REVIEW ARTICLE

Primary hyperparathyroidism: diagnosis and management in 2017

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KEY WORDS

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ABSTRACT

Primary hyperparathyroidism is a relatively common endocrine condition, which is being increasingly identified in its asymptomatic stage, following routine evaluation of serum calcium levels. Parathyroid hormone and calcium excess impact multiple organ systems. The greatest effects are seen on the skeleton and the kidney. This overview describes the current advances in the diagnosis, presentation, and management of primary hyperparathyroidism.

Diagnosis Primary hyperparathyroidism (PHPT) is caused by a single parathyroid adenoma in approximately 85% of patients. In 15% of individuals, it can be associated with hyperplasia, and, fortunately, parathyroid carcinoma is rare.[1]

PHPT is diagnosed in the presence of hypercalcemia and an elevated or inappropriately normal parathyroid hormone (PTH) levels, following exclusion of other conditions that can mimic PHPT.[1,2] The use of hydrochlorothiazide and lithium can result in elevations in serum calcium and PTH levels. Hydrochlorothiazide should be discontinued and the laboratory profile should be repeated 3 months later to confirm the diagnosis of PHPT. Hydrochlorothiazide enhances renal calcium reabsorption; it can result in elevations in serum calcium levels and must be discontinued prior to confirming the diagnosis. Lithium elevates the set point for serum calcium levels. It may be difficult to discontinue lithium and the patient may require management decisions to be made during ongoing lithium use.

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant condition that can mimic PHPT. It is caused by an inactivating mutation of the calcium-sensing receptor gene. The less common variant is FHH2, which is caused by an inactivating mutation of the G protein alpha 11 subunit.[3] The FHH3 variant is caused by inactivating mutations of the adaptor protein 2 sigma subunit.[4] FHH is excluded by evaluating the calcium-to-creatinine clearance ratio, which is calculated using the following formula: (urinary calcium × serum creatinine)/(urinary creatinine × serum calcium). The ratio is lower than 0.01 in 80% of individuals with FHH. However, approximately 20% of individuals have the ratio between 0.01 and 0.02, and in these individuals, other factors that can lower the ratio need to be considered. Possible conditions include renal insufficiency or severe calcium or vitamin D deficiency. The calcium-to-creatinine clearance ratio can also be low in individuals of African descent.[5] On the other hand, 80% of individuals with PHPT have a calcium-to-creatinine clearance ratio exceeding 0.02; an overlap of PHPT and FHH can occur in 20% of individuals and the ratio can be between 0.01 and 0.02.[5] FHH should be excluded prior to confirming the diagnosis of PHPT, because hypercalcemia will persist even after parathyroid surgery, and it is important not to refer individuals with FHH for surgery because it is unnecessary and of no benefit.

As the focus of the article is on diagnosis and management of PHPT, calcium homeostasis is described only briefly. The main regulator of serum calcium is PTH. The synthesis and secretion of PTH is stimulated by a decrease in extracellular calcium levels. PTH enhances renal calcium reabsorption, bone resorption, and the hydroxylation of 25-hydroxyvitamin D in the kidney, resulting in elevations in serum calcium levels into the normal reference range (FIGURES 1 and 2). Extracellular calcium binds to the calcium-sensing receptor on the chief cells in the parathyroid glands and inhibits the synthesis and secretion of PTH (FIGURE 3).

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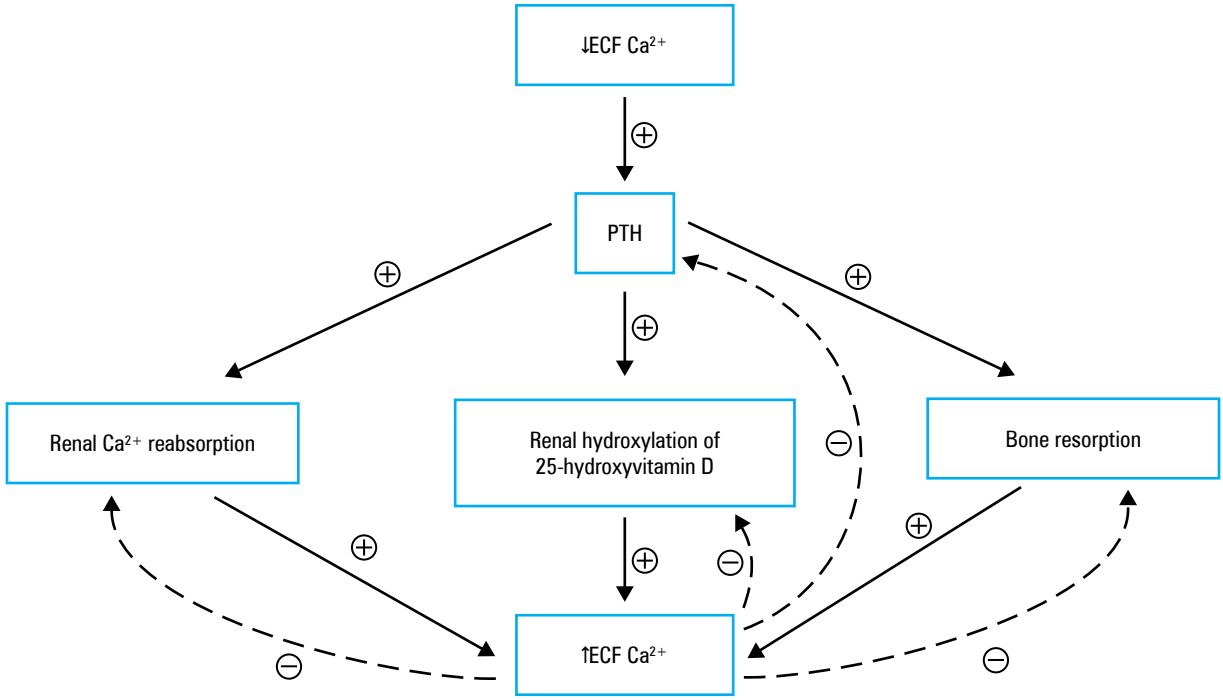

FIGURE 1 Effects of parathyroid hormone on calcium regulation
Abbreviations: ECF, extracellular fluid; PTH, parathyroid hormone

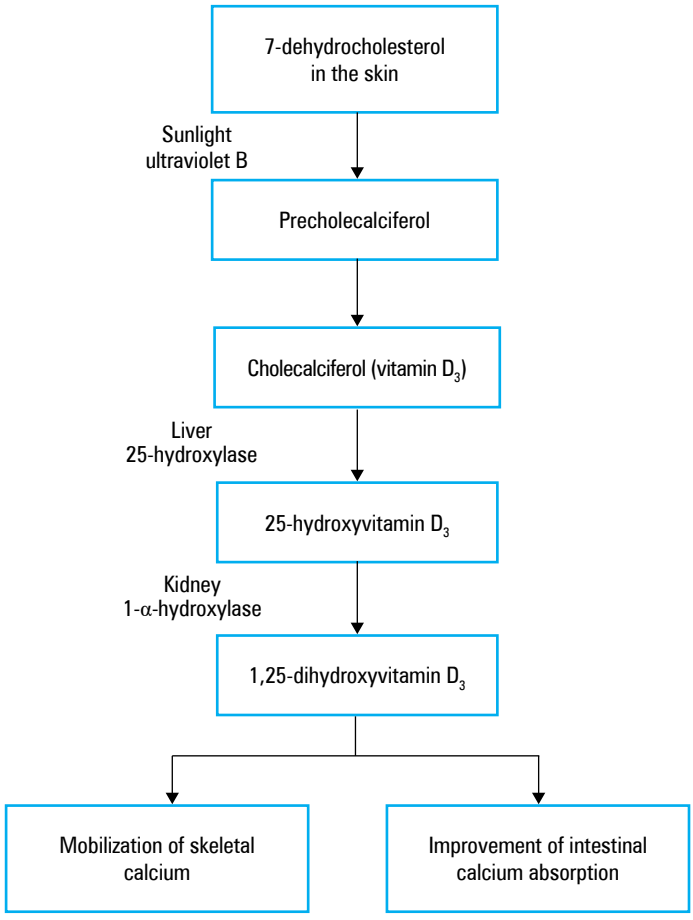

FIGURE 2 Vitamin D synthesis

Presentation PHPT presents at an asymptomatic stage in approximately 85% of individuals.[6] Low bone mineral density (BMD) is noted most commonly at the one-third radius, with the lumbar spine and hip BMDs being relatively well preserved.[7] The risk of vertebral and nonvertebral facture appears to be increased, as suggested by data from epidemiologic studies and cohort studies.[8,9] Following parathyroidectomy, improvements in the fracture risk as well as significant improvements in BMD are observed.[10] Improvements in microarchitecture, cortical thickness, and estimated bone strength have also been observed using high-resolution peripheral quantitative computed tomography imaging.[11] The radiographic features of overt PHPT include the salt-and-pepper appearance of the skull due to demineralization, subperiosteal bone resorption, and brown tumors. However, these features are rarely seen today.[1]

Renal involvement Kidney stones are a complication of PHPT and are present in approximately 7% of patients in comparison with 1.6% of the general population.[12] The stones seen in PHPT are usually calcium phosphate or calcium oxalate stones.[12] The risk of kidney stones is increased by the presence of hypercalciuria, which is an indication for parathyroidectomy.[1] Parathyroidectomy results in a significant reduction in the risk of kidney stones; however, the risk does not normalize and is still higher than that in the general population with normal calcium levels.[1]

Individuals with kidney stones and PHPT should undergo a 24-hour urine collection to

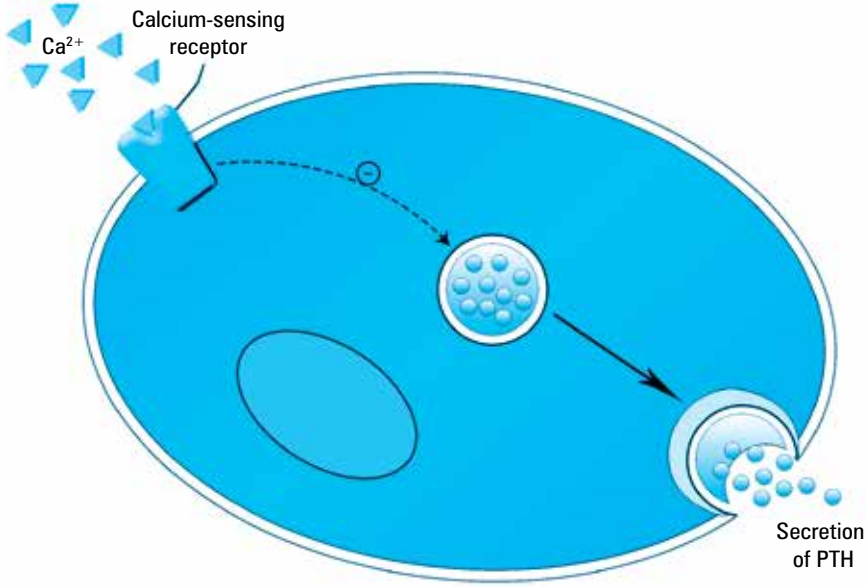

FIGURE 3 Activation of calcium-sensing receptor on the chief cells
Abbreviations: see FIGURE 1

assess calcium as well as uric acid, oxalate, citrate, and cystine levels.[13] Higher PTH levels are associated with reductions in estimated glomerular filtration rate (GFR).[14] A GFR of less than 70 ml/min/1.73 m^2 has been associated with lower BMD in comparison with individuals who have a GFR greater than 70 ml/min/1.73 m^2.[15] Following parathyroidectomy, renal function is relatively well maintained in comparison with progressive decline in renal function observed in individuals who have PHPT and do not undergo surgery.[16]

An increased risk of cardiovascular mortality has been observed in individuals with severe PHPT (serum calcium levels >11.2 mg/dl [2.79 mmol/l]).[17] Severe PHPT is associated with an increased risk of myocardial calcification, impaired diastolic filling, and left ventricular hypertrophy.[18-20] Mild PHPT with a serum calcium level of less than 2.9 mmol/l has also been associated with an increased risk of cardiovascular and cerebrovascular disease in comparison with age- and sex-matched general population with normal calcium levels.[21] This study, however, has been criticized because vitamin D levels were not evaluated, and vitamin D inadequacy may have contributed to higher PTH levels and mortality rates.

Literature data have not consistently shown improvements in cardiovascular disease following parathyroidectomy, and the impact of PHPT on cardiovascular and all-cause mortality requires further research.

Surgical management A recent Canadian and international consensus on PHPT recommends surgery if any of the guideline criteria, presented in TABLE 1, are met.[1,28] Surgery should be performed in any patient with symptomatic PHPT, in individuals meeting the criteria for surgical intervention, and in individuals who would prefer surgery and do not have contraindications to a surgical intervention.

Medical management Medical management is suitable for individuals who have failed surgery or who have recurrent disease, as well as for those who have significant comorbidity and an increased risk of surgical complications. It is also suitable for individuals who are unable or unwilling to proceed with surgery, as well as those who have asymptomatic disease and do not meet the criteria for surgery and prefer medical observation.[1]

Medical management includes ensuring that adequate vitamin D supplementation is provided, because vitamin D insufficiency is associated with more significant bone disease and an increased risk of hungry bone syndrome following parathyroidectomy.[22] Vitamin D supplementation is safe and effective in lowering PTH levels by up to 26% without increasing serum calcium levels.[23,24] The consensus recommends that vitamin D levels be optimized and maintained at more than 75 nmol/l.[1]

Amino-bisphosphonates and hormone replacement therapy have been demonstrated to improve BMD and lower bone remodeling.[1] Data on fractures are currently unavailable, and amino--bisphosphonates can be safely administered for up to 5 years in individuals with PHPT, providing a relatively well-maintained renal function with a GFR of more than 35 ml/min/1.73 m^2. Hormone replacement therapy has also been associated with improvements in BMD and reductions in bone remodeling.[25] However, ionized calcium and PTH levels are not lowered with amino-bisphosphonate or hormone replacement therapy.[1] These medical interventions may be provided to individuals who have osteoporosis confirmed either by bone densitometry or clinically in the presence of a fragility fracture.[1]

Cinacalcet is an allosteric modulator of the calcium-sensing receptor and increases its sensitivity to extracellular calcium.[26] Cinacalcet is able to

TABLE 1 Indications for surgery for the treatment of primary hyperparathyroidism

Age <50 years
Serum calcium levels >1 mg/dl or >0.25 mmol/l of the upper limit of the reference range for total calcium and >0.12 mmol/l for ionized Ca^{2+}
Bone mineral density T-score ≤–2.5 at the lumbar spine, femoral neck, total hip, or the one-third radius for postmenopausal women or men aged >50 years. A prevalent low-energy fracture (ie, in the spine) is also considered an indication for surgery, which requires a routine X-ray of the thoracic and lumbar spine (or vertebral fracture assessment by dual-energy X-ray absorptiometry)
Glomerular filtration rate <60 ml/min/1.73 m^2. Further evaluation of an asymptomatic patient with renal imaging (X-ray, computed tomography, or ultrasound) in order to detect silent kidney stones or nephrocalcinosis is advised.2 A complete urinary stone risk profile should be performed in individuals with urinary calcium excretion >400 mg/d. If stone(s), nephrocalcinosis, or high stone risk is determined, surgery should be recommended.

normalize serum calcium levels and maintain this effect for over 5 years.[26] It has no impact on BMD or bone remodeling.[26] Cinacalcet has been evaluated in a multicenter randomized controlled trial and has effectively normalized serum calcium levels while being well tolerated.[27]

Summary PHPT is a relatively common endocrine condition, identified at an early asymptomatic stage. Surgery is effective in reducing the risk of kidney stones, preserving renal function, and reducing the risk of subsequent fracture. Medical management is effective in lowering serum calcium levels and providing skeletal protection. The medical management options do not currently have fracture data and are of limited duration, and the degree of evidence for medical management is significantly lower than that for surgical intervention. Surgery is always a suitable option for individuals with PHPT. In individuals who have failed surgery, have recurrent disease, or have significant comorbidity and are unwilling or unable to proceed with surgery, the medical management becomes a necessary option.

Advances in the current evidence-based management of PHPT are defined by the recent Canadian and international consensus guidelines.[1]

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