

Current Status and Treatment of Primary Hyperparathyroidism

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Abstract

Primary hyperparathyroidism (HPT) is diagnosed in approximately 100,000 patients in the US each year, with a 2–3:1 female-to-male distribution. In most cases, occurrence is sporadic rather than familial, and 80% to 85% of cases of sporadic primary HPT are caused by a solitary parathyroid adenoma. The diagnosis is made by hypercalcemia with an inappropriately elevated parathyroid hormone (PTH) level and a 24-hour urine calcium excretion level that is normal or high. Truly asymptomatic primary HPT is rare, as most patients have symptoms or metabolic complications when carefully evaluated by standardized health questionnaires. The National Institutes of Health (NIH) published guidelines in 2002, recommending parathyroidectomy for all symptomatic patients and for asymptomatic patients less than age 50 years or those who cannot participate in medical surveillance. These criteria have been called into question as being too limited, because multiple studies have demonstrated symptomatic and metabolic benefits of parathyroidectomy in “asymptomatic” patients. Given the studies showing an improvement in quality-of-life measures, future risk for developing renal calculi, bone density, cardiovascular health, and risk of death, we believe that virtually all patients with primary HPT should undergo surgical resection. An improvement in preoperative localization studies as well as the development of a rapid intraoperative PTH assay has changed the approach to parathyroid surgery since the 1980s. Because most sporadic primary HPT is caused by a single gland adenoma, our preferred procedure has now changed from a bilateral neck exploration to a focused or unilateral approach, with similar rates of success in patients with a solitary tumor identified preoperatively.

Background

Primary hyperparathyroidism (HPT), which is characterized by the autonomous overproduction of parathyroid hormone, is diagnosed in approximately 100,000 patients in the US each year.¹ It is two to three times more common in women than in men, affecting 1 in 500 women

and 1 in 1100 men older than age 60 years.² Its incidence increases with age, affecting about 1% of the population overall and 2% of people older than age 55 years.³

Primary HPT may be sporadic or familial. In most cases (80%–85%), sporadic primary HPT is caused by a solitary parathyroid adenoma,

with the remainder of cases due to double adenomas (about 4%), multiple-gland hyperplasia (10%–15%), and parathyroid carcinoma (<1%).^{3–6} Familial syndromes associated with primary HPT include multiple endocrine neoplasia types 1 and 2 (MEN1 and MEN2), non-MEN familial HPT, HPT–jaw tumor syndrome, and familial neonatal HPT. These familial syndromes are associated with (usually asymmetric) multiple-gland hyperplasia. In addition, nonMEN familial HPT and HPT–jaw tumor syndrome are associated with an increased risk of parathyroid cancer.^{7,8}

The exact cause of sporadic primary HPT is unknown and is likely multifactorial, with environmental and genetic causes. It is associated with a history of radiation exposure^{9,10} as well as with prolonged lithium use.^{11,12} Genetic associations in sporadic primary HPT include overexpression of the PRAD1 oncogene (encoding cyclin D1) and an inactivating mutation of the MEN1 tumor-suppressor gene (encoding menin).¹³ The MEN1 gene is also associated with familial HPT, as are RET (associated with MEN2), HRPT2 (encoding parafibromin, associated with HPT–jaw tumor syndrome), and the CASR gene (encoding the calcium-sensing receptor, associated with neonatal primary HPT).



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Parathyroid disease is a relatively recent discovery in modern medicine, as the parathyroid glands themselves were the last major organ to be recognized in humans. They were first described by Ivar Sandström, a Swedish medical student, in 1879.¹⁴ The first parathyroidectomy for HPT was performed in a patient with von Recklinghausen disease and crippling bone disease by Felix Mandl in Vienna in 1925. In the US, HPT was first diagnosed in 1926 by Eugene DuBois. The patient, Captain Charles Martell, had severe bone demineralization and fractures and underwent six negative neck explorations before finally having a mediastinal parathyroid adenoma resected via median sternotomy by Edward Churchill and Oliver Cope at the Massachusetts General Hospital in 1932.¹⁵

Prior to 1932, all patients with HPT presented with osteitis fibrosa cystica, a bone disease characterized by increased osteoclastic resorption of bone and replacement by fibrous tissue. It was, in fact, initially thought that this bone disease caused parathyroid enlargement. Since that time, we have gained an understanding of calcium metabolism and parathyroid hormone physiology and know that it is the HPT that is responsible for bone demineralization, which in its most severe form is manifested by osteitis fibrosa cystica.

Diagnosis

Common symptoms of HPT are described by the pentad “painful bones, kidney stones, abdominal groans, psychic moans, and fatigue overtones,” which refers to typical signs and symptoms, including a decrease in bone mineral density with osteopenia, osteoporosis, or osteitis fibrosa cystica; joint or bone aches and pains; gout; nephrolithia-

sis; heartburn; peptic ulcer disease; pancreatitis; constipation; neuropsychiatric changes; and fatigue.¹⁶ A complete list of symptoms and associated conditions of HPT appears in Table 1. Even patients who are thought to be asymptomatic will often have symptoms or metabolic complications when carefully evaluated with standardized health questionnaires.^{17,18} Truly asymptomatic HPT is rare, occurring in only 2% to 5% of patients.^{16,19}

Even so, HPT is most often diagnosed by routine laboratory screening for serum calcium.³ HPT is the most common cause of hypercalcemia in the outpatient setting, and the diagnosis is made on the basis of hypercalcemia, with an inappropriately elevated intact parathyroid hormone (PTH) level, and a normal or increased 24-hour urinary calcium concentration. Occasionally patients with primary HPT can have intermittently elevated or normal serum calcium levels (intermittent or normocalcemic primary HPT); these patients will usually have an elevated ionized calcium level.³ Other causes of an elevated serum calcium with an inappropriately elevated PTH level include thiazide diuretics, lithium, and benign familial hypocalciuric hypercalcemia (BFHH), an autosomal-dominant condition caused by a heterozygous mutation in the CASR gene. To exclude these as causes for hypercalcemia with an elevated PTH level, the physician should have the patient discontinue medications such as thiazides and lithium and should have the patient retested. It is also important to exclude BFHH as a cause for hypercalcemia with an elevated PTH level, as these patients will not benefit from parathyroidectomy. BFHH can be excluded by documenting a previous normal blood calcium level or

Table 1. Symptoms and associated conditions in patients with primary hyperparathyroidism

Symptoms	
Fatigue	Depression
Weakness	Memory loss
Polydipsia	Loss of appetite
Polyuria	Nausea
Nocturia	Heartburn
Joint/bone pain	Pruritus
Constipation	
Associated conditions	
Nephrolithiasis	
Hematuria from passage of stones	
Renal dysfunction	
Osteopenia/osteoporosis/bone fracture	
Hypertension	
Joint swelling	
Gout/pseudogout	
Weight loss	
Gastric/duodenal ulcer	
Pancreatitis	

if the 24-hour urine calcium level is not low (ie, not less than 100 mg per 24 hours), with a ratio of urine calcium to creatinine clearance of >0.02 (this ratio is usually <0.01 in patients with BFHH).²⁰

Other laboratory derangements sometimes seen in patients with primary HPT include a low or low-normal phosphorous level, an increased chloride-to-phosphorous ratio (>33), a high or high-normal 1,25-dihydroxy vitamin D level, and an increased alkaline phosphatase level.^{21,22} The latter signifies high-turnover bone disease, and these patients are at risk for developing hypocalcemia after parathyroidectomy.

Treatment

The treatment of primary HPT is parathyroidectomy. For those patients who are symptomatic (eg, those with nephrolithiasis, fractures, or neuromuscular symptoms), this treatment recommendation is obvious. However, when the patient is “asymptomatic,” the referring physician may be reluctant to rec-

Common symptoms of HPT are described by the pentad “painful bones, kidney stones, abdominal groans, psychic moans, and fatigue overtones ...”

commend surgery and the patient may be reluctant to accept the recommendation, given the lack of symptoms or signs.

The recommendations regarding which patients should undergo surgery have changed since the 1980s.

The effects of HPT on fracture rates and cardiovascular disease have also been demonstrated.

In 1990, the National Institutes of Health (NIH) convened a consensus conference on the management of asymptomatic primary hyperparathyroidism.¹ These guidelines were then revised in 2002, at the Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century.²³ Table 2 summarizes the differences in recommendations between these two conferences. The 2002 guidelines currently recommend parathyroidectomy for patients 1) with a serum calcium >1.0 mg/dL (0.25 mM) above the reference range; 2) with 24-hour calcium excretion >400 mg (10 mmol); 3) with creatinine clearance reduced by 30% compared with age-matched control subjects; 4) with forearm, lumbar spine, or hip T score reduced by >2.5SD on bone mineral density scan; 5) who are younger than age 50 years; and 6) for whom medical surveillance is either not desirable or possible.

The current recommendations for patients with primary HPT who do not undergo surgery include biannual serum calcium measurements and annual serum creatinine measurements and bone mineral density scans.

Multiple studies have shown symptomatic and metabolic benefits of parathyroidectomy for patients with "asymptomatic" primary HPT, raising the question of whether the NIH criteria are too limited. One study concerned 178 patients who underwent parathyroidectomy and were divided into two groups on the basis of whether they met the NIH criteria for parathyroidectomy; they were compared with a control group of 63 patients who underwent thyroidectomy.²⁴ Of 14 symptoms queried on a preoperative and postoperative questionnaire, both groups with primary HPT who underwent parathyroidectomy experienced a significant improvement in symptoms at an average follow-up of one month, and there was no difference in the frequency of improvement between the NIH and nonNIH groups. Another study of 100 patients, 82 of whom were followed for more than one year, similarly demonstrated an improvement in general health, muscle strength, mood, level of anxiety, and energy

level after parathyroidectomy.²⁵ An additional study, which randomized 53 patients to parathyroidectomy versus regular follow-up, demonstrated a statistically significant increase in bone density at the femoral neck and total hip, as well as a modest improvement in quality of life and psychologic function as measured by a standardized health survey form.²⁶

In addition to improvement of symptoms after parathyroidectomy, multiple studies have shown an improvement in conditions associated with primary HPT. The effect of parathyroidectomy on the future risk for developing renal calculi was studied in a cohort of 258 patients in Milwaukee, Wisconsin with primary HPT who underwent parathyroidectomy.²⁷ The authors found that of 71 patients with nephrolithiasis documented preoperatively, only four passed stones postoperatively, resulting in a decrease in the rate of stone formation per patient per year from 0.36 to 0.02.

The effects of HPT on fracture rates and cardiovascular disease have also been demonstrated. A retrospective study of 1569 patients (452 underwent parathyroidectomy versus 1117 were observed) found that parathyroidectomy was independently associated with a decreased fracture risk (hazard ratio,

Table 2. Differences between the 1990 and 2002 National Institutes of Health recommendations for parathyroidectomy as the treatment of primary hyperparathyroidism

	1990 recommendations	2002 recommendations
Serum calcium level	>1.0–1.6 mg/dL (0.25–0.4 mM) above reference range	>1.0 mg/dL (0.25 mM) above reference range
24-hour urine calcium excretion	>400 mg (10 mmol)	Unchanged
Creatinine clearance	Reduced by 30% compared with age-matched controls	Unchanged
Bone mineral density	Reduced by >2 SD compared with age-, sex-, and race-matched controls (Z score; forearm)	Reduced by >2.5 SD compared with sex- and race-matched controls (T score; forearm, lumbar spine, or hip)
Patient age	<50 years	Unchanged
Other	Patients for whom medical surveillance is either not desirable or possible	Unchanged

0.68) on multivariate analysis.²⁸ Similarly, a cohort study of 674 patients who underwent parathyroidectomy compared with 2021 age- and sex-matched controls showed that the patients with HPT had an increased relative rate of fracture before surgery (1.8) but that the rate returned to normal (1.0) after surgery.²⁹ Furthermore, the increased risk of fracture was evident for up to ten years before parathyroidectomy and was independent of serum calcium concentration. A separate analysis of this same cohort³⁰ showed an increased risk of acute myocardial infarction for up to ten years prior to surgery (relative risk, 2.5) and within the first year after surgery (relative risk, 3.6) but decreased to a normal level more than one year after surgery. This may be related to a regression of left ventricular hypertrophy, as demonstrated in a study using echocardiography to evaluate left ventricular hypertrophy in 43 patients with HPT compared to 43 age- and sex-matched controls.³¹ This study found that the left ventricular mass index was statistically significantly higher in those with HPT than in the controls and that this correlated with PTH values. Furthermore, there was statistically significant decrease in left ventricular mass index six months after parathyroidectomy.

As a further consequence of the increased risk of cardiovascular events in patients with untreated HPT, there is also an increased risk of death. A study from a national patient registry in Sweden of 4461 patients who underwent parathyroidectomy between 1987 and 1994 demonstrated a significantly increased risk of death compared with the general population.³² This was due to cardiovascular disease, with a risk ratio of 1.71 for men and 1.85 for women.

Given the data demonstrating improvements in quality-of-life measures, future risk for developing renal calculi, bone density, cardiovascular health, and risk of death after parathyroidectomy, we believe that virtually all patients with a diagnosis of primary HPT should undergo surgical resection. The surgical gold standard is a bilateral neck exploration with identification of all four parathyroid glands and resection of the abnormal gland(s). This procedure has a success rate of approximately 97% for curing primary HPT, with complication rates of 1% to 2% when performed by experienced endocrine surgeons.³ However, given that 80% to 85% of patients will have only a solitary adenoma, a bilateral neck exploration subjects 15% to 20% of patients to unnecessarily extensive surgery, with the attendant risks of recurrent laryngeal nerve injury and postoperative hypocalcemia.

There has been an evolution in the approach to surgery in these patients since the 1980s because of an improvement in preoperative localization studies and the development of intraoperative PTH (IO-PTH) monitoring. By incorporating these tests into their algorithm, most endocrine surgeons have now adopted a focused or unilateral approach to parathyroidectomy, with exploration of the contralateral side if two normal or abnormal parathyroid glands are seen on the ipsilateral side, or if the IO-PTH fails to decrease. A bilateral approach is still indicated for those with familial or lithium-associated HPT. A retrospective study of 338 patients with sporadic primary HPT found that ultrasound alone had a sensitivity of 65% in detecting a parathyroid adenoma, sestamibi scan alone had a sensitivity of 80%, and the use of both techniques together increased

the sensitivity to 96%, which is similar to the success rate associated with a bilateral neck exploration.³³ The distribution of pathologies (81% single adenoma, 10% hyperplasia, 7% double adenoma, and 2% carcinoma) was similar to that generally reported in the literature.

The development of a rapid IO-PTH assay³⁴ further influenced the idea that unilateral neck exploration may be sufficient. However, a prospective study evaluating the use of ultrasound, sestamibi scan, and IO-PTH assay in 350 patients with sporadic primary HPT found that the combination of the 3 studies had a 9% failure rate if a unilateral approach was undertaken, though these data may be related to the lower number of solitary adenomas (69%) and higher number of double adenomas or hyperplasia (14% and 17% respectively) found than that generally reported in the literature.³⁵ As one might expect, a criticism of the unilateral approach is that it may underestimate the incidence of multiple-gland disease. A study of 45 patients who underwent bilateral neck exploration found an incidence of double adenoma or hyperplasia of 13% compared with 0% in 35 patients who underwent focal neck exploration.³⁶ All patients were normocalcemic at a mean follow-up point of 17 months. A larger review of the literature demonstrated similar findings. This review of 2095 patients in 31 studies who underwent a unilateral approach found that 92.5% had a single adenoma and only 5.3% had multiple-gland disease, compared with 79.7% and 20.6%, respectively, in a review of 2166 patients in 14 studies who underwent a bilateral neck exploration.³⁷ The difference in these data was statistically significant.

To better address the question, researchers conducted a prospec-

tive randomized trial of unilateral versus bilateral neck exploration in 91 patients in Sweden.³⁸ Unilateral neck explorations were guided by preoperative sestamibi subtraction scintigraphy and IO-PTH testing. There was no statistically significant difference in the incidence of multiglandular disease (5/41 vs 4/40), costs (\$2258 ± \$509 vs \$2097 ± \$505), or cure rate (95.1% vs 97.5%) between unilateral versus bilateral exploration. Patients who had a solitary adenoma, however, had a significantly shorter mean time in surgery (62 ± 29 vs 84 ± 38 minutes) when the surgeon used a unilateral versus a bilateral approach. Furthermore, patients in the bilateral group experienced a higher incidence of transient postoperative hypocalcemia and consumed more oral calcium than those in the unilateral exploration group. There were no cases of permanent recurrent laryngeal nerve paralysis in either group. Thus, this randomized trial demonstrated no difference in the incidence of multiglandular disease or cure rate between a unilateral versus a bilateral neck exploration.

Conclusion

Primary HPT is the most common cause of hypercalcemia in the outpatient setting. It is more common in women and more likely to be sporadic than familial. Most patients with primary HPT have symptoms or metabolic complications when carefully evaluated, and we recommend parathyroidectomy for virtually all patients, even for those who do not meet the NIH criteria for parathyroidectomy. This recommendation is based on studies documenting the natural history of untreated primary HPT and on multiple studies that show an improvement in quality-of-life measures, decreased future risk for

developing renal calculi, improved bone density and cardiovascular health, and decreased risk of premature death after parathyroidectomy. Because most patients with sporadic primary HPT have a single gland adenoma, preoperative localizing studies, IO-PTH testing, and a focused or unilateral approach is our preferred procedure when one tumor is identified preoperatively, with exploration of the contralateral side if two normal or abnormal parathyroid glands are seen on the ipsilateral side, or if the IO-PTH fails to decrease. This can be done with success rates similar to those of bilateral neck exploration. ♦

Acknowledgment

Katharine O'Moore-Klopf of KOK Edit provided editorial assistance.

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Clarke's First Law

When a distinguished but elderly scientist states that something is possible,
he is almost certainly right.
When he states that something is impossible,
he is very probably wrong.

— Sir Arthur C Clarke, b 1917, British science fiction author and inventor