear to be protective (10,11). Acknowledging these points, the workshop panel reasonably concluded that the *T* score by dual-energy x-ray absorptiometry, nevertheless, should continue to be used and that the cut point to recommend surgical intervention should be less than −2.5 SD at any site—the distal one-third of the radius, the hip, or the lumbar spine. Although the guidelines for BMD did not change, it was noted that if a patient has a history of a fragility fracture, surgical treatment would be recommended. In a patient who has a history of such a fracture or if it is detected by an imaging modality such as vertebral fracture assessment, a surgical procedure would also now be recommended. This addition to the guidelines for surgical therapy raises an interesting question, not addressed in the published proceedings. Because the revised guidelines identify the asymptomatic vertebral fracture as an indication for surgical treatment, is it prudent to conduct a search for this fracture in the routine assessment of the patient? One could make this argument in view of the fact that two-thirds of vertebral fractures are not accompanied by a clinical event.

Renal Involvement

Urinary Calcium Excretion—Urinary calcium excretion in asymptomatic PHPT is not a risk factor for stones or for nephrocalcinosis in subjects who have never had a kidney stone (12). This point seems counterintuitive because in other situations hyper-calciuria is a risk

factor for nephrolithiasis. This point was discussed at the time of the second workshop in 2002 and came up for further discussion at the most recent workshop. On the basis of the data and that discussion, the panel has removed hypercalciuria as a surgical indication. It is important to note, however, that the 24-hour urinary calcium excretion continues to be an important element for the evaluation of PHPT, particularly to rule out familial hypocalciuric hypercalcemia.

Renal Function—The 2008 workshop focused on renal function and developed an operational cut point for glomerular filtration rate of <60 mL/min per 1.73 m^2 to be the revised surgical guideline. On the basis of the most recent epidemiologic data from the US National Health and Nutrition Examination Survey, this value in euparathyroid subjects is associated with the onset of secondary increases in PTH level. If subjects with PHPT behave similarly to those without PHPT in this regard, then reduced renal function below this limit would superimpose on the primary hyperparathyroid process a secondary one; thus, at least theoretically, the PHPT state would be worsened. The new guidelines state more clearly the creatinine clearance value of 60 mL/min, below which surgical treatment is now recommended.

FEATURES OF ASYMPTOMATIC PHPT THAT DID NOT LEAD TO CHANGES IN THE GUIDELINES

Serum Calcium Concentration

There was no additional evidence presented at the workshop to warrant a revision of the limit of serum calcium concentration above which surgical intervention is reasonable. The limit is 1.0 mg/dL or 0.25 mmol/L above the upper limits of normal.

Age

No additional evidence was presented at the workshop to warrant a revision of age younger than 50 years as a guideline for operative treatment in PHPT. As was noted at the time of the second workshop, patients younger than 50 years are at increased risk for having complications of PHPT (13).

ASPECTS OF ASYMPTOMATIC PHPT THAT WERE DISCUSSED BUT NOT INCLUDED IN THE REVISED GUIDELINES

Vitamin D

In PHPT, 25-hydroxyvitamin D (25-OHD) levels are typically low, in the neighborhood of 20 ng/mL (50 nmol/L) or lower. The idea that low vitamin D levels in PHPT may fuel processes associated with further elevations in PTH levels has currency, based on the control of PTH secretion by vitamin D. As the 25-OHD level declines below normal, PTH levels increase. The workshop discussion focused on how this regulatory loop between vitamin D and PTH is likely to be valid in patients with PHPT as well as in euparathyroid subjects. For replacement of vitamin D in PHPT, the parent vitamin, cholecalciferol or ergocalciferol, is used, not 1,25-dihydroxyvitamin D, but it is not clear how best to use vitamin D in vitamin D-deficient patients with PHPT. One could refer to the study by Grey et al (14), in which large doses of cholecalciferol were used. Although it remains controversial as to how vitamin D should be replaced in PHPT, there was consensus that normalization of vitamin D in patients with PHPT is desirable and that the goal should be maintenance of 25-OHD levels above the lower limits of the reference range. There was also the view expressed that vitamin D replacement in PHPT should proceed cautiously and that serum calcium levels should be monitored specifically during the replacement period.

Neurocognitive and Neuropsychologic Aspects of PHPT

The discussion of the neurocognitive and neuropsychologic aspects of PHPT was perhaps one of the most controversial at the workshop. Silverberg et al (4) pointed out key limitations in experimental design in many of the published studies. One of the major limitations is that most of the studies lack adequate controls. They also indicated that instruments that have been used to quantify neurocognitive and neuropsychologic elements can be problematic. Moreover, the complaints themselves, such as weakness, easy fatigability, and reduced cognitive acuity, are seen in a host of medical disorders and lack specificity for PHPT. Finally, the 3 prospective studies in which a control group was used showed considerable variability in which neurocognitive features of PHPT, if any, were improved or not after successful parathyroid surgical treatment (15–17). Because of this uncertainty and inconsistency of data, the workshop panel concluded quite reasonably that these potential aspects of PHPT should not be considered as an indication for surgical intervention.

Cardiovascular Aspects

The panel acknowledged a literature that clearly delineates physiologic and pathophysiologic vascular and cardiovascular properties of PTH (18). The panel also acknowledged that in cohorts with more active disease, and most likely in symptomatic individuals with more severe hypercalcemia than is generally found in patients with asymptomatic PHPT, cardiovascular abnormalities can be demonstrated (4). Increased morbidity and mortality have been described. In asymptomatic PHPT, however, the situation is far less clear. In fact, in a Mayo Clinic series (9), only study subjects in the highest quartile of serum calcium concentration had increased cardiovascular mortality. More recently, Rubin et al (19) have begun to study vascular and cardiovascular aspects of PHPT in asymptomatic patients. Their findings, particularly with regard to vascular stiffness and left ventricular function, are of interest. The hope is that this early finding that vascular stiffness was increased in patients with mild PHPT will be followed by more conclusive data. Currently, uncertainty in this area led the workshop panel to conclude that these potential aspects of PHPT should not be used as guidelines for surgical intervention. Similarly, the panel acknowledged that although hypertension is epidemiologically associated with PHPT, blood pressure does not seem to change after successful parathyroid operative treatment.

Natural History

Reference to the 15-year natural history study by Rubin, Bilezikian, Silverberg, and their colleagues (20), along with 3 randomized controlled trials by Rao et al (15), Bollerslev et al (16), and Ambrogini et al (17), was helpful. If all patients with PHPT were inevitably going to show progression of disease, then the argument for surgical intervention in all patients at the time of diagnosis could be made. Their findings, however, do not give support to this proposition. Postoperatively, biochemical and densitometric features improve, a result that has been seen in several other studies, including those that have focused on asymptomatic patients who do not meet the criteria for surgical treatment. During a 15-year period, however, approximately two-thirds of the study subjects did not show evidence of progressive disease leading to a guideline for operative therapy. Although the numbers of subjects still being followed at 15 years became limiting, it is nevertheless evident that if patients who do not meet guidelines for surgical treatment undergo follow-up without operative intervention, they are more likely to have stable PHPT than to show progression. This point is important because it continues to validate the need for surgical guidelines. The revised guidelines are shown in Table 1.

SURGICAL TREATMENT OF ASYMPTOMATIC PHPT

The panel also acknowledged that even though patients may not meet the guidelines for surgical intervention, it is always a reasonable option in those who do not have medical contraindications. The panel included expert parathyroid surgeons, who emphasized that this procedure should be done only by surgeons who are true experts. Failed operations as well as surgical complications are more likely to occur if the operation is performed by surgeons who are not experienced. Before performance of a parathyroid surgical procedure, it has become routine to search for the offending parathyroid gland by use of imaging studies such as radiolabeled sestamibi or ultrasonography. In special circumstances, other imaging modalities can be helpful, such as magnetic resonance imaging or computed tomographic scanning. Because imaging is not a diagnostic approach but a localization approach, the panel emphasized the additional point that the decision for surgical treatment should be made before imaging is performed. With the advent of minimally invasive technology, the parathyroid operation has become much more straightforward than in the past and, in many medical centers, is being conducted in the ambulatory care setting. The ability to obtain postoperative PTH levels within minutes after removal of the parathyroid gland, and to compare levels with those obtained in the operating room immediately preoperatively, helps to ensure that all abnormal tissue has been removed.

PHARMACOLOGIC APPROACHES TO MANAGEMENT OF ASYMPTOMATIC PHPT

Although there was discussion about 3 potential pharmacologic classes that have been studied in PHPT (selective estrogen receptor modulators, bisphosphonates, and calcimimetics), there is not enough evidence with any medical approach to recommend their use as an alternative to surgical treatment at this time. Currently, fracture outcome data are not available for any of the potential medical options. The panel, however, did note the work of Khan et al (21), in which the bisphosphonate, alendronate, was shown to improve the BMD in the lumbar spine of patients with PHPT. The serum calcium concentration did not change. In addition, the panel noted the study by Peacock et al (22), in which the calcimimetic, cinacalcet, was shown to normalize the serum calcium level in patients with PHPT. With this agent, the BMD does not appear to improve. Cinacalcet is approved in the United States for parathyroid cancer and for end-stage renal disease. It has broader approval for PHPT in Switzerland and elsewhere in Europe. In patients in whom surgical treatment is not possible but in whom there is a desire to lower the serum calcium level or to increase BMD, it would be reasonable to use cinacalcet (to lower the serum calcium level) or alendronate (to increase bone density).

THE CASE FOR MONITORING

In light of the fact that the workshop acknowledged that certain patients with asymptomatic PHPT can undergo follow-up without surgical treatment, the best approach to monitoring was discussed. The work by Rubin, Bilezikian, Silverberg, and their colleagues (20) was again useful. Although biochemical and densitometric stability was noted during the first 10 years of their 15-year longitudinal study, a slight increase in the mean serum calcium concentration and a more notable reduction in BMD of the hip and distal one-third of the radius during years 10 to 15 were appreciated. This point underscores the importance of monitoring patients who are not candidates for a parathyroid surgical procedure. The revised guidelines for monitoring are shown in Table 2.

FUTURE CONSIDERATIONS

The changing recognition of PHPT from a rare disorder with symptoms in the era before the availability of the auto-analyzer to a condition that has become primarily asymptomatic in the era with the presence of the autoanalyzer led the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism to recommend several areas for future research. Along with better delineation of normocalcemic PHPT, the panel suggests more research on the role of vitamin D and on the potential involvement of neurocognition and the cardiovascular system. While awaiting this new information, we believe that the revised guidelines will be helpful to endocrinologists who manage this disorder.

Abbreviations

BMD	bone mineral density
25-OHD	25-hydroxyvitamin D
PHPT	primary hyperparathyroidism
PTH	parathyroid hormone

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Table 1

Current Guidelines Favoring Parathyroid Surgical Treatment in Asymptomatic Primary Hyperparathyroidism

Measurement	Surgery recommended if
Serum calcium	>1.0 mg/dL (0.25 mmol/L) above normal
Creatinine clearance (calculated)	Reduced to less than 60 mL/min/1.73 m^2
Bone mineral density	*T* score less than −2.5 SD at spine, hip (total or femoral neck), or radius (distal 1/3 site predominantly cortical bone) or presence of fragility fracture
Age	Patient younger than 50 years

Table 2

Guidelines for Monitoring Asymptomatic Primary Hyperparathyroidism

Measurement	Frequency
Serum calcium	Annually
Creatinine clearance (calculated)	Annually
Bone mineral density	Every 1–2 years