

# Indications for Surgical Management of Hyperparathyroidism

## A Review

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**IMPORTANCE** Primary hyperparathyroidism (pHPT) is a common clinical entity, with approximately 100 000 new cases diagnosed each year in the United States. Most patients with pHPT have a relatively mild form of the disease and present with few if any overt signs or symptoms. This has led to a dilemma regarding which patients should be considered for parathyroid surgery. In this article, we review the established literature on the indications for surgery in asymptomatic pHPT and discuss the most recent consensus conference guidelines.

**OBSERVATIONS** The reviewed literature suggests that there were improved outcomes among patients with asymptomatic pHPT who underwent curative surgery.

**CONCLUSIONS AND RELEVANCE** Most patients with pHPT should be considered for parathyroidectomy. More randomized clinical trials are needed to strongly support a surgical recommendation for all asymptomatic patients with pHPT.

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Primary hyperparathyroidism (pHPT) was first recognized in the early 1900s, and patients presented with a significant clinical disease, as described by Fuller Albright and his contemporaries as “stones, bones, and groans.” With the introduction of the automated serum chemistry analyzer in the 1970s, the prevalence of the disease initially rose dramatically because much milder forms were discovered. Currently, most patients with primary hyperparathyroidism are found to be asymptomatic at the time when they receive a diagnosis. The term *asymptomatic pHPT* is used to describe patients who receive a diagnosis from routine laboratory testing results and who do not present with obvious clinical sequelae. Although this term is widely used, it is somewhat vague and poorly defined. Asymptomatic patients might have disease manifestations on the results of bone densitometry or renal ultrasonography, and it is often not possible to know whether nonspecific neuromuscular, psychiatric, or cognitive symptoms are caused by the disease. This shift in the disease paradigm presents a therapeutic dilemma for the clinician regarding the need for surgery in patients with seemingly absent or mild clinical manifestations. The only known cure for pHPT is surgery with exploration of the parathyroid gland(s) and the removal of enlarged and hyperfunctioning parathyroid tissue. Patients with symptomatic episodes of nephrolithiasis, clinically evident bone disease, or episodes of hypercalcemic crisis are clearly candidates for surgery, but this group represents less than 20% of patients with pHPT at an initial presentation. While most cases are diagnosed at a relatively early and mild stage, clinicians are confronted with important questions regarding asymptomatic patients, notably how to appropriately evaluate these patients and,

once this evaluation is complete, how to determine which patients should be recommended to undergo surgery.

In an effort to address these questions, the National Institutes of Health convened a Consensus Conference on Asymptomatic Primary Hyperparathyroidism in 1990, and guidelines for identifying surgical indications and evaluating asymptomatic patients were published. The guidelines were most recently revised at the fourth international workshop on the management of asymptomatic pHPT that was held in 2013, and the revisions were published in 5 articles.<sup>1-5</sup> The articles provide guidelines for how patients with asymptomatic pHPT should be evaluated after they receive a diagnosis and who should be recommended to undergo surgery (Box 1 and Box 2). The current and most updated surgical indications, as outlined in the 2014 consensus conference publications, are summarized in Box 2.

In general, the published guidelines for patients with asymptomatic pHPT recommend surgery for patients who meet at least 1 of 4 criteria: age, serum calcium level, bone density, and kidney health. However, some patients who do not meet the specified workshop criteria could still benefit from surgery, and it is noted in the summary statement that undergoing a parathyroid exploration is an option for all patients with pHPT because surgery is the only cure for pHPT.

The intent of this review is to identify and analyze the most recent literature on the indications for surgery in pHPT. To our knowledge, most published research investigates the effects of pHPT on bone density, renal function, and neurocognitive symptoms, as well as the potential for curative surgery in patients with asymptomatic pHPT.

**Box 1. Recommended Evaluation of Patients Who Received a Diagnosis of Primary Hyperparathyroidism<sup>a</sup>****Recommended**

- Biochemistry panel (calcium, phosphate, alkaline phosphatase activity, BUN, creatinine), 25(OH)D
- PTH by second- or third-generation immunoassay
- BMD by DXA (lumbar spine, hip, distal 1/3 radius)
- Vertebral spine assessment (radiography or VFA by DXA)
- 24-hour urine sample results for:
  - Calcium, creatinine, creatinine clearance
  - Stone risk profile
- Abdominal imaging by radiography, ultrasonography, or CT scan

**Optional**

- HR-pQCT
- TBS by DXA
- Bone turnover markers (bone-specific alkaline phosphatase activity, osteocalcin, P1NP [select one]; serum CTX, urinary NTX [select one])
- Fractional excretion of calcium on timed urine sample

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BUN, blood urea nitrogen; BMD, bone mineral density; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; HR-pQCT, high-resolution peripheral quantitative computed tomography; PTH, parathyroid hormone; TBS, trabecular bone score; VFA, vertebral fracture assessment.

<sup>a</sup> Adapted with permission.<sup>1</sup>

**Box 2. Guidelines for Surgery in Asymptomatic pHPT as Outlined in the 2014 Consensus Conference<sup>a</sup>**

**Serum Calcium (>upper limit of normal): 1.0 mg/dL (for millimoles per liter, multiply by 0.25)**

**Skeletal**

- BMD by DXA: T score of less than -2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius
- Vertebral fracture by radiography, CT, MRI, or VFA

**Renal**

- Creatinine clearance of less than 60 mL/min
- 24-hour urine sample results for calcium more than 400 mg/dL (>10 μmol/d) (for millimoles per liter, multiply by .25) and increased stone risk by biochemical stone risk analysis
- Presence of nephrolithiasis or nephrocalcinosis by radiography, ultrasound, or CT

**Age Younger Than 50 y**

Abbreviations: BMD, bone mineral density; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; pHPT, primary hyperparathyroidism; VFA, vertebral fracture assessment.

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## Methods

PubMed was searched for terms that included "primary hyperparathyroidism," "parathyroidectomy," "indications for surgery," and "bone density in primary hyperparathyroidism." In addition, the most recent consensus conference guidelines, published as a series of articles in 2014, were reviewed in detail. Throughout this article, the information in these publications are referred to as the 2014 guidelines.

## Results and Discussion

The findings of our literature search and review are summarized here. For organizational purposes, we chose to categorize the topics based on the most common and well-defined manifestations of pHPT.

### Bone Density

Primary hyperparathyroidism is associated with lower bone mineral density levels, particularly at sites that are composed of predominantly cortical bone, such as the distal third of the radius. The 2014 guidelines for surgical indications regarding skeletal manifestations of asymptomatic pHPT include bone density data, but compared with the previously published guidelines, they broaden the assessment of skeletal health by also including the results from other skeletal imaging techniques. Regarding measurements of bone density levels, it is recommended that the dual-energy x-ray absorptiometry (DXA) score be assessed at the lumbar spine, total hip, femoral neck, and distal 1/3 radius, with a T score of less than -2.5 at any 1 of these sites used as an indication for surgery. Interestingly, a recent study<sup>6</sup> noted that the distal radius, a site commonly affected

by pHPT, is often excluded in preoperative DXA examinations. Prior fractures, or the detection of a vertebral fracture on the results of radiography, even if not previously diagnosed, are also a clear indication for parathyroid surgery. A recent study<sup>7</sup> provided evidence that vertebral fractures are not rare, even among asymptomatic patients. Thirty-four percent of asymptomatic patients had evidence of vertebral fractures, and 66% had osteoporosis by DXA.

However, what remains less clear regarding surgical referrals is the management of patients with pHPT who do not meet any of the criteria but who experience bone loss over time. Clinicians, both endocrinologists and surgeons, might suspect that some patients with mild bone loss could benefit from a surgical cure of pHPT. A study of the natural history of pHPT treated with or without surgery showed a disease progression among 37% of asymptomatic patients who did not undergo surgery, and increased bone mineral density (BM) levels in patients who underwent surgery that were sustained for the 15 years of follow-up.<sup>8</sup> Beneficial effects on bone health have been difficult to study because the benefits may take several years to manifest.

One current research focus is to provide better tools to assess bone quality and strength using new technologies. It has been proposed that the more traditional bone density assessment (a DXA scan) may not adequately reflect fracture risk among patients with pHPT.<sup>9</sup> New skeletal imaging techniques are emerging, and their roles in assessing skeletal health in pHPT are being studied. Vertebral fracture assessment evaluates existing DXA images for the presence of previously undiagnosed fractures. The trabecular bone score is a tool that is approved by the US Food and Drug Administration that is complementary to DXA images and calculates a score derived from the texture of the DXA images, providing additional information related to bone microarchitecture and fracture risk.<sup>10,11</sup> High-resolution peripheral quantitative computed tomography allows for the assessment of trabecular microarchitecture and volumetric BMD at the distal radius and tibia.<sup>12</sup> Although these modalities are not yet

widely available, they hold promise for better predicting which patients would most benefit from surgery, in particular in patients with asymptomatic pHPT.

Several studies have documented that surgery for pHPT is associated with improved skeletal outcomes compared with observation alone. In 3 randomized clinical trials (RCTs), patients who underwent a successful parathyroidectomy were noted to have a significant increase in bone density levels, in particular at the lumbar spine and hip.<sup>13-15</sup> A 2013 cohort study of 236 patients noted significant postoperative bone density level improvements at the hip and the spine after successful parathyroidectomy.<sup>16</sup> Another recent study noted improvements in bone density levels at the spine and hip in patients with both hypercalcemic and normocalcemic pHPT 1 year after surgery.<sup>17</sup> Prospective studies with relatively long follow-up periods also documented BMD increases after parathyroidectomy.<sup>2,3,18</sup>

Overall, these studies provide convincing evidence that many patients with pHPT benefit from curative parathyroid surgery compared with observation alone in terms of bone health. However, it is less clear whether surgery is superior to medical antiresorptive therapy in patients with asymptomatic pHPT. A meta-analysis published in 2010<sup>19</sup> compared surgical treatment and antiresorptive therapies among patients with mild pHPT and noted similar increases in bone density levels, as measured by traditional DXA scans, concluding that parathyroidectomy and medical treatment of osteoporosis are both reasonable options for patients with mild pHPT and low BMD. More recently, however, a large retrospective cohort study investigated the effectiveness of parathyroidectomy on fracture risk in pHPT.<sup>20</sup> The investigator used data from the Kaiser Permanente health care system in Southern California and identified 6272 patients who received a biochemical diagnosis of pHPT between 1995 and 2010. By querying *International Classification of Diseases, Ninth Revision (ICD-9)* codes, they determined that 22% of patients underwent parathyroid exploration, 22% of patients were treated with bisphosphonates, and 55% of patients were managed by observation alone. Parathyroidectomy was found to be associated with a 64% reduction in the absolute risk of hip fractures compared with observation, whereas bisphosphonate treatment was not found to be superior to observation. While this study is limited by its retrospective design, it supports the notion that parathyroid surgery is beneficial for bone health, particularly among patients with osteopenia or osteoporosis.

### Neurocognitive and Psychiatric Symptoms

The classic description of pHPT includes psychological and neurocognitive symptoms, such as depression, anxiety, difficulty with concentration and memory, low energy, and personality changes. However, most patients with pHPT have mild disease, and evidence for improvement in neurocognitive and psychiatric symptoms with parathyroidectomy is inconsistent. The challenge in our current era of mostly asymptomatic pHPT is that these symptoms are often subtle and nonspecific and might not be related to pHPT. It is also unclear whether these symptoms correlate with calcium and parathyroid hormone (PTH) levels, as patients with relatively mild calcium and PTH elevations may experience these symptoms, and those with more significant biochemical abnormalities may not. The subjective nature of these often subtle and vague symptoms has resulted in challenges regarding the ability to assess patients for their presence and

severity, and to measure improvements following a successful parathyroid surgery. While anecdotally noted improvements in energy levels, cognitive function, and an overall sense of well-being after successful parathyroidectomy can be impressive, we do not have results of large prospective RCTs available to prove this. In addition, we may currently lack the right instruments and assessment tools to reliably measure these symptoms.

There have been RCTs that have investigated the effects of surgery on neuropsychiatric symptoms among patients with mildly asymptomatic pHPT.<sup>13-15</sup> Despite the fact that all 3 of these studies used the Short Form 36 general health survey, the results were inconsistent. The largest of the 3 trials (191 patients) noted baseline differences between patients with asymptomatic pHPT compared with matched controls, but no changes after surgery.<sup>14</sup> Another RCT noted declines in 5 of the 9 domains measured by the Short Form 36 among the group receiving medical treatment, but only in 1 of the 9 domains among the group who underwent surgery, concluding that this constitutes a small but significant benefit of undergoing surgery.<sup>13</sup> A third RCT noted improvements in 4 domains of quality of life (QOL) after surgery compared with observation alone.<sup>15</sup> These studies were noted in the 2008 consensus conference on the management of asymptomatic pHPT, and their conclusion was that the data were suggestive of improvements in neuropsychiatric symptoms following surgery but were not consistent enough to justify that these symptoms be used alone as an indication for surgery.<sup>21</sup> A more recent RCT studied the effect of surgery vs observation on brain function and sleep patterns among patients with asymptomatic pHPT. Improvements were noted at both 6 weeks and 6 months after surgery; this study included only 18 patients.<sup>22</sup>

In contrast to the lack of convincing evidence found in the RCTs described earlier, several case-control or observational studies reported improvements in neuropsychiatric parameters after parathyroidectomy. Weber et al<sup>23</sup> reported on the effect of parathyroidectomy on QOL and neuropsychological symptoms among 66 patients undergoing surgery and noted a decrease in the overall proportion of patients with anxiety and depression 12 months postoperatively. Pasioka et al<sup>24</sup> published the results of a 10-year prospective surgical outcome study, noting significant QOL improvement in patients 10 years after successful parathyroidectomy. A case-control study noted higher symptom scores for depression and anxiety among women with pHPT at baseline compared with controls, and also noted significant improvements after parathyroidectomy.<sup>25</sup> Another case-control study confirmed these findings, noting improved Patient Health Questionnaire-9 scores among patients undergoing parathyroidectomy.<sup>26</sup> A prospective cohort study published in 2011 noted improvements in depression and anxiety symptoms among patients with pHPT after a successful parathyroid surgery, as well as in visuospatial and verbal memory, which correlated with a postoperative reduction in PTH levels.<sup>27</sup> A 2005 study analyzed several prospective studies on cognitive function and health-related QOL following parathyroidectomy.<sup>28</sup> Several studies did not show consistent results; however, 7 well-designed studies of health-related QOL reported improvement in parameters included in the Short Form 36 after surgery.<sup>28</sup> Finally, a 2013 prospective multicenter study assessed anxiety, depression, suicidal ideation, and health-related QOL in a large series of patients (n = 194) with pHPT before and after undergoing a parathyroidectomy, and noted reduced psychopathologic symptoms and im-

**Box 3. A List of the 3 Published Randomized Clinical Trials on Surgery vs Surveillance/Medical Management Among Patients With Mild Asymptomatic pHPT**

- Rao et al<sup>13</sup>
- Bollerslev et al<sup>14</sup>
- Ambrogini et al<sup>15</sup>
- Perrier et al<sup>22</sup>

Abbreviation: pHPT, primary hyperparathyroidism.

proved QOL after a successful surgery.<sup>29</sup> In summary, neurocognitive symptoms were a classic feature of pHPT when patients presented with a more advanced disease. The presence of such symptoms in asymptomatic patients with pHPT currently is difficult to assess because they are nonspecific and hard to quantify. The RCTs described earlier do not provide consistent results, and the observational studies that show positive results after surgery may not provide strong enough evidence to use the presence of neuropsychiatric symptoms alone as an indication for surgery. Therefore, the 2014 guidelines did not add neuropsychiatric and cognitive dysfunction to the list of indications for parathyroid surgery, although it is acknowledged in the consensus statement that some patients experience symptomatic improvements after surgery.

### Renal Manifestations

The kidneys play a key role in calcium excretion, and hypercalciuria is seen in patients with hypercalcemia because of pHPT. Hypercalciuria is a risk factor for renal stone disease, and for this reason, renal manifestations are common in pHPT. In fact, the most frequent overt complications of pHPT are nephrolithiasis and nephrocalcinosis.<sup>2</sup> Overall, approximately 15% to 20% of patients with pHPT will present with kidney stones, and 3% of patients with kidney stones have pHPT.<sup>30</sup> *Nephrocalcinosis* is a term used to describe mineralization and calcium deposits in kidney tissue, and this is typically seen in more advanced forms of pHPT. In general, most patients with pHPT will not display overt signs of kidney disease or dysfunction, yet many clinicians strongly suspect that untreated pHPT, even in a relatively mild and “asymptomatic” form, has the potential to affect kidney health over time.

The recommendations for surgery in pHPT, as outlined in the 2014 guidelines, with regard to renal complications include a reduced creatinine clearance (<60 mL/min), 24-hour urine calcium level of more than 400 mg/dL and increased stone risk by biochemical stone risk analysis, and the presence of nephrolithiasis or nephrocalcinosis by radiography, ultrasonography, or computed tomography scan. These recommendations represent a major change from the 2008 guidelines, in which the only surgical recommendation related to the kidneys was a glomerular filtration rate of <60 mL/min. The additional work up recommended by the 2014 guidelines on asymptomatic pHPT addresses 2 issues that were not previously included in past published guidelines: the importance of a comprehensive radiologic evaluation to detect renal calcification at an earlier, subclinical stage, and the need for a complete biochemical analysis to assess the risk of stone formation, in addition to the cal-

cium excretion. This expanded recommended workup clearly aims to address an important concern regarding patients with asymptomatic HPT: what is the long-term risk of untreated pHPT on renal function, and what is the risk-benefit ratio of a surgical cure of pHPT?

### Other Considerations

In addition to bone health, QOL, and renal complications of pHPT, there are other potential manifestations that may affect the decision to proceed with parathyroid surgery for patients with pHPT. One such area is the potential cardiovascular effects of pHPT, including elevated blood pressure levels. Although there may be observational evidence of cardiovascular dysfunction in patients with mild pHPT, studies have not demonstrated improvements in cardiovascular end points for patients undergoing curative surgery and, pending further study, it should not be used as justification for a surgical referral.<sup>1</sup>

Another potential consideration in the decision to recommend parathyroid exploration is the evolution of preoperative imaging and advances in surgical approaches and techniques. The past 2 decades have witnessed marked improvements in available localization studies, including better ultrasonography machines and scanning techniques, the addition of 3-dimensional imaging to parathyroid scintigraphy, and the introduction of 4-dimensional computed tomography. Publications on the outcomes and success rates of various operative strategies, including focused or limited exploration guided by intraoperative parathyroid hormone monitoring, has provided more options for patients with different surgical and anesthetic considerations. The American Association of Endocrine Surgeons recently convened a multidisciplinary panel to summarize the important issues for the safe and effective practice of parathyroidectomy. This was published in *JAMA Surgery* in 2016 and provides a detailed focus on the important surgical considerations for patients with pHPT.<sup>31</sup>

## Conclusions

Most patients with pHPT have no overt signs or symptoms of disease. The most recent 2014 guidelines emphasize a complete initial work-up to identify patients who are most likely to benefit from undergoing surgery. The 2014 guidelines remain relatively conservative regarding recommending surgery, but they include new evaluation recommendations designed to specifically identify patients with fracture risks or kidney stones. Neuropsychiatric symptoms, although part of the classical description of pHPT, are harder to identify in the current, often mild forms of the disease, and they are still not considered alone an indication for surgery. Important areas for further study include the development of new tools to assess bone health and fracture risks, and better measures of neuropsychiatric symptoms. The currently published RCTs are listed in **Box 3**, and as emphasized in the 2014 guidelines, further randomized, prospective, and collaborative trials are necessary to determine if surgical intervention is appropriate for all patients with pHPT.<sup>3</sup> Finally, it has become well recognized that surgery is the only known cure and should be considered for most patients with pHPT.

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