

## Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop

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**Objective:** Asymptomatic primary hyperparathyroidism (PHPT) is a common clinical problem. The purpose of this report is to guide the use of diagnostics and management for this condition in clinical practice.

**Participants:** Interested professional societies selected representatives for the consensus committee and provided funding for a one-day meeting. A subgroup of this committee set the program and developed key questions for review. Consensus was established at a closed meeting that followed and at subsequent discussions.

**Evidence:** Each question was addressed by a relevant literature search (on PubMed), and the data were presented for discussion at the group meeting.

**Consensus Process:** Consensus was achieved by a group meeting. Statements were prepared and reviewed by all authors who represented the Planning Committee and the participating professional societies. (*J Clin Endocrinol Metab* 94: 335–339, 2009)

All patients with biochemically confirmed primary hyperparathyroidism (PHPT) who have specific symptoms or signs of their disease should undergo surgical treatment. This Workshop was focused upon asymptomatic PHPT, a condition defined as hyperparathyroidism that lacks specific symptoms or signs traditionally associated with hypercalcemia or PTH excess. This third Workshop on the Management of Asymptomatic Primary Hyperparathyroidism found, as had the two previous workshops on this topic, that medical monitoring rather than surgery is appropriate in certain patients with asymptomatic PHPT. Because surgery is always considered to be definitive therapy in this disease, even in asymptomatic subjects, a decision to elect medical monitoring should follow guidelines regarding se-

verity of the manifestations of disease (Table 1), and patients should be appropriately monitored (Table 2).

The current Workshop was prompted by a number of issues that have arisen over the last 6 yr since the second workshop on the topic. The following four papers (see Refs. 1–4) address a total of 22 questions that were specifically considered by the panel members in four categories based upon current issues in: 1) diagnosis of PHPT (questions 1–7); 2) presentation of PHPT (questions 8–13); 3) surgery for PHPT (questions 14–18); and 4) medical management of PHPT (questions 19–22).

1. Do we now have optimal reference intervals for PTH? Are these intervals based on individuals who are vitamin D replete?

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in U.S.A.

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doi: 10.1210/jc.2008-1763 Received August 11, 2008. Accepted November 14, 2008.

\* The Summary Statement is written on behalf of all Workshop Participants. They should be regarded as co-authors of this paper. Members of The Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism: John P. Bilezikian, Aliya Khan, Andrew Arnold, Maria Luisa Brandi, Edward Brown, Roger Bouillon, Pauline Camacho, Orlo Clark, Pierre D'Amour, Richard Eastell, David Goltzman, David A. Hanley, E. Michael Lewiecki, Stephen Marx, Leif Mosekilde, Janice L. Pasieka, Munro Peacock, Dan Rao, Ian R. Reid, Misheala Rubin, Dolores Shoback, Shonni Silverberg, Cord Sturgeon, Robert Udelsman, J. E. M. Young, and John T. Potts.

Abbreviations: BMD, Bone mineral density; GFR, glomerular filtration rate; PHPT, primary hyperparathyroidism.

**TABLE 1.** Comparison of new and old guidelines for parathyroid surgery in asymptomatic PHPT<sup>a</sup>

Measurement	1990	2002	2008
Serum calcium (>upper limit of normal)	1–1.6 mg/dl (0.25–0.4 mmol/liter)	1.0 mg/dl (0.25 mmol/liter)	1.0 mg/dl (0.25 mmol/liter)
24-h urine for calcium	>400 mg/d (>10 mmol/d)	>400 mg/d (>10 mmol/d)	Not indicated <sup>b</sup>
Creatinine clearance (calculated)	Reduced by 30%	Reduced by 30%	Reduced to <60 ml/min
BMD	Z-score <–2.0 in forearm	T-score <–2.5 at any site <sup>c</sup>	T-score <–2.5 at any site <sup>c</sup> and/or previous fracture fragility <sup>d</sup>
Age (yr)	<50	<50	<50

<sup>a</sup> Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.

<sup>b</sup> Some physicians still regard 24-h urinary calcium excretion >400 mg as an indication for surgery.

<sup>c</sup> Lumbar spine, total hip, femoral neck, or 33% radius (1/3 site). This recommendation is made recognizing that other skeletal features may contribute to fracture risk in PHPT and that the validity of this cut-point for any site vis-à-vis fracture risk prediction has not been established in PHPT.

<sup>d</sup> Consistent with the position established by the International Society for Clinical Densitometry, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 yr.

- Do third-generation PTH assays perform better clinically than the second-generation PTH assay for diagnosis of PHPT?
- Have genetic tests for the calcium-sensing receptor gene and multiple endocrine neoplasia-related genes become suitable for routine evaluation of all genetic forms of PHPT?
- Is normocalcemic hyperparathyroidism, which is defined as normal serum calcium with raised PTH in the absence of any common cause of secondary normocalcemic hyperparathyroidism, part of the diagnostic spectrum?
- Should we measure 25-hydroxyvitamin D in all patients with suspected PHPT? How should the different reference ranges for different assays be interpreted? What represents the threshold for overtreatment?
- Should renal stones be routinely sought in asymptomatic PHPT?
- For assessment of renal function, what is the precision and accuracy of the estimated glomerular filtration rate (GFR)? Can it replace the measured creatinine clearance? Do we have accurate reference intervals to determine what is at least 30% below GFR expected for age?
- Are there cardiovascular manifestations of asymptomatic PHPT? Can they be routinely detected?
- Can neurocognitive dysfunction be detected in asymptomatic PHPT? What is the evidence for a causal relationship?
- What is the natural history of asymptomatic PHPT?
- Should hypercalciuria (>10 mmol/d or 400 mg/d) in the absence of kidney stones be considered an indication for surgery?
- What degree of reduction in bone mineral density (BMD) makes surgical recommendation advisable? Is this still a T-score of –2.5? Does one distinguish between younger and older individuals? Aside from BMD, what other elements of skeletal assessment weigh into the skeletal evaluation of PHPT? How important is the one third distal forearm site with regard to a target of PTH action in PHPT? Does BMD predict fracture in PHPT? Is fracture risk increased in PHPT? And if so, at what sites?
- For management of asymptomatic PHPT, what represents a clinically important change in serum calcium, serum creatinine, and BMD, considering long-term variability in these parameters?
- What are the indications for surgery in patients with PHPT?
- Who should perform parathyroid surgery?
- What is the role of preoperative imaging?
- What is the appropriate operation, and what are the expected cure and complication rates?
- What operative adjuncts are available to assist the surgeon?
- How effective are bisphosphonates in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium?
- How effective is hormone replacement therapy in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium?
- How effective is raloxifene in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium?

**TABLE 2.** Comparison of new and old management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroid surgery

Measurement	1990	2002	2008
Serum calcium	Biannually	Biannually	Annually
24-h urinary calcium	Annually	Not recommended	Not recommended
Creatinine clearance (24-h urine collections)	Annually	Not recommended	Not recommended
Serum creatinine	Annually	Annually	Annually
Bone density	Annually (forearm)	Annually (3 sites)	Every 1–2 yr (3 sites) <sup>a</sup>
Abdominal x-ray (±ultrasound)	Annually	Not recommended	Not recommended

<sup>a</sup> This recommendation acknowledges country-specific advisories as well as the need for more frequent monitoring if the clinical situation is appropriate.

22. How effective is the calcimimetic, cinacalcet, in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium?

In addition, whereas these questions were analyzed and addressed by the panel members and cooperating experts [as outlined in the four reviews (Refs. 1–4)], other issues related to guidelines for surgery and recommendations for monitoring patients who are not selected for and/or do not elect to have surgery were discussed. This Statement summarizes these points and outlines a blueprint for future research in this disease over the next decade.

This Summary Statement is a synopsis of the material presented in each of the subsequent papers, and brings together the responses to the questions under each of the four topics. This document also reflects the diversity of opinion and practice globally as well as the need for more data in addressing the questions in a more comprehensive manner. Areas for which more data are needed are indicated in this Summary Statement as well as in the individual articles.

## 1. Current Issues in the Diagnosis of PHPT

It was agreed that both second- and third-generation PTH assays are highly useful in the diagnosis of PHPT, but the prevalence of vitamin D deficiency complicates assay interpretation. More research on establishing optimal reference ranges for PTH based on adequate vitamin D repletion as well as renal function and other demographic parameters would be helpful. The need to establish optimal minimum and safe upper ranges is stressed. The level of 25-hydroxyvitamin D should be assessed in all patients suspected of having PHPT, and vitamin D deficiency should be cautiously corrected at the time it is detected. It is important to monitor renal function and to establish a precise level below which surgery is recommended ( $<60$  ml/min), both at the time of diagnosis and during follow-up of patients who are monitored without surgery (Tables 1 and 2). Screening for kidney stones is not recommended in those who do not have a history of kidney stones or nephrolithiasis. Finally, advances in the field support testing for the genetic forms of PHPT in special circumstances.

## 2. Current Issues in the Presentation and Intervention of PHPT

New data on the natural history of asymptomatic PHPT have favored surgery because bone density does not appear to be indefinitely stable. Moreover, up to one third of patients who are monitored long term develop signs of disease progression. It has also been demonstrated that BMD increases consistently after parathyroidectomy in association with decreases in bone turnover. These surrogate endpoints suggest that remaining lifetime fracture risk will decrease after parathyroidectomy. Cohort studies completed to date support this expectation; however, this requires confirmation in randomized controlled studies. Thus, there is growing consensus that surgery may eventually be appropriate in the majority of patients with asymptomatic disease. The argument is stronger among those whose bone density is low or falling. New data on potential cardiovascular manifestations

of PHPT as well as some reversible neurocognitive elements are of interest but not yet definitive and, thus, cannot be used in current decision-making algorithms.

### Guidelines for surgery

- The threshold value for serum calcium, above which surgery would seem to be appropriate, has been maintained at more than 1 mg/dl ( $>0.25$  mm/liter) above the upper limits of normal.
- Hypercalciuria, in the absence of renal stones or nephrolithiasis, is no longer regarded as an indication for parathyroid surgery. The basis for this change in recommendation is that hypercalciuria *per se* has not been established specifically as a risk factor for kidney stones in PHPT. It is one of several factors contributing to stone formation. Urinary calcium excretion does vary with age, gender, and race. Although the presence of hypercalciuria is no longer considered to be a guideline for surgery, it is recommended to obtain a 24-h urine for calcium as part of the initial evaluation of the patient. A 24-h urinary calcium, adjusted for the GFR, can be helpful diagnostically if familial hypocalciuric hypercalcemia is part of the differential diagnosis. A GFR less than  $60$  ml/min  $\cdot 1.73$  m<sup>2</sup> defines a stage 3 level of renal insufficiency according to the K/DOQI guidelines. Although patients may have reached that level of renal function due to age or comorbidity and not due to the presence of PHPT, it is still regarded by many as a threshold of concern. Below this level, elevations in serum PTH occur, and pathophysiological abnormalities associated with declining renal function may influence negatively the hyperparathyroid state. However, there is no evidence that this threshold is actually associated with increasing levels of PTH in PHPT. There is also no evidence from controlled, randomized trials that correction of PHPT by successful surgery leads to an improvement in GFR. This revised guideline, using a numerical cut-point for GFR, acknowledges a return to an absolute standard of renal function, as opposed to age- and sex-specific norms. It is now consistent with the densitometric guidelines that are also based upon an age-invariant standard (the T-score) in postmenopausal women and in men over 50. Clinical judgment guides intervention, particularly in the elderly individual who may have other comorbidity affecting operative risk.
- Reductions in bone density continue to be a cause for concern in PHPT, either as patients present or as they are monitored. The previous densitometric criteria are maintained. Surgery is recommended for peri- or postmenopausal women and men age 50 and older who have a T-score of  $-2.5$  or less at the lumbar spine, femoral neck, total hip, or 33% (one third) radius. In premenopausal women and in men younger than 50, the Z-score of  $-2.5$  or less is recommended as the cut-point below which surgery is advised. The use of Z-scores instead of T-scores is consistent with the International Society of Clinical Densitometry (ISCD) official position in evaluating BMD in this population. This recommendation recognizes, however, that in PHPT, other effects of PTH on bone size and structure could influence fracture proclivity in this disease. It

is attractive to consider application or modification of a 10-yr absolute fracture risk model, such as the FRAX tool, in those with low bone density and asymptomatic PHPT. This would allow assessment of fracture risk based on other important predictors of fracture independent of BMD. Because there are no data validating the FRAX tool in PHPT, this remains a goal for future research. In recognition of the fact that the presence of a fragility fracture provides clinical confirmation of the presence of osteoporosis, the presence of a fragility fracture is now included in the guidelines for surgical intervention.

- Age less than 50 continues to be a guideline for surgery, with evidence supporting a greater risk of complications of PHPT in these individuals over time than in those who are older than 50.

At the time of the last Workshop on Asymptomatic Primary Hyperparathyroidism in 2002, the entity now known as normocalcemic hyperparathyroidism was not specifically addressed. It was appreciated then that patients with asymptomatic PHPT could occasionally have normal calcium values. Now, it is clear that another entity, namely normocalcemic hyperparathyroidism, characterized by consistently normal calcium concentrations in the face of persistently abnormal PTH levels, exists in the absence of a recognizable underlying cause of elevated PTH levels. Its frequency, natural history, and optimal management remain key topics for further evaluation. Because so little is known about normocalcemic PHPT, guidelines for surgical or medical management cannot be established at this time.

### 3. Current Issues in Surgical Management of PHPT

Growing evidence for reversible aspects of PHPT vis-à-vis improvement in bone density, reduction in fractures (cohort studies), reduced frequency of kidney stones (among those with a history of kidney stones), and improvements in some neurocognitive elements (not yet validated by randomized clinical trials) all support a greater utilization of parathyroidectomy in PHPT. Advances in the effectiveness and safety of surgical techniques have brought added confidence to its recommendation. Although imaging is not recommended for diagnostic purposes, it has become routine for preoperative localization. The most commonly employed preoperative imaging techniques are parathyroid radionuclide imaging (*i.e.* sestamibi) and ultrasound. The success of these procedures is highly dependent upon the operator and the experience of the centers performing the imaging studies. Computed tomography, magnetic resonance imaging, and positron emission tomography scanning, arteriography, and selective venous sampling for PTH are usually reserved for patients who have not been cured by previous explorations or for whom other localization techniques are uninformative or discordant.

Preoperative imaging is particularly important for those who have undergone prior parathyroid or other neck surgery. Intraoperative measurements of PTH have helped to limit the

scope and duration of parathyroidectomy to the site of the imaged, potentially abnormal gland. Another argument advanced to support the surgical approach to this disease is the durability and overall cost-effectiveness of surgery. It is emphasized that parathyroid surgery should be performed only by surgeons who are highly experienced in this operation; otherwise failure and complication rates are unacceptably high.

### 4. Current Issues in Medical Management of PHPT and Monitoring

The advisability of nonsurgical approaches to PHPT acknowledges several conclusions of the Workshop. The consensus remains that asymptomatic patients who do not meet surgical guidelines can be followed safely without surgery, pending the outcome of further research on cardiovascular manifestations, neurocognitive changes, and long-term stability of BMD in this disease. When surgery is not recommended because of patient and/or physician preference or perceived medical contraindications, or when the indications for surgery (Table 1) are not met, monitoring is critical (Table 2). The frequency of monitoring with dual-energy x-ray absorptiometry in PHPT may vary internationally, as reflected in country-specific differences in guidelines for monitoring in subjects with osteoporosis. Considering the least significant change of the measurement and expected rates of loss in BMD in PHPT (when and if bone loss occurs), a monitoring interval of 2 yr would be consistent with current practices. The appropriate monitoring interval suitable for individual patients will be guided by clinical judgment allowing accommodation for comorbidity. In some individuals, it may be appropriate to monitor more frequently, namely on an annual basis. All monitored patients should be replete in vitamin D, to achieve a serum level of 25-hydroxyvitamin D greater than 20 ng/dl (50 nmol/liter). Guidelines for calcium intake should be the same as for patients without PHPT. It was emphasized that diets restricted in calcium can be detrimental in this disease.

Pharmacological approaches were covered in detail. At this time, there are insufficient long-term data to recommend as an alternative to surgery any of the four classes of potential medical approaches: bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), or calcimimetic. It is also important to note that in certain European countries, but not in the United States, the calcimimetic, cinacalcet, is approved for PHPT (cinacalcet is approved for parathyroid cancer and dialysis patients in many countries). The bisphosphonate, alendronate, has been shown to increase bone density at the lumbar spine and hip regions in patients with PHPT, whereas the serum calcium does not appear to change. In contrast, cinacalcet, is very effective in reducing the serum calcium, often to normal, in PHPT without major changes in BMD. These results suggest potential utility of these agents in patients who are going to be managed without surgery because they refuse surgery or are considered poor operative risks.

### Blueprint for future research

The Workshop identified a number of areas that are recommended for more research over the next 5–10 yr. They are listed here as broad categories for further investigation.

1. Normocalcemic PHPT: natural history and pathophysiology.
2. Vitamin D replacement in PHPT.
3. PTH as a potential predictive index of activity and complications of PHPT.
4. Prospective cohort studies of nontraditional aspects of PHPT with particular emphasis upon neurocognitive function and cardiovascular involvement and impact of parathyroidectomy.
5. Effect of renal impairment on PHPT.
6. Relationship of bone density and other indices of bone strength to fracture risk in PHPT and appropriate modalities of assessment.
7. Effect of clinical risk factors for fracture, independent of BMD, on fracture risk in PHPT and establishment of a FRAX-equivalent tool assessing absolute fracture risk in PHPT.
8. Fracture incidence in PHPT, before and after successful surgery.
9. Pharmacological approaches to PHPT.
10. Value of pharmacological therapy postparathyroidectomy.

### Conclusion

The Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism reviewed evidence that has become available since the last Workshop in 2002. Although surgery is clearly an attractive choice in many subjects

with asymptomatic PHPT who meet surgical guidelines, it is also recognized that medical management can be appropriate in those who do not meet surgical indications or are unable or unwilling to proceed with parathyroidectomy. If the patient meets surgical guidelines but is a poor operative risk, specific medical therapy targeting hypercalcemia and/or osteoporosis may be of value. The benefits of pharmacological intervention, however, have not been adequately evaluated at this time and require further study.

### Acknowledgments

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Disclosure Statement: All authors have nothing to declare.

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