

Primary hyperparathyroidism

Update on presentation, diagnosis, and management in primary care

Shelley Pallan MD Aliya Khan MD FRCPC FACP FACE

Abstract

Objective To discuss the presentation, diagnosis, and management of primary hyperparathyroidism (PHPT) in family medicine.

Quality of evidence MEDLINE was searched from 2002 to 2009 using the terms *presentation, diagnosis, and treatment* of PHPT. Proceedings and guidelines from the Third International Workshop on Primary Hyperparathyroidism in May 2008 were reviewed in detail. Most studies offered level II and III evidence, although there were a number of single randomized controlled trials on PHPT (level I evidence). References from pertinent papers were also searched for relevant articles. Articles most relevant to family medicine and primary care practitioners are presented.

Main message Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients. In the Western world, most patients with PHPT present with nonspecific symptoms such as fatigue, mood disturbances, and cognitive impairments. Diagnosis is established when intact parathyroid hormone levels are elevated or at the high end of the normal range in the setting of elevated total or ionized calcium levels (following exclusion of conditions that can mimic PHPT). Criteria for surgery have recently been modified. Surgery is always a suitable option in those with symptomatic PHPT and no contraindications. Those with contraindications or with asymptomatic PHPT not meeting the criteria for surgery can generally be safely monitored and considered for medical management. This might include treatment with bisphosphonates, hormone replacement therapy, raloxifene, or calcimimetic agents; however, there are currently no fracture data for any of these options.

Conclusion The definitive therapy for symptomatic and asymptomatic PHPT is parathyroidectomy. In patients with asymptomatic PHPT not meeting the criteria for surgery, monitoring is safe and medical management designed to target skeletal protection or lower serum calcium is a suitable option.

Résumé

Objectif Rappeler le mode de présentation, le diagnostic et le traitement de l'hyperparathyroïdie primaire (HPTP) en médecine familiale.

Qualité des preuves On a consulté MEDLINE entre 2002 et 2009 à l'aide des rubriques *presentation, diagnosis* et *treatment* de l'HPTP. On a révisé minutieusement les comptes rendus et directives du *Third International Workshop on Primary Hyperparathyroidism* de mai 2008. La plupart des études contenaient des preuves de niveaux II et III, quoiqu'il y avait un certain nombre d'essais cliniques randomisés sur l'HPTP (preuves de niveau I). Les articles les plus pertinents pour la médecine familiale et les médecins de première ligne sont inclus.

Principal message L'hyperparathyroïdie primaire est la cause la plus fréquente d'hypercalcémie chez les patients externes. En occident, la plupart des cas d'HPTP présentent des symptômes non spécifiques tels que

KEY POINTS Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient clinical setting. There are no specific physical findings in PHPT, and parathyroid adenomas or carcinomas are rarely palpable; however, it is important to exclude neck masses. Definitive therapy for PHPT is a parathyroidectomy. For asymptomatic PHPT not meeting criteria for surgery, monitoring is a suitable option. Medical management targeting skeletal protection or lowering serum calcium can be useful in those with contraindications to, or who do not wish to have, surgery. In the absence of nephrolithiasis, a 24-hour urine calcium above 10 mmol/d is no longer an indication for parathyroidectomy, as urinary calcium excretion is affected by other factors.

POINTS DE REPÈRE L'hyperparathyroïdie primaire (HPTP) est la cause la plus fréquente d'hypercalcémie chez les patients en consultation externe. Il n'y a pas de signe clinique spécifique à l'HPTP et les adénomes ou carcinomes parathyroïdiens sont rarement palpables; néanmoins, il est important d'exclure toute masse cervicale. Le traitement définitif de l'HPTP est la parathyroidectomie. Pour l'HPTP asymptomatique qui ne répond pas aux critères chirurgicaux, le monitoring est une option acceptable. Un traitement médical visant à protéger le calcium osseux ou à abaisser le calcium sérique peut être utile chez les patients qui présentent des contre-indications à la chirurgie ou qui ne veulent pas être opérés. En absence de néphrolithiase, une quantité de calcium supérieure à 10 mmol/d dans l'urine de 24 heures n'est plus une indication pour une parathyroidectomie, puisque l'excrétion urinaire du calcium est affectée par d'autres facteurs.

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Cet article a fait l'objet d'une révision par des pairs.

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fatigue, changements d'humeur et problèmes cognitifs. Le diagnostic repose sur des niveaux de parathormone intacte élevés ou se situant dans le haut du spectre normal en présence de niveaux élevés de calcium total ou ionisé (après exclusion des conditions qui peuvent imiter l'HPTP). Les critères pour la chirurgie ont été récemment modifiés. La chirurgie est toujours une option valable quand l'HPTP est asymptomatique et qu'il n'y a pas de contre-indication. En présence de contre-indications ou d'une HPTP asymptomatique ne répondant pas aux critères chirurgicaux, on peut généralement faire un suivi sans danger et envisager un traitement médical. Ce traitement pourrait comporter l'administration de bisphosphonates, une hormonothérapie de suppléance, du raloxifène ou des agents calcimimétiques; toutefois, il n'existe actuellement aucune donnée concernant les fractures avec ces options de traitement.

Conclusion Le traitement définitif de l'hyperparathyroïdie symptomatique ou asymptomatique est la parathyroïdectomie. En cas d'HPTP asymptomatique chez des patients ne répondant pas aux critères chirurgicaux, le monitoring est sécuritaire et un traitement médical visant à protéger le calcium osseux ou à abaisser le calcium sérique est une option acceptable.

PPrimary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient clinical setting.¹ This condition can occur at any age, but it more commonly affects those older than 50 years of age and postmenopausal women.^{1,2} The prevalence of PHPT ranges from 1 to 4 per 1000 people.³

The 4 parathyroid glands are located in the neck on the posterior surface of the thyroid gland, which is situated between the cricoid cartilage and the suprasternal notch on the anterior surface of the trachea. Uncommonly, the parathyroid glands might also be found in the carotid sheath, anterior mediastinum, and intrathyroidal tissue. The chief cells of the parathyroid glands secrete parathyroid hormone (PTH), which is the main regulator of calcium homeostasis in the body. In response to low serum ionized calcium levels, PTH production and secretion are upregulated. Parathyroid hormone normalizes calcium by enhancing calcium reabsorption in distal renal tubular cells, stimulating osteoclast-mediated bone resorption and catalyzing the conversion of 25-hydroxyvitamin D₃ (25[OH]D) to 1,25-dihydroxyvitamin D₃, which in turn enhances calcium reabsorption from the gastrointestinal tract.³

Patients with PHPT have abnormal regulation of PTH secretion. Primary hyperparathyroidism is characterized by elevated serum calcium in the setting of elevated or upper normal PTH levels; PTH levels that fall within the upper normal range are inappropriately elevated in the presence of high calcium levels. Almost 90% of PHPT cases are caused by sporadic PTH-secreting solitary

adenomas. Multiglandular hyperplasia and parathyroid carcinoma account for only about 5% and less than 1% of PHPT cases, respectively.⁴ Ectopic locations of adenomatous parathyroid tissue, such as intrathoracic adenomas,⁵ have also been reported.

Primary hyperparathyroidism is also associated with rare familial disorders, including multiple endocrine neoplasia (MEN) type 1 and type 2A syndromes, familial hypocalciuric hypercalcemia (FHH), familial hyperparathyroidism–jaw tumour syndrome, neonatal severe hyperparathyroidism, and familial isolated hyperparathyroidism.³ The MEN type 1 and type 2A syndromes are caused by mutations in the *MEN1* and *RET* genes, respectively; they are hereditary syndromes associated with multiple endocrine tumours, including parathyroid tumours.⁶ Familial hypocalciuric hypercalcemia mimics PHPT and is caused by an inactivating mutation of the calcium-sensing receptor gene, which makes the receptor less sensitive to calcium in the parathyroid glands and the kidneys. As a result, a higher serum calcium level is required to reduce PTH secretion. As the mutation also affects the calcium-sensing receptors in the kidney, renal calcium clearance is inappropriately low. Familial hypocalciuric hypercalcemia is inherited as an autosomal dominant condition with high penetrance and is a benign cause of hypercalcemia.^{6,7} Familial hyperparathyroidism–jaw tumour syndrome, associated with mutations in the *HRPT2* gene,⁸ is a rare autosomal dominant condition affecting young adults, which can present as single parathyroid adenomas, bony lesions of the jaw, renal hamartomas, or cystic kidney disease.⁹

Certain drugs, such as thiazide drugs and lithium, might also alter calcium homeostasis. Thiazide diuretics might unmask underlying PHPT, as they cause mild hypercalcemia by reducing urinary calcium excretion; PHPT is likely if hypercalcemia persists after stopping the medication.¹⁰ Although most patients taking lithium therapy do not develop hypercalcemia, lithium decreases the parathyroid gland's sensitivity to calcium, and shifts the set-point of the calcium-PTH curve to the right, causing increases in serum levels of calcium and PTH.¹¹ Hence, lithium can also unmask pre-existing parathyroid adenomas or induce parathyroid hyperplasia with prolonged use. A history of radiation exposure to the head and neck region and radioactive iodine therapy might also contribute to the development of PHPT, but there are only small case series supporting this pathogenesis (level II evidence).^{12,13}

Quality of evidence

We searched MEDLINE from 2002 to 2009 using the terms *presentation*, *diagnosis*, and *treatment* of PHPT. Proceedings and guidelines from the Third International Workshop on Primary Hyperparathyroidism in May 2008

were thoroughly reviewed. Level of evidence is cited where appropriate. Most studies offered level II and III evidence, although there were a number of single randomized controlled trials on PHPT (level I evidence). Reference lists of pertinent papers were also searched for relevant articles. Articles most relevant to family medicine and primary care practitioners are presented.

Main message

Clinical presentation. Patients with PHPT might present with symptomatic hypercalcemia, asymptomatic hypercalcemia detected incidentally, or normocalcemic hyperparathyroidism.

Symptomatic hypercalcemia occurs with longstanding elevated levels of PTH. It is usually found in developing countries where biochemical screening is not widely available. The patients in such countries are younger and might have debilitating renal and skeletal complications of hyperparathyroidism at the initial presentation of PHPT.¹⁴ The spectrum of bone disease in PHPT can include bony pain, low bone mineral density (BMD) commonly most substantial at cortical sites, fragility fractures, or rarely PHPT bone disease (ie, osteitis fibrosa cystica). Renal manifestations of PHPT include nephrolithiasis, nephrocalcinosis, polyuria, and renal insufficiency. Patients with PHPT might also have gastrointestinal symptoms of nausea, vomiting, peptic ulcer disease, constipation, and pancreatitis. Neuropsychiatric disturbances vary and include lethargy, decreased cognitive and social function, depressed mood, psychosis, and coma in those with severe hypercalcemia.¹⁵ Recent randomized controlled trials have provided inconsistent results about the exact nature of neuropsychological dysfunction in asymptomatic PHPT (level I evidence).¹⁶⁻¹⁸ Rheumatologic diseases such as gout and pseudogout might also be associated with PHPT.¹⁹ Although patients with PHPT sometimes have left ventricular hypertrophy, conduction abnormalities, endothelial dysfunction, and shortened QT intervals, the effects of mild PHPT on the development of cardiovascular disease are not known.²⁰ In recent years, initial presentation of PHPT as brown tumours of the maxilla,²¹ sphenoid sinus, and occipital bone²²; nephrocalcinosis; and depressive psychosis²³ have also been reported outside of North America. It is

important to note that the symptoms of hypercalcemia do not necessarily correlate with the degree of biochemical abnormality. A hypercalcemic crisis is usually precipitated by an intercurrent illness or volume depletion, and generally presents with very high serum calcium and PTH levels, as well as a combination of the findings listed above.

The classic features of hypercalcemia are very uncommon initial complaints in the Western world. Most patients in developed countries have asymptomatic forms of PHPT or nonspecific symptoms such as fatigue, mild depression, or cognitive impairment. This article will focus mainly on the diagnosis and medical management of asymptomatic PHPT.

Less commonly, patients can present with normal serum calcium and persistently elevated PTH levels in the absence of vitamin D insufficiency or chronic kidney disease. This form of presentation is termed *normocalcemic hyperparathyroidism*. These patients might initially present for evaluation of low BMD, osteoporosis, or fragility fractures.²⁴ The natural history of normocalcemic hyperparathyroidism is not well known, but some patients progress to hypercalcemic hyperparathyroidism, as reported in a few observational studies (level II evidence).²⁵ Before confirming this diagnosis, it is essential to exclude vitamin D deficiency and chronic kidney disease, as these conditions can present with increased PTH levels and normal calcium.

There are no specific physical findings in PHPT, and parathyroid adenomas or carcinomas are rarely palpable; however, it is important to exclude neck masses. Band keratopathy, which is the deposition of calcium phosphate in the exposed regions of the cornea (detected by a slit-lamp examination) is exceedingly rare and occurs with very high serum calcium and phosphate levels.¹⁵

Laboratory findings. Primary hyperparathyroidism is diagnosed when intact PTH levels are elevated or at the high end of the normal range in the setting of elevated total or ionized calcium levels. Because about 40% of calcium is bound to albumin, serum calcium levels should be corrected for albumin. Repeat measurements (usually 3) of calcium and PTH should be taken before establishing the diagnosis of PHPT. The main goal of further laboratory testing is to rule out other causes of hypercalcemia. Findings suggestive of FHH include a urinary calcium-to-creatinine clearance ratio of less than 0.01. It is important to distinguish FHH from PHPT because a parathyroidectomy is not recommended for FHH, as it does not cure the condition. Family members of the patient should also be assessed for FHH if it is suspected. The levels of 25(OH)D can be measured in order to exclude vitamin D insufficiency as a cause of elevated PTH. Repletion with vitamin D increases urinary calcium

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

excretion in mild PHPT but not in FHH.⁶ Moreover, vitamin D insufficiency is commonly seen in PHPT and has been linked to lower BMD, higher bone turnover (level II evidence),²⁶ higher risk of postoperative hypocalcemia, and hungry-bone syndrome after parathyroidectomy.²⁷

Renal function tests can indicate the extent of kidney involvement in the hyperparathyroid state. In patients who present with family history of multiple endocrine tumours, genetic testing for mutations in the *MENIN* and *RET* genes should be considered. Evaluating serum and 24-hour urinary calcium excretion in the family members of the patient is helpful in confirming the presence of a familial parathyroid condition. Analysis for mutations in the calcium-sensing receptor gene can be completed if a de novo case of FHH is suspected. Other tests helpful in establishing the diagnosis of PHPT include serum phosphorus levels (decreased or low-normal in PHPT). The markers of bone turnover, such as osteocalcin and bone-specific alkaline phosphate, might be mildly elevated in cases of PHPT and reflect increased bone remodeling.^{2,6,28}

Excluding other causes of hypercalcemia is necessary before confirming the diagnosis. An accurate history of skeletal fragility, renal disease, calcium intake, symptoms suggestive of malignancy, thyroid disease, adrenal insufficiency, previous bariatric surgery, and pancreatic disease, and a thorough review of medications including thiazide diuretics and lithium are necessary. After exclusion of malignancy, granulomatous diseases, or other causes of hypercalcemia, PHPT can be confirmed. This is particularly important if the serum PTH is not elevated.

Management. Definitive therapy for symptomatic and asymptomatic PHPT is parathyroidectomy. A hypercalcemic crisis is managed by volume repletion, administration of loop diuretics once the patient is euvoletic, and pamidronate or zoledronate to further decrease bone resorption. This article focuses on the current guidelines for the surgical and medical management of asymptomatic PHPT, as this is the most common presentation in Canada.

Surgical management: The decision for parathyroid surgery in asymptomatic PHPT is dependent upon patient characteristics such as age, creatinine clearance, and BMD. The guidelines for parathyroid surgery in asymptomatic PHPT according to the Third International Workshop on Primary Hyperparathyroidism are listed in **Table 1**.²⁹ In the absence of nephrolithiasis, a 24-hour urine calcium level greater than 10 mmol/d is no longer an indication for parathyroidectomy, as urinary calcium excretion is also affected by other factors, including age, ethnicity, sex, dietary calcium intake, vitamin D stores, and glomerular filtration rate (level III evidence).^{25,29} However, a 24-hour urine calcium measurement should still be ordered in the initial evaluation of patients suspected to have PHPT in order to rule out the diagnosis of FHH. The

Table 1. Guidelines for parathyroid surgery in patients with asymptomatic PHPT

MEASUREMENT	RECOMMENDATION
Serum calcium (above upper limit of normal)	0.25 mmol/L
24-h urinary calcium	Not indicated
Creatinine clearance (calculated)	Reduced to <60 mL/min
Bone mineral density	T score less than -2.5 at any site or previous fragility fracture
Age, y	<50

PHPT—primary hyperparathyroidism.

Data from Bilezikian et al.²⁹

new international guidelines state that a creatinine clearance below 60 mL/min is an indication for surgery (compared with a creatinine clearance reduced by 30% recommended by older guidelines published in 2002). A creatinine clearance less than 60 mL/min might be associated with further rises in PTH in PHPT, and it also represents stage 3 renal insufficiency as defined by the Kidney Disease Outcomes Quality Initiative guidelines. Declining renal function might thus further fuel the hyperparathyroid condition, and surgery is recommended (level III evidence).²⁹

Primary hyperparathyroidism is associated with decreases in BMD, particularly at cortical skeletal sites; however, the relationship between BMD and fracture risk in asymptomatic PHPT has not been established. Expert consensus guidelines recommend parathyroid surgery when the T score is -2.5 or less at the lumbar spine, femoral neck, total hip, or distal one-third of the radius in perimenopausal and postmenopausal women, and in men aged 50 and older. For premenopausal women and in men younger than 50 years of age, a Z score of less than -2.5 is recommended for consideration of parathyroid surgery (level III evidence).²⁹ In an observational study of patients with asymptomatic PHPT followed by conservative management for 15 years, serum calcium was found to be stable without surgery; however, calcium was noted to rise after 13 years of follow-up, suggesting the need for long-term monitoring (level II evidence).³⁰

In patients with mild PHPT, studies have shown that parathyroidectomy, as compared with medical observation, increased BMD at the femoral neck and total hip (level I evidence)¹⁶ and lumbar spine (level I evidence).¹⁸ These studies also showed normalization of serum calcium and PTH with surgery. Fracture risk appears to decrease with parathyroidectomy in those with asymptomatic PHPT. In those who do not proceed to parathyroidectomy, regular monitoring of serum calcium and 3-site BMD measurements are recommended.

Imaging of the parathyroid before surgery is of value, particularly if a limited exploration is planned. Imaging

options include technetium 99m-labeled sestamibi scanning, ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography. A sestamibi scan is a widely used noninvasive imaging localizing technique; it has an accuracy rate of 50% to 70%, but can be nonlocalizing in patients with multi-glandular parathyroid disease or small adenomas.³¹ Imaging should not be used to establish the diagnosis of PHPT or to screen patients for surgical referral. It is essential to ensure that the surgery is performed by an experienced surgeon. The type of surgical technique employed, be it total open parathyroidectomy or a minimally invasive procedure with or without the use of intraoperative PTH assays, will be chosen by the surgeon based on his or her surgical expertise.³¹

Medical management: In patients with asymptomatic PHPT, medical management designed to target skeletal protection or lower serum calcium might be a suitable option. It can be of value for those with contraindications to, or those who do not wish to have, surgery. Among drugs in the bisphosphonate class, alendronate in particular has been shown to decrease bone turnover and increase BMD in PHPT (level I evidence).³²⁻³⁴ Hormone replacement therapy (HRT) also improved BMD in postmenopausal women with mild PHPT (level I evidence).³⁵ It is not known whether these treatments also reduce fracture risk.³⁶


Bisphosphonates are usually the agent of choice for skeletal protection, owing to the adverse effects of HRT related to cardiovascular disease and breast cancer. Raloxifene, a selective estrogen receptor modulator, decreases bone turnover in postmenopausal women with PHPT, but more research is needed to elucidate its effects on BMD (level I evidence).³⁷ Bisphosphonates, HRT, and raloxifene do not lower serum calcium or PTH levels. A calcimimetic agent, cinacalcet, reduces both serum calcium and PTH levels in patients with mild PHPT but does not have any effects on bone turnover or BMD.³⁶ Cinacalcet is not routinely used for management of asymptomatic PHPT, and its use is generally limited to treating symptomatic hypercalcemia. The most recent guidelines for the follow-up of patients who are being medically managed for PHPT are listed in **Table 2**.²⁹

Patients should be encouraged to engage in physical activity (to decrease bone resorption) and to maintain adequate hydration (to reduce the risk of developing serious hypercalcemia or nephrolithiasis). Moderate calcium and vitamin D intake should be maintained. In patients with concomitant vitamin D deficiency, vitamin D should be repleted carefully, to reduce the risk of worsening hypercalcemia. Serum 25(OH)D levels above 50 nmol/L are recommended, although the optimal vitamin D level for patients with PHPT is not known (level III evidence).⁶ Patients should also be advised to avoid

Table 2. Guidelines for medical surveillance for patients with asymptomatic PHPT

MEASUREMENT	RECOMMENDATION
Serum calcium	Annually
24-h urinary calcium	Not recommended
Creatinine clearance (24-h urine collection)	Not recommended
Serum creatinine	Annually
Bone mineral density	Every 1-2 y (3 sites)
Abdominal x-ray scan (with or without ultrasound)	Not recommended

PHPT—primary hyperparathyroidism.
Data from Bilezikian et al.²⁹

factors that can exacerbate hypercalcemia, such as lithium or hydrochlorothiazide therapy, immobilization, and intravascular volume depletion. 

Dr Pallan is a second-year internal medicine resident at McMaster University in Hamilton, Ont. **Dr Khan** is Clinical Professor of Medicine at McMaster University and Director of the Calcium Disorders Clinic at St Joseph's Health Care in Hamilton.

Contributors

Both authors contributed to the literature review and preparing the article for submission.

Competing interests

None declared

Correspondence

Dr Shelley Pallan, 19 Invitational Rd, Brampton, ON L6P 2H1; e-mail pallans@mcmaster.ca

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