

ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM: STANDARDS AND GUIDELINES FOR DIAGNOSIS AND MANAGEMENT IN CANADA

*Consensus Development Task Force on Diagnosis and Management of
Asymptomatic Primary Hyperparathyroidism**

Abbreviations:

BMD = bone mineral density; **CT** = computed tomography; **FHH** = familial hypocalciuric hypercalcemia; **MIP** = minimally invasive parathyroidectomy; **MRI** = magnetic resonance imaging; **NIH** = National Institutes of Health; **PHPT** = primary hyperparathyroidism; **PTH** = parathyroid hormone

INTRODUCTION

Severe hypercalcemia, osteitis fibrosa cystica, and nephrolithiasis are no longer common presenting features of primary hyperparathyroidism (PHPT). Most frequently, PHPT is now recognized in its asymptomatic stage, as a result of the detection of hypercalcemia on "routine serum chemistry" facilitated by the widespread use of the autoanalyzer for serum chemistry studies (1). In 1990, the National Institutes of Health (NIH) convened a consensus development conference on the diagnosis and management of asymptomatic primary hyperparathyroidism. The guidelines resulting from that conference identified patients who could safely be managed by follow-up surveillance without surgical intervention as well as those for whom surgical treatment was most advisable (2). Recent advances in the diagnosis of PHPT, imaging technology, surgical approaches to the condition, and medical therapy for PHPT led to the convening of an NIH-sponsored workshop on April 8 and 9, 2002. Canadian participation was invited. An ad hoc panel recommended new guidelines for the management of asymptomatic primary hyperparathyroidism (3,4). Although the initial manifestations of PHPT are similar in the United States and Canada, differences in the Canadian medical practice environment have led to this Canadian position paper on the management of asymptomatic

primary hyperparathyroidism. These consensus statements were developed by a multidisciplinary task force with representatives from the Canadian Society of Endocrinology and Metabolism and the Canadian Association of Nuclear Medicine as well as Canadian representatives of the American Association of Endocrine Surgery. This report outlines the new guidelines for surgical intervention, the role of imaging, the use of intraoperative parathyroid hormone (PTH) assays, and the new approaches to medical therapy and monitoring in Canada.

DIAGNOSIS OF PHPT

The diagnosis of PHPT is established by the presence of hypercalcemia and elevated or inappropriately high levels of serum PTH for the level of serum calcium (5). Modern assays for PTH are sensitive and specific for this condition (5). The new second-generation whole PTH assays almost exclusively measure intact PTH (6,7). Other laboratory abnormalities in PHPT are nonspecific and inconsistent: the serum phosphorus level is low in approximately 25 to 30% of patients, hypercalciuria is present in approximately 40%, and a high level of 1,25-dihydroxyvitamin D is found in approximately 30 to 40% of patients (8). We recommend performance of the studies listed in Table 1 as part of the initial assessment of patients diagnosed with PHPT.

Familial hypocalciuric hypercalcemia (FHH), also referred to as familial benign hypocalciuric hypercalcemia, is an autosomal dominant genetic disorder due to an inactivating mutation in the calcium-sensing receptor. The result is decreased sensitivity to calcium in parathyroid and renal tubular cells. FHH is associated with mild hypercalcemia, often present from birth, and hypocalciuria. The urinary calcium/creatinine clearance ratio is typically less than 0.01 (9); this determination necessitates a 24-hour urine collection for calcium and creatinine clearance at the time of initial patient assessment. In patients with FHH, PTH levels are in the upper range of normal, but may be slightly elevated, and can be considered inappropriately high for the level of serum calcium. For this reason, parathyroid surgical treatment is sometimes mistakenly recommended for these patients. Evaluation for FHH is important because parathyroidectomy is contraindicated in this setting.

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Table 1
Indications for Parathyroidectomy on Initial Assessment
of Patients With Mild, Asymptomatic Primary Hyperparathyroidism

Measurement	1990 guidelines	2002 guidelines
Serum calcium (above upper limits of normal)	0.25-0.4 mmol/L or 1.0-1.6 mg/dL	0.25 mmol/L or 1.0 mg/dL
Urine calcium (24-hour specimen)	>10 mmol/day or >400 mg/day	>10 mmol/day or >400 mg/day
Creatinine clearance	Reduced by 30%	Reduced by 30%
Bone mineral density	Z-score <-2.0 at forearm	T-score <-2.5 at any site
Age (yr)	<50	<50

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MANIFESTATIONS OF PHPT

PHPT is associated with reductions in bone mineral density (BMD)—most notably, at skeletal sites enriched in cortical bone, such as the distal third of the radius (10). In some patients with PHPT, the BMD is preferentially reduced in the lumbar spine (11). The risk of fractures in patients with PHPT is still unknown. PHPT apparently places patients at risk for cortical fractures, but whether sites of cancellous bone (for example, lumbar spine) are also at risk for fracture is not known (12,13). Prospective fracture data are needed. The relationship between BMD and fracture risk in PHPT is not fully understood. Histomorphometric studies in patients with PHPT have shown characteristics that, in some respects, may confer a protective effect with respect to fractures (14).

As has been described in a review on PHPT, the risk of nephrolithiasis and nephrocalcinosis is increased (1). These findings are clear indications for surgical treatment. Other effects of PHPT can include the presence of associated nonspecific symptoms, such as fatigue, malaise, and difficulties with concentration (15). These symptoms are not easily quantifiable; some investigators have indicated that most patients labeled as “asymptomatic” actually are not (15). Other physicians emphasize that the nonspecific features of PHPT make it extremely difficult to attribute such complaints to the disease per se (11). The nonspecific symptoms diminish in most, but not all, patients after parathyroidectomy (15). Nevertheless, not all patients with mild PHPT choose to undergo a parathyroid surgical procedure, and many patients remain medically stable without such intervention.

ROLE AND LIMITATIONS OF IMAGING IN PHPT

Preoperative localization techniques are available to determine the site of abnormal parathyroid tissue. The

most commonly used tests for imaging parathyroid tissue are technetium-labeled cationic complexes (sestamibi and tetrofosmin) and ultrasonography. Computed tomography (CT) and magnetic resonance imaging (MRI) of the neck and mediastinum are often recommended for patients with persistent or recurrent PHPT but rarely before an initial operation. Each of these modalities has advantages and disadvantages. The technetium scan and ultrasonography are readily available in most centers and are less costly and more precise in comparison with CT and MRI. The technique used most widely with the greatest success is the dual-phase ^{99m}Tc -sestamibi scan with or without single-photon emission computed tomographic imaging. Preoperative imaging is most usefully performed with the ^{99m}Tc -sestamibi scan, and in combination with ultrasonography.

The dual-phase ^{99m}Tc -sestamibi scan is based on the principle that a differential washout period exists between tracer in parathyroid tissue and in the thyroid gland, with the faster washout occurring in the thyroid gland (16,17). In more difficult cases, a dual-isotope technique can be used (with either ^{99m}Tc pertechnetate or ^{123}I) after the parathyroid phase of the dual-phase sestamibi technique. The second radiopharmaceutical image can be subtracted from the ^{99m}Tc -sestamibi image after the parathyroid phase. This approach is helpful in complicated cases in which thyroid disease may be concurrently present.

INDICATIONS FOR PARATHYROID IMAGING

Imaging of the parathyroid glands should not be used to establish the diagnosis of PHPT or to determine whether surgical treatment should be undertaken. Our position is that this technology should be used after the decision for surgical intervention has been made and the medical and surgical team believes that imaging technology will be helpful for preoperative preparation.

A controversial issue is whether localization technology should be used in all patients who are to undergo parathyroidectomy, regardless of whether they have had a previous neck surgical procedure. Advocates of this approach state that the success rates are higher and the operating time is shortened. Opponents of this approach indicate that, with expert parathyroid surgeons, the success rates approach 95% in patients who have not had previous neck surgery. This figure is not appreciably improved by any currently available preoperative imaging modality (18).

If minimally invasive parathyroidectomy (MIP) or unilateral parathyroid exploration is planned, preoperative localization is essential. Similarly, if the patient has had prior neck surgery, preoperative localization is generally considered a requirement. Intraoperative approaches are also of value in locating abnormal parathyroid tissue (discussed below).

SURGICAL INTERVENTION FOR PHPT

Parathyroidectomy is the only curative therapy for PHPT. Until the mid-1990s, a four-gland surgical exploration was the procedure of choice for PHPT. This conventional approach allowed the surgeon to identify all parathyroid tissue. Such procedures were associated with high success rates.

With the introduction of better localization techniques, a more limited neck exploration—MIP—has been used with increasing frequency (19-21). With the enhanced sensitivity of preoperative imaging and the use of intraoperative PTH measurements, several approaches to MIP have been described, from video-assisted parathyroidectomy to directed local excision (22-24). In a typical MIP, most surgeons prefer a small cervical incision and a focused exploration, and the patient is given local anesthesia, in conjunction with an intravenously administered sedative, or “light” general anesthesia plus local anesthetic augmentation. The advantages of local anesthesia versus general anesthesia are unproven. The proclaimed advantages of MIP are shorter operating times, briefer hospital stay, quicker recovery, and earlier return to work. The disadvantages include the added cost of preoperative imaging and the potential of failure in the setting of multiglandular disease. In a publicly funded health-care system as in Canada, the additional costs of intraoperative PTH measurements and of preoperative imaging in all patients need to be analyzed.

Availability of a rapid PTH assay, providing results within 15 minutes, makes intraoperative use feasible (25-28). The measurement of PTH intraoperatively allows the surgeon to confirm that all abnormal parathyroid tissue has been removed and reduces the potential for failure to identify all abnormal parathyroid tissue (19). Intraoperative PTH measurement can be used for MIP procedures, to verify that the procedure does not need to be expanded to a four-gland neck exploration. The adequacy of the MIP is confirmed by a rapid decline in blood PTH by more than 50% at 10 minutes after tumor removal. If

this decrease in PTH is not confirmed, the surgeon must proceed with a more complete exploration of the entire neck.

In patients who have undergone previous parathyroid surgery, the surgical field may be more difficult to interpret, and intraoperative PTH measurements may be extremely useful in confirming that the abnormal parathyroid tissue has been removed. The cost-effectiveness of using intraoperative PTH measurements in all parathyroid surgical procedures, however, has been questioned (29,30).

The Canadian Consensus Development Task Force emphasizes the necessity of identifying and referring the patient to a surgeon with particular expertise in parathyroid surgery. The success of the parathyroidectomy, whether a conventional exploration or MIP, depends on the skill and experience of the surgeon, who must interpret the preoperative scans, direct the surgical approach, and assess intraoperative PTH results.

MEDICAL FOLLOW-UP AND MANAGEMENT

Although surgical intervention remains the only curative strategy for patients with PHPT, patients with mild PHPT can clearly be managed safely when a surgical procedure is not the recommended option. The revised guidelines for parathyroidectomy after the initial assessment of the patient and confirmation of the diagnosis of PHPT are summarized in Table 1. The main change from the 1990 guidelines is the use of the BMD definition of osteoporosis as a criterion for parathyroidectomy. The adoption of the *T*-score of <-2.5 as the criterion for parathyroidectomy on both initial assessment and monitoring of patients who do not undergo surgical treatment at diagnosis is a significant change. The earlier BMD criterion for recommendation for parathyroidectomy (*Z*-score of <-2.0) probably captured more patients in a younger age-group than does the use of the currently accepted BMD definition of osteoporosis, whereas the *T*-score of <-2.5 will capture a larger proportion of patients with PHPT who are older than 65 years (31). As noted in the foregoing material, the effects of PHPT on bone are variable, but bone density improves after surgery (11). Therefore, recommending parathyroidectomy to patients with PHPT who have osteoporosis seems reasonable.

Patients for whom surgical treatment is not recommended or those who are unwilling or unable to proceed with parathyroidectomy require medical monitoring. A comparison of the current (2002) recommendations with those of 1990 is shown in Table 2. Current recommendations include annual bone mass measurements at the lumbar spine, hip, and distal radius sites. Serum calcium assessments every 6 months are also recommended. Follow-up 24-hour urinary specimens for assessment of calcium excretion and creatinine clearance are no longer regarded as necessary. Instead, the serum creatinine is used as the initial monitoring test. In the presence of deteriorating renal function, a more intensive evaluation of renal function should be initiated, but declining renal

function should be considered an indication for surgical management of the PHPT. Follow-up abdominal radiography or ultrasonography for the assessment of nephrolithiasis is generally not necessary after the initial baseline assessment.

Several specific antiresorptive therapies have been evaluated with respect to their effects on serum calcium, PTH, and BMD. Estrogen seems to be of value in maintaining BMD in postmenopausal women with PHPT (32-34). Estrogen has not been shown to lower the serum calcium concentration consistently in the doses currently accepted for use in postmenopausal women. The overall effect of estrogen or hormone replacement therapy on patient health status must also be considered.

Data regarding the use of bisphosphonates are promising. In a double-blind placebo-controlled trial, alendronate increased lumbar spine BMD and maintained BMD at the hip and radius skeletal sites in both men and women with PHPT (35). These results correspond to the findings of other investigators (36-39). Raloxifene has been shown to reduce the serum calcium concentration in patients with PHPT (40,41). Early data on use of calcimimetic agents indicate that PTH and serum calcium levels are effectively decreased in postmenopausal women with PHPT (42,43). These agents are investigational; thus, further study is needed. Bisphosphonates, raloxifene, and calcimimetic agents are the most attractive alternatives to surgical intervention for those patients who are not surgical candidates or who are unable or unwilling to proceed with operative treatment.

RECOMMENDATIONS

The Canadian panel of medical and surgical experts is in agreement with the revised guidelines recommended by the ad hoc panel of the NIH-sponsored workshop. Not all

patients with mild "asymptomatic" PHPT need parathyroidectomy. For symptomatic patients, as well as those identified by the revised NIH working group guidelines, however, surgical treatment should be considered. The MIP procedure is currently being successfully used in Canada. Intraoperative PTH assays are necessary for patients undergoing MIP. Because the cost-effectiveness of intraoperative PTH measurements has been questioned, further study is warranted as more surgeons adopt the MIP procedure.

CONCLUSION

Advances in the diagnosis of PHPT have facilitated earlier identification of this common disease, usually in an asymptomatic phase. Preoperative localization imaging in conjunction with intraoperative PTH assays has supported the use of minimally invasive surgical procedures for some patients. The cost-effectiveness of preoperative imaging and intraoperative PTH assays must be further evaluated. Surgical intervention by an experienced parathyroid surgeon is associated with excellent success rates and very low morbidity. Monitoring of skeletal and renal status is necessary in patients declining to undergo parathyroidectomy. In patients with mild asymptomatic PHPT, use of medical rather than surgical management has not been shown to affect morbidity and mortality adversely. Specific medical therapies, including bisphosphonates, raloxifene, and calcimimetic agents, are undergoing further evaluation and remain potential alternatives to surgical treatment in selected patients. A cost-benefit analysis for surgical intervention versus medical monitoring has not been undertaken in Canada, although early studies in the United States suggested that the surgical option was less expensive and usually curative (44).

Table 2
Recommended Monitoring After Establishment of
Diagnosis of Asymptomatic Primary Hyperparathyroidism

Measurement	1990 guidelines	2002 guidelines
Serum calcium	Every 6 months	Every 6 months
Urine calcium (24-hour specimen)	Annually	Not recommended
Creatinine clearance (24-hour specimen)	Annually	Not recommended
Serum creatinine	Annually	Annually
Bone mineral density	Annually, forearm	Annually, 3 sites—lumbar spine, hip, forearm
Abdomen radiography (\pm ultrasonography)	Annually	Not recommended

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