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Diagnosis and Management of Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is a common disorder of dysregulated calcium homeostasis. In 2013, its incidence in the US is estimated at 66 per 100 000 person-years among women and 25 per 100 000 among men.[1]

Audio

The adoption of routine chemistry panel testing in the 1970s led to increased discovery of PHPT and changed its clinical presentation in developed nations from a rare, highly symptomatic disease to a milder, more subtle condition.

PHPT may present as a symptomatic or asymptomatic disease. Symptomatic patients experience kidney stones and osteoporotic fractures. In developed nations, about 15% of patients with PHPT present with overt symptoms,[2] whereas this figure may be higher in countries where routine laboratory screening is less common. Asymptomatic patients, whose disease is discovered incidentally, may have measurable end-organ manifestations, such as decreased cortical bone mineral density, hypercalciuria, nephrocalcinosis, and reduced creatinine clearance. PHPT is frequently a progressive disease; approximately a quarter of patients without initial evidence of disease develop end-organ manifestations within 5 years of diagnosis.[2] The probability of disease progression appears to be independent of the severity of hypercalcemia.[2]

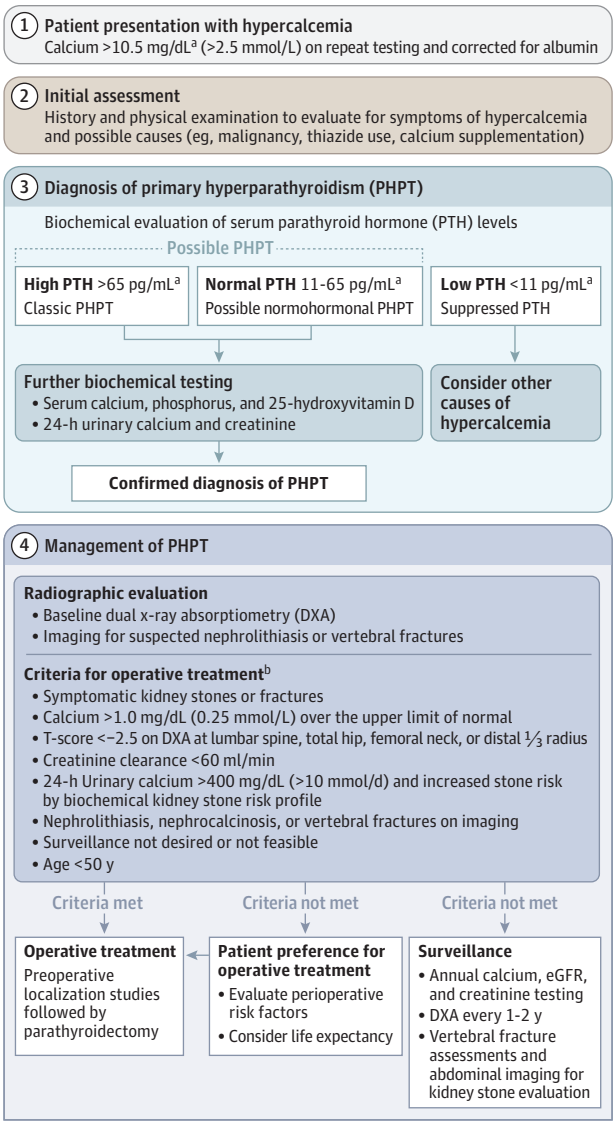
Patients with asymptomatic PHPT often report nonspecific symptoms, such as fatigue, anxiety, depression, and cognitive dysfunction. These neuropsychiatric symptoms appear to be more common in patients with PHPT than in the general population,[3] but a causal relationship has not been well established. Patients with very mild PHPT might not have any objective or subjective manifestations of disease.

Diagnosis

PHPT is the most common cause of hypercalcemia in the outpatient setting. After repeat laboratory confirmation of hypercalcemia, a careful history should be taken to evaluate for symptoms and potential causes of hypercalcemia (**Figure**). Causes of secondary hyperparathyroidism (eg, vitamin D deficiency, kidney failure, diuretic usage) should be excluded in the evaluation process. The diagnosis of PHPT is confirmed by biochemical evaluation, but the spectrum of biochemical abnormalities can complicate the diagnosis. In classic PHPT, serum calcium levels and serum parathyroid hormone (PTH) levels are elevated. Normohormonal PHPT is a variant characterized by elevated serum calcium levels and inappropriately normal (nonsuppressed) serum PTH levels. A third variant is normocalcemic PHPT, characterized by normal serum calcium levels and elevated serum PTH levels, which may represent a precursor to classic PHPT, as a fraction of these patients develop hypercalcemia over time. The biochemical profile in PHPT is dynamic; up to two-thirds of patients with normohormonal PHPT may revert temporarily to a normal profile and up to three-quarters of patients with classic PHPT may exhibit a milder biochemical state at some point within 5 years.[4] The clinical importance of these fluctuations is unclear.

Imaging studies for localization of abnormal gland(s) have no role in the diagnosis of PHPT. Rather, they should be used to inform surgical strategy once the decision for surgery has been made based on biochemical and clinical grounds.

Figure. Proposed Diagnostic and Management Algorithm for Suspected Primary Hyperparathyroidism



Suspected primary hyperparathyroidism (PHPT) requires a thorough history and physical and biochemical evaluation to make the diagnosis. Laboratory testing: (1) serum creatinine should be obtained to evaluate for renal insufficiency, which may occasionally cause spuriously high serum calcium levels. (2) Serum phosphorus is depressed in PHPT. (3) Vitamin D deficiency frequently coexists with PHPT, resulting in higher serum PTH levels. Vitamin D should be repleted if deficient before making the diagnosis of PHPT. (4) Optional: 24-hour urinary testing (calcium, creatinine) may be obtained if there is ambiguity in the diagnosis of PHPT. This test is used to differentiate PHPT from familial hypocalciuric hypercalcemia, a rare, benign condition that features a calcium:creatinine clearance ratio of less than 0.01 and usually does not require treatment. eGFR indicates estimated glomerular filtration rate.

[a] Reference values may vary by laboratory service.

[b] Adapted from Wilhelm et al.[3]

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When Is Surgery Indicated?

Parathyroidectomy is the definitive treatment for PHPT and is indicated for patients with symptomatic disease.[3] However, the selection of asymptomatic patients for parathyroidectomy has been the subject of considerable debate. The American Association of Endocrine Surgeons (AAES) also released a set of guidelines in 2016.[3] Most of the surgical indications for asymptomatic patients are similar to those recommended by other guidelines apart from a recommendation by the AAES for surgery in patients with neuropsychiatric symptoms. This was based on several small randomized clinical trials that demonstrated symptomatic improvement after parathyroidectomy.[3]

Outcomes of Parathyroidectomy

Cortical bone loss is observed over time in most untreated patients with PHPT.[5] Bone mineral density improves after parathyroidectomy, and this is associated with reduced fracture risk. These benefits are equally observed in patients who meet guideline criteria for surgery and those who do not.[5] A recent report demonstrated that fracture risk after failed parathyroidectomy is greater than that associated with successful parathyroidectomy and similar to that associated with nonsurgical management.[6] Data on skeletal outcomes after parathyroidectomy are primarily based on observational studies, which are limited by confounding factors. The literature is lacking in randomized clinical trials comparing parathyroidectomy and observation, although the small number that exist appear to support some findings of bone mineral density improvement after surgery.[3]

The prevalence of symptomatic nephrolithiasis is falling due to earlier diagnosis of PHPT, but nephrolithiasis still affects approximately 10% of untreated patients.[2] After parathyroidectomy, the rate of new kidney stone formation declines steeply, although recurrence risk is not completely mitigated,[3] which may be due to injured urothelium providing a nidus for recurrent stone formation.

When performed by experienced surgeons, parathyroidectomy has a cure rate of more than 95% and low rates of complications, including bleeding, hypocalcemia, and recurrent laryngeal nerve injury.[7,8] The risk of recurrence after parathyroidectomy may be greater than previously believed. A study reported a recurrence rate of 14.8% over a 10-year follow-up period.[8] Reoperative parathyroidectomy has higher risks of complications and operative failure compared with initial surgery.[7]

PHPT may be an undertreated condition. A recent nationwide study across the Veterans Affairs health system found low rates of parathyroidectomy for both symptomatic patients and asymptomatic patients meeting surgical criteria (23% and 26%, respectively).[9] Subgroup analysis of patients who met surgical criteria and had an Elixhauser Comorbidity Index score of 0 also found a low rate of treatment (17%).[9]

Nonoperative Management

Nonoperative management of PHPT consists of surveillance for the development of end-organ damage. Surveillance should be offered to asymptomatic patients not meeting surgical criteria. Annual laboratory testing and bone densitometry every 1 to 2 years is recommended (Figure). Long-term observational studies have shown that many patients with asymptomatic PHPT have stable disease and can be safely followed with observation for several years.[3]

The evidence for nonoperative management of PHPT is limited because of the small number of randomized clinical trials in the literature. Long-term data to assess adverse events, such as fractures, nephrolithiasis, and the development of worsening chronic kidney disease, are needed. Future research in this field would benefit from a clinical trial for patients with mild PHPT randomized to parathyroidectomy or surveillance with a long follow-up period, likely longer than 10 years, to compare differences in rates of adverse outcomes. Ideally, such a study would involve a large-scale multicenter design.

Conclusions

The adoption of routine serum calcium testing has simultaneously led to the increased discovery of PHPT and a change in its typical clinical presentation. Asymptomatic PHPT is the most common clinical phenotype in developed nations. Despite the publication of guidelines for treatment of asymptomatic patients, rates of surgical treatment remain low (20%-30%).[5,9] Recent studies on skeletal outcomes after parathyroidectomy suggest improvements in bone mineral density that correspond to decreased fracture risk. However, the literature is limited by a lack of high-quality randomized clinical trials concerning the treatment of asymptomatic PHPT, and current understanding of the benefits of parathyroidectomy are based primarily on observational data. Surveillance should be offered to patients who do not meet surgical criteria. Patients who wish to have surgery despite not meeting criteria should be engaged in a risk/benefit discussion. Careful consideration should be given to the patient's life expectancy, potential benefits of parathyroidectomy, risks of surgical complications, medical comorbidities, and surgeon experience.

ARTICLE INFORMATION

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