Diagnosis and Management of Primary Hyperparathyroidism

Clinical Practice Today CME

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Learning Objectives

Upon completion, participants should be able to:

- Identify patients with primary hyperparathyroidism
- Understand the clinical indications for surgical referral in patients with primary hyperparathyroidism
- Understand medical treatment options for patients with primary hyperparathyroidism

Introduction

The autonomous overproduction of parathyroid hormone (PTH) disrupts calcium regulation, leading to persistent hypercalcemia and a condition called primary hyperparathyroidism (PHPT).[1] The disorder can have broad physiologic effects, including reduced bone density, nephrolithiasis, cardiovascular dysfunction, and sometimes neurologic symptoms.[1,2] For many years, PHPT was diagnosed by the presentation of these symptoms, most commonly renal calculi and/or osteoporosis with fractures.[1] However, the broad implementation of biochemical panels in routine care has uncovered PHPT in patients who are generally asymptomatic or who have vague, unrecognized symptoms that may still affect quality of life.[2,3] Of note, it is also possible to have high levels of PTH without a corresponding rise in serum calcium, a condition currently classified as normocalcemic PHPT.[2,4]

Introduction (cont.)

Surgical resection of the overproducing parathyroid gland(s) is the only way to cure PHPT.[1] After surgery, patients experience lower PTH levels, normalized calcium metabolism, and improved skeletal and renal symptoms.[4] The value of surgery in asymptomatic patients, however, is determined on a case-by-case basis, taking into consideration age, skeletal involvement, renal function, and other factors that predict a higher risk of worsening PHPT outcomes.[4] To offer guidance in such situations, the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism convened in 2013 to discuss the management of asymptomatic PHPT and provide recommended clinical approaches.[4-8]

Incidence

PHPT is the most common hypercalcemic disorder, present in 1% of the general adult population.[1] In the United States (US), a large healthcare system database of Californians reported the incidence of PHPT in a racially mixed cohort.[9] During the 15-year period analyzed, the average overall incidence of PHPT was 65.5 cases per 100,000 person-years in women (range, 34.0-120.2 per 100,000 person-years) and 24.7 cases per 100,000 person-years in men (range, 13.4-35.6 per 100,000 person-years). Further analysis by age group confirmed a low incidence in persons younger than 50 years, whereas the sex differences broadened with each higher age group, such that among patients 70 to 79 years, the incidences were 94.6 per 100,000 person-years for men and 195.7 per 100,000 person-years for women. Consistent with previous reports of higher prevalence in women, the prevalence ratio of women to men with PHPT was approximately 2.5 to 1. The prevalence of the disorder grew 3-fold during the 15-year study period, from 76 to 233 per 100,000 (women) and 30 to 85 per 100,000 (men).[9]

Incidence (cont.)

Globally, similar trends in prevalence and severity are being observed.[6] Regions that have adopted routine serum calcium testing have higher rates of diagnosis, and the severity at presentation is higher in regions that do not broadly perform biochemical panels.[6]

Pathophysiology

The peptide hormone PTH regulates serum calcium concentration, primarily through effects on bone remodeling and renal calcium handling.[10] In bone, PTH stimulates calcium release during remodeling; overproduction of PTH stimulates bone resorption more than bone formation, leading to decreased bone density and higher fracture risk.[10] PTH also promotes calcium reabsorption in the renal distal tubule, and aberrant signaling in this pathway increases the risk of nephrolithiasis.[6]

Pathophysiology (cont.)

Single adenomas in the parathyroid account for 80% to 85% of PHPT cases, with the remaining cases attributed to multiple gland hyperplasia (10%), double adenomas (4%), and parathyroid carcinomas (1%).[1] Approximately 10% of all patients have gene mutations known to be associated with PHPT.[4] These genes include *MEN1-4*, which are associated with multiple endocrine neoplasia syndromes.[5] This syndromic presentation of PHPT is typically inherited, and a comprehensive family history may suggest this etiology. It remains important to distinguish between PHPT from secondary causes of PTH overproduction, such as treatment with thiazides, bisphosphonates, lithium, and denosumab.[5] Similarly, other causes of hypercalcemia include malignancy, sarcoidosis, and increased calcium intake; these causes should be excluded, although they are generally associated with low levels of PTH.[3]

Clinical Presentation

Symptomatic Primary Hyperparathyroidism

Approximately 20% of patients with PHPT present with overt symptoms, but the severity of disease symptoms at presentation has diminished with the routine use of extensive biochemical screening, including serum calcium, and the earlier identification of the disorder.[4,11] Classic signs and symptoms include renal calculi, low bone density (osteopenia or osteoporosis), peptic ulcer disease, and changes in mental status—colloquially described as "stones, bones, groans, and moans."[3]

Clinical Presentation (cont.)

Renal issues. The most common symptom is calcium stone disease, affecting 15% to 20% of all PHPT patients.[6] Conversely, approximately 3% of patients with stone disease have PHPT. Nephrolithiasis occurs with mineral dysregulation in the renal tubules, such as hyperabsorption of calcium and phosphate, increased absorption of oxalate when oxalate levels are high, and higher urinary pH.[6] All patients suspected of having PHPT should be evaluated for stone risk, nephrolithiasis, or subclinical stones (nephrocalcinosis) through renal imaging.[4] Present imaging techniques, however, may be unable to detect small calcium-phosphate deposits that may precede stone development.[6] Additionally, calcifications in other locations may not be detected by standard imaging protocols.[6] Importantly, there is limited evidence that PHPT affects renal function directly, and patients with severe chronic kidney disease do not necessarily have severe forms of PHPT.[12]

Clinical Presentation (cont.)

Bone disease. Skeletal fractures at presentation are rare in the US, but they are still seen in some parts of the world.[6] Bone remodeling leads to extensive bone resorption, including preferential reductions in cortical bone density, whereas cancellous bone density is often preserved.[3,6] Typically, skeletal sites composed primarily of cortical bone (eg, the distal 1/3 radius) have the greatest amount of decrement, although trabecular bone loss at the spine and other sites have also been reported.[6,13,14] In long-term studies that track the natural history of PHPT patients, bone loss at cortical sites accelerated approximately 10 years after diagnosis, while other sites remain stable.[10,15] Markers of bone turnover can be monitored in automated immunoassays and roughly correlate with bone loss in patients with PHPT.[6] Reduced bone mineral density (BMD) is generally associated with a higher fracture risk, but this risk is highest in patients with symptomatic PHPT. Additionally, low levels of vitamin D may increase fracture risk in patients with PHPT.[6] It remains unclear, however, whether the tools used for evaluating bone microstructure in other skeletal disorders, such as osteoporosis, can be useful in predicting fracture risk in PHPT.[4,6]

Clinical Presentation (cont.)

Cardiovascular complications. Cardiovascular complications are considered a nonclassic feature of PHPT, but the observed higher prevalence of cardiovascular issues in patients with PHPT suggests that hypercalcemia and PTH overproduction influence the cardiovascular system in some way.[6] Increased mortality from cardiovascular events has been reported in patients with PHPT, but data linking PHPT itself as causally related are inconclusive.[6]

Clinical Presentation (cont.)

Neurocognitive issues. Another nonclassic symptom of PHPT is neurocognitive sequelae.[3,6] A range of presentations have been described, from depression to sleep disorders, although studies in this area have been limited by design flaws.[1,6] Additionally, cognitive function may be reduced in patients with PHPT compared with normal controls.[16] These vague symptoms can reduce quality of life for patients, but often normalize with a reduction in PTH levels.[1,6] However, because these symptoms are not specific or quantifiable, neurocognitive sequelae are not considered to be an indication for surgical management.[2,6]

Clinical Presentation (cont.)

Asymptomatic Primary Hyperparathyroidism

Approximately 80% of patients with PHPT are diagnosed after a routine serum biochemistry evaluation reveals hypercalcemia.[11] Although overt symptoms may not initially be reported by the patient, a full medical history may uncover additional symptoms.[3] Common symptoms include[17]:

- Pain in the bones
- Feeling tired easily
- Mood swings
- Feeling “blue” or depressed
- Pain in the abdomen
- Feeling weak
- Headaches
- Difficulty getting out of a car or chair
- Itchy skin
- Feeling irritable
- Pain in the joints
- Being forgetful

Clinical Presentation (cont.)

Asymptomatic Primary Hyperparathyroidism (cont.)

In general, physicians should measure BMD, renal function, and changes in serum calcium concentration that may underlie these symptoms.[4] The presentation of asymptomatic PHPT later in life (> 50 years of age), however, can lead to confusion about whether symptoms are associated with the normal aging process, menopause, or other health conditions.[3] Direct questions about bone-related signs and symptoms may uncover height loss or bone pain. Patients and physicians alike may overlook this symptom, but it could be related to a subclinical vertebral compression fracture(s). Similarly, cognitive or memory difficulties may be blamed on an aging brain, but these effects could improve when PTH levels normalize.[6]

Clinical Presentation (cont.)

Asymptomatic Primary Hyperparathyroidism (cont.)

The challenge in diagnosing and managing asymptomatic PHPT is identifying the most appropriate time for intervention. Studies of the natural history of PHPT indicate that after years of little to no symptoms, a rapid progression of accelerating bone loss and development of kidney stones can occur.[1,10,15] These features can be associated with increased risk of fractures and impaired renal function.[1] Moreover, the reports of reduced quality of life in asymptomatic PHPT, tentatively attributed in part to vague neurocognitive symptoms, suggest that the disease impact may be unrecognized.[3,6] Although disease monitoring and medical management can be the clinical strategy for patients with asymptomatic PHPT, the only cure for the disorder is parathyroidectomy.[1,6] Surgery should therefore always be an option considered for all patients.[1,4,7] Nonetheless, not all will elect to or be appropriate candidates for surgical intervention, as the benefits may not outweigh the risks for some individuals.[4]

Clinical Presentation (cont.)

Evaluating Patients for Asymptomatic Primary Hyperparathyroidism

The Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism, which convened in 2013, recommended several evaluations to broadly assess the severity of PHPT presentation and provide insight on when to consider parathyroidectomy.[4-8]

Table 1. Recommended Tests for Patients With Suspected Asymptomatic PHPT

Recommended
Biochemistry panel (calcium, phosphate, alkaline phosphatase activity, BUN, creatinine), 25(OH)D
PTH by second- or third-generation immunoassay
BMD by DXA for lumbar spine, hip, and distal 1/3 radius
Vertebral spine assessment by x-ray or VFA by DXA
24-hour urine for calcium, creatinine, creatinine clearance, and stone risk profile
Abdominal imaging by x-ray, ultrasound, or CT scan
Optional
High-resolution peripheral quantitative CT
Trabecular bone score 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
DNA testing if genetic basis for PHPT is suspected

BMD = bone mineral density; BUN = blood urea nitrogen; CT = computed tomography; CTX = C-telopeptide cross-linked collagen type I; DNA = deoxyribonucleic acid; DXA = dual-energy x-ray absorptiometry; NTX = N-telopeptide of type I collagen; P1NP = procollagen type 1 N-propeptide; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone; VFA = vertebral fracture assessment.

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Clinical Presentation (cont.)

Biochemistry panel. For the majority of patients with asymptomatic PHPT, hypercalcemia is first documented through the course of routine laboratory testing.[1] Upon diagnosis of PHPT, total serum calcium should be reevaluated with adjustments for albumin, the major calcium-binding protein.[4] If the patient is receiving thiazide or lithium, the medication should be withdrawn, if medically feasible, and the total serum calcium and albumin should be evaluated again in 3 months.[4,5] The total level of 25(OH)D, which is the best measure of vitamin D stores, should also be measured in each patient at diagnosis of asymptomatic PHPT.[4,18] Vitamin D insufficiency (< 20 ng/mL) or frank deficiency (< 10 ng/mL) has been associated with active PHPT, and PTH levels are generally inversely related to the serum levels of 25(OH)D.[4] At present, evidence does not support measuring the vitamin D metabolite, 1,25-dihydroxyvitamin D. Additional serum components that should be evaluated at diagnosis are phosphate, alkaline phosphatase activity, blood urea nitrogen, and creatinine.[4]

Clinical Presentation (cont.)

PTH by second- or third-generation assay. The most common condition associated with high levels of intact PTH and hypercalcemia is PHPT.[1] When coming to this diagnosis, PTH levels should be measured with second- or third-generation assays.[4] First-generation assays mainly detect C-terminal fragments of PTH and only a portion of intact PTH.[5] More-sensitive, second-generation assays detect intact PTH (1-84) and large amino-truncated fragments, which are more clinically relevant for PHPT; this technique is known as the “intact PTH assay.” The third-generation assay, known as the “whole PTH assay,” is less commonly used but is more specific for the PTH (1-84) protein and for a posttranslationally modified form of PTH.[5]

Clinical Presentation (cont.)

Bone density screening. BMD screening by dual-energy x-ray absorptiometry (DXA) is recommended for all patients with PHPT.[1] Recommended sites of analysis are the lumbar spine, total hip, femoral neck, and distal 1/3 radius.[4] Bone loss at the forearm is typically associated with PHPT and is considered to be a specific disease marker.[4] Bone loss and attendant fractures at vertebral or hip bones are associated more with morbidity and mortality.[1] Each patient should be evaluated for osteoporosis, defined as a BMD of greater than or equal to 2.5 standard deviations below that of a gender-matched individual at peak bone mass.[1] At present, it is unknown whether fracture-risk tools developed for osteoporosis, such as FRAX, are useful in evaluating patients with PHPT.[4]

Clinical Presentation (cont.)

Bone density screening (cont.). Importantly, because standard DXA does not evaluate vertebral morphometry, the use of standard x-ray or a vertebral fracture assessment (VFA) is recommended for evaluating density at vertebral sites. Any evidence of vertebral fracture should supersede other disease features in treatment decisions.[4] Finally, although investigational and unproven at present, high-resolution peripheral quantitative computed tomography (HRpQCT) can evaluate changes in trabecular structure that portend higher skeletal fragility and may eventually become a clinical tool by which to better stratify patients in need of surgical intervention.[4,6]

Clinical Presentation (cont.)

24-hour urine test for renal function. An analysis of renal function serves two purposes: (1) to evaluate any impairment of renal function that would indicate a need for and possible benefit from surgery and (2) to distinguish from other hypercalcemic disorders, such as familial hypercalcemic hypercalciuria.[3,4] Values suggestive of PHPT include urine calcium of more than 400 mg/d and a creatinine clearance of less than 60 cc/min, although the latter could certainly be due in part to other clinical factors (eg, age, hypertension, diabetes mellitus).[4] The risk of developing kidney stones can also be evaluated by 24-hour urine analysis for stone components in patients with hypercalciuria higher than 400 mg/d as well as through the measurement of other parameters (eg, urinary oxalate, citrate, uric acid).[4]

Clinical Presentation (cont.)

Abdominal imaging by x-ray, ultrasound, or computed tomography scan. Imaging of the kidney is recommended to detect stones or nephrocalcinosis.[4] Evaluation by plain x-ray, ultrasound, or computed tomography (CT) is appropriate. The presence of a stone would indicate a recommendation for surgery.[4]

Clinical Presentation (cont.)

Diagnostic Evaluations

More than 10% of PHPT cases are attributable to 1 of 11 genes associated with PHPT.[4,5] Good candidates for genetic testing include patients with a known family history of PHPT and/or those who have multiple endocrine neoplasia.[5] However, some patients may have a mutation in the absence of a family history, either through the occurrence of a spontaneous mutation or lack of knowledge of PHPT history in a relative.[5] As such, any patient with multiple gland hyperplasia should be considered for genetic testing even in the absence of renal disease, as should patients with comorbid jaw tumors.[1,5] Classifying PHPT of syndromic origin (ie, familial) versus nonsyndromic (ie, sporadic) can direct medical management strategies, including surgical approaches.[5,7]

Surgical Management

As noted previously, surgery remains the only clinical approach that can cure PHPT.[1,7] Patients who undergo a successful surgery typically experience improved bone density and reduced fracture risk, and patients with recurring kidney stones develop fewer stones postoperatively.[4] Recent evidence also suggests that parathyroidectomy is cost effective in asymptomatic patients when incorporating an individual's risk of fracture.[19]

Although indicated for all patients with symptomatic PHPT, the decision to recommend parathyroidectomy in asymptomatic patients with PHPT requires an understanding of which features of the disease suggest disease stability and which features suggest ongoing or impending progression.[4]

Table 2. Guidelines for Surgery in Asymptomatic PHPT

Measurement	Value
Serum calcium (> upper limit of normal)	1.0 mg/dL
Skeletal	A. BMD by DXA: T-score < -2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. Creatinine clearance < 60 cc/min B. 24-h urine for calcium > 400 mg/d and increased stone risk by biochemical stone risk analysis C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age	< 50 years

BMD = bone mineral density; CT = computed tomography; DXA = dual-energy x-ray absorptiometry; MRI = magnetic resonance imaging; VFA = vertebral fracture assessment.

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Surgical Management (cont.)

In addition to performing a physical examination and taking a medical and family history, imaging is often helpful in localizing the suspect parathyroid gland(s) before surgery; appropriate modalities include ultrasound, nuclear scintigraphy, 4D-CT, magnetic resonance imaging, and occasionally positron emission tomography scans.[4,7] When evidence suggests that only one parathyroid gland is enlarged, the surgeon may choose minimally invasive parathyroidectomy (MIP)—an outpatient procedure in which the surgeon makes a small (2-cm) incision; this is an option for a majority of patients (85%), and most see lasting improvements in symptoms upon surgical cure with this approach.[3,7] Furthermore, patients undergoing MIP have a lower risk of hypocalcemia and recurrent laryngeal nerve injury than do those undergoing bilateral neck exploration.[20] When more than one adenoma is suspected, or in patients with known parathyroid hyperplasia or anticipated multigland involvement based on family history and/or genetic testing, exploration of the 4 parathyroid glands can be performed. Endoscopic parathyroidectomy provides visualization of the nerves and blood vessels, and surgeons can evaluate nearby glands.[3,7] Intraoperative measurement of PTH levels, with "real-time" confirmation of an appropriate PTH decline after adenoma resection, helps identify patients who will be cured and those potentially at risk of recurrent or persistent PHPT, but the threshold of PTH decay most likely to predict recurrence is under debate.[1,7,21] Importantly, only experienced surgeons should perform the surgery because of its complicated nature and the role of underlying genetics and embryologic development in adenoma location and structure.[3,4,22]

Surgical Management (cont.)

Evidence suggests that all asymptomatic patients with any of the following characteristics should be referred for a surgery consult[3,4]:

- Age younger than 50 years
- Inability to commit to the follow-up required by medical management
- Serum calcium levels more than 1.0 mg/dL above the normal reference range
- Urinary calcium levels higher than 400 mg/24 hours
- A creatinine clearance of less than 60 cc/min

For patients who do not meet these criteria, further evaluation is necessary to determine whether surgery is appropriate.[3]

Surgical Management (cont.)

Postoperative Monitoring

After parathyroidectomy, the patient's airway should be monitored for hematomas, and steps should be taken to minimize nausea or vomiting that could open or interfere with wound healing.[3] Time to discharge will vary with the procedure performed, from 4 to 6 hours of observation for patients who undergo MIP, to 12 to 36 hours after a 4-gland exploration.[3] Patients who have complete parathyroidectomy may experience hypocalcemia, given the removal of all parathyroid tissue; patients undergoing subtotal parathyroidectomy with removal of 3 and 1/2 glands are also at risk of hypocalcemia, though the administration of calcitriol and calcium postoperatively in both clinical situations can normalize calcium levels.[3,7] Hypocalcemia may remit in the latter group of patients with the resolution of suppression of remaining parathyroid tissue, and postoperative assessment of PTH levels can be informative in these patients.[3]

Surgical Management (cont.)

Postoperative Monitoring (cont.)

The surgical site should be evaluated 1 to 2 weeks after the operation.[3] A biochemical panel of calcium, PTH, alkaline phosphatase, and vitamin D is suggested to assess residual parathyroid function for evidence of persistent disease. Patients with normalized calcium levels have a high likelihood of cure.[3]

Patients typically report significant improvement in PHPT symptoms within 6 weeks of surgery, often accompanied by continued improvement at 6 and 12 months after surgery, even among those considered to be asymptomatic.[23,24] Reevaluation at 6 months can help assess the durability of the treatment response.[3]

Surgical Management (cont.)

Postoperative Hypocalcemia Risk

Patients with PHPT and high bone turnover have a risk of experiencing severe and prolonged hypocalcemia after parathyroidectomy.[25] Colloquially called “hungry bone syndrome,” the skeletal response to a reduction in PTH levels is to reduce bone resorption while bone formation is relatively maintained. This process, in turn, decreases serum calcium and phosphate levels.[25]

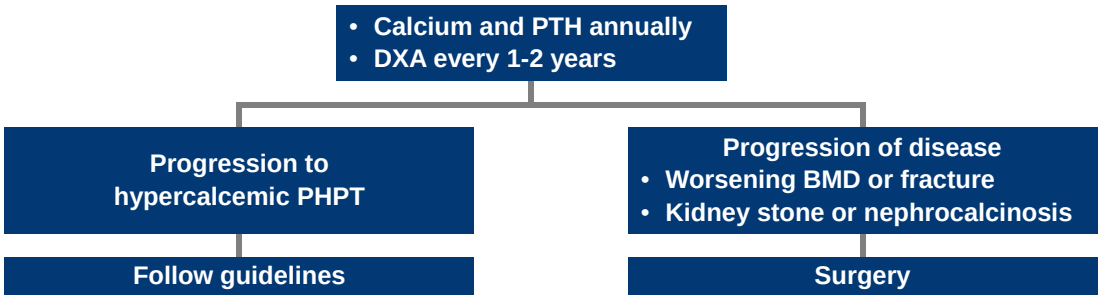
Patients with severe hypocalcemia may experience neuromuscular irritability, demonstrated by perioral paresthesias, carpopedal spasms, tingling extremities, Trousseau sign, and Chvostek sign.[25] Hungry bone syndrome is unusual in asymptomatic patients, but patients with high alkaline phosphatase activity in the preoperative workup have a higher risk.[7] The early administration of oral calcium supplementation with or without calcitriol can reduce the risk of symptomatic hypocalcemia.[7]

Nonsurgical Management

Monitoring

Patients who do not undergo surgery should be monitored annually or biannually for calcium and PTH levels, and DXA for BMD should be performed every 1 to 2 years (Figure 1).[4] Patients should be evaluated for vertebral fractures by VFA.[4]

Figure 1. Algorithm for Monitoring Patients With Normocalcemic PHPT



BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; PHPT = primary hyperparathyroidism; PTH = parathyroid hormone.

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Nonsurgical Management

Monitoring (cont.)

Additionally, vitamin D–deficient patients should take supplements to reach a minimum serum 25(OH)D level of 20 ng/mL, and all patients should follow guidelines for calcium intake.[4,8]

Nonsurgical Management

Medical Management

Several pharmacologic agents are available for symptom management in PHPT, but there are few long-term efficacy and safety data.[4] Importantly, patients should avoid other treatments that increase serum calcium levels (eg, thiazide diuretics).[1]

Nonsurgical Management (cont.)

Medical Management (cont.)

Multiple pharmacologic agents can be used to improve BMD in patients with PHPT, including estrogen, raloxifene, and bisphosphonates (all off label).[8] Postmenopausal women with PHPT may be candidates for treatment with estrogen or raloxifene. These agents can lower bone resorption levels but do not measurably affect serum calcium or PTH.[8] Side effects of estrogens include abdominal pain, back pain, headache, nausea, breast pain, endometrial hyperplasia and leucorrhea, vaginal hemorrhage, and vaginitis. Black-box warnings associated with estrogen therapy include endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia.[26] Side effects of raloxifene include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating. Black-box warnings include increased risk of venous thromboembolism and increased risk of death due to stroke in women with documented coronary heart disease or with an increased risk of major coronary events.[27]

Nonsurgical Management (cont.)

Medical Management (cont.)

Bisphosphonates are associated with higher BMD at the lumbar spine and lower levels of bone turnover markers, but serum calcium and PTH levels tend to remain unchanged, and there are no data confirming anti-fracture efficacy in patients with PHPT taking these agents.[8] Side effects of bisphosphonates include reflux, heartburn, and abdominal pain, as well as less-common side effects such as headache, myalgia, and bone, joint, or muscle pain. Rare reports of osteonecrosis of the jaw and atypical femur fractures have been reported, and hypocalcemia must be corrected before use.[28-30] Inflammation of the eye is a rare side effect, and bisphosphonates are not recommended for those with severe kidney disease.[30,31]

For hypercalcemia, the calcium-sensing receptor agonist cinacalcet is indicated for adult patients with PHPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy.[32] This agent reduces serum calcium to normal levels, but it is reversible, and calcium will revert to pretreatment levels upon cessation of the medication.[33]

Nonsurgical Management (cont.)

Medical Management (cont.)

Studies that have looked at the efficacy of cinacalcet in patients with PHPT include a 52-week randomized, double-blind, placebo-controlled study that evaluated 78 patients with PHPT.[34] Cinacalcet was titrated from 30 to 50 mg twice daily during a 12-week dose-titration phase. Efficacy was assessed during the 12-week maintenance and 28-week follow-up phases. Serum calcium levels (< 10.3 mg/dL) were normalized in 73% of the subjects compared with only 5% of the placebo group ($P < .001$) during the maintenance phase and remained normal throughout the 52-week study.[34] In a 4.5-year, open-extension study, the proportion of subjects with a serum calcium concentration of 10.3 mg/dL or lower remained stable during the study (ranging from 74%-92%).[35] Serum PTH levels declined only modestly with cinacalcet treatment, and no consistent changes in BMD had been detected in studies up to 4.5 years in duration.[8] The most common side effects reported were nausea and vomiting. Warnings include those for hypocalcemia, adynamic bone disease, and hepatic impairment.[32]

Conclusion

Current guidelines developed at the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism aim to inform clinical decision making for the assessment and management of PHPT, particularly with regard to the identification of surgical candidates. Parathyroidectomy is the only curative option for PHPT and should be a management option considered for all asymptomatic patients. For patients who cannot or will not undergo surgery, physicians should focus on monitoring disease progression and managing symptoms. Pharmacologic approaches to symptom management have value, but the long-term benefits remain to be proven.

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