Mild Primary Hyperparathyroidism: A Literature Review

MEGAN K. APPLEWHITE,^a DAVID F. SCHNEIDER^b

^aDepartment of General Surgery, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA; ^bSection of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, Wisconsin, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hypercalcemia • Primary hyperparathyroidism • Hyperparathyroidism • Nephrolithiasis • Parathyroid hormone • Parathyroidectomy

ABSTRACT

The biochemical profile of classic primary hyperparathyroidism (pHPT) consists of both elevated calcium and parathyroid hormone levels. The standard of care is parathyroidectomy unless prohibited by medical comorbidities. Because more patients are undergoing routine bone density evaluation and neck imaging studies for other purposes, there is a subset of people identified with a biochemically mild form of the pHPT that expresses itself as either elevated calcium or parathyroid hormone levels. These patients often do not fall into the criteria for operation based on the National Institutes of Health consensus guidelines, and they can present a challenge of diagnosis and management. The purpose of this paper is to

review the available literature on mild pHPT in an effort to better characterize this patient population and to determine whether patients benefit from parathyroidectomy. Evidence suggests that there are patients with mild pHPT who have overt symptoms that are found to improve after parathyroidectomy. There is also a group of patients with biochemically mild pHPT who are found to progress to classic pHPT over time; however, it is not predictable which group of patients this will be. Early intervention for this group with mild pHPT may prevent progression of bone, psychiatric, and renal complications, and parathyroidectomy has proven safe in appropriately selected patients at high volume centers. *The Oncologist* 2014;19:919–929

Implications for Practice: Mild primary hyperparathyroidism (pHPT) is a disease that is being diagnosed with increased frequency; however, recommendations for treatment are not uniform. Current NIH guidelines do not recommend parathyroidectomy for these patients if they are asymptomatic; however, upon focused questioning, many of these patients are found to have subtle symptoms. The biochemically mild nature of the disease has been found to delay diagnosis and treatment, but after it is identified, surgery has shown to provide an improvement in quality of life and bone health. Although the current body of literature suggests that patients with mild pHPT benefit from parathyroidectomy, careful patient and surgeon selection is critical to ensuring safety and efficacy. Universal acceptance of parathyroidectomy in this subset of patients will require more high quality, prospective studies and improved definitions of long-term cure.

INTRODUCTION

In the U.S., primary hyperparathyroidism (pHPT) has an incidence of approximately 100,000 patients annually with an overall prevalence of 0.2%–1% [1]. The prevalence is higher in patients >65 years old (1.5%) [2] and is most common in postmenopausal women (2.1%–3.4%) [3]. pHPT is typically characterized by elevated serum calcium associated with inappropriately elevated parathyroid hormone (PTH) levels. This disease is the most common cause of hypercalcemia in the outpatient setting [4].

In general, the incidence of pHPT has been rising as methods of detection improve and become more widespread. In Rochester, Minnesota, the total incidence of pHPT treated at the Mayo Clinic decreased since its peak in 1974–1982; however, the number of parathyroidectomies performed increased over the same period of time at that institution [5]. Outside the U.S., a Hong Kong study found a sevenfold increase in operative pHPT

over the past decade [6], in Denmark the diagnosis of pHPT has increased fivefold in women and threefold in men over the past 20 years [7], and in China the percentage of patients with pHPT who were asymptomatic at the time of their diagnosis has increased from <21% to 52.5% over 10 years [8].

Amid the growing numbers of patients diagnosed with pHPT, there is a subset of patients now recognized more frequently with biochemically “mild” pHPT, who are either normocalcemic with elevated PTH or hypercalcemic with an inappropriately normal or high-normal PTH. With the advent of multichannel autoanalyzer testing of PTH, increasing neck imaging studies, and calcium measurements taken for screening and bone health evaluation, patients with biochemically mild profiles are frequently identified [9–11].

Correspondence: David F. Schneider, M.D., Department of Surgery, University of Wisconsin, K3/738 Clinical Science Center, 600 Highland Avenue, Madison, Wisconsin 53792, USA. Telephone: 608-263-1387; E-Mail: schneiderd@surgery.wisc.edu Received February 28, 2014; accepted for publication June 20, 2014; first published online in *The Oncologist Express* on July 25, 2014. ©AlphaMed Press 1083-7159/2014/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2014-0084>

With mild pHPT being increasingly recognized in these patients, the purpose of this paper is to review the current data and literature on mild pHPT in an effort to bring some clarity to this confusing topic. We will begin by defining mild pHPT and then describe theories on etiology, presentation, diagnosis, and management, both medically and surgically. We will then address outcomes after treatment including quality of life, cardiovascular effects, bone disease and metabolic abnormalities and persistence or recurrence of disease.

DEFINITION OF MILD HYPERPARATHYROIDISM

Normocalcemic Hyperparathyroidism

Normocalcemic primary hyperparathyroidism (NCHPT) is defined as a normal calcium level in the presence of elevated PTH. At the third NIH international workshop on asymptomatic pHPT, NCHPT was determined to be part of the diagnostic spectrum of classic pHPT and should be considered when all other causes of elevated PTH have been excluded [12, 13] including use of bisphosphonates, thiazide diuretics, lithium or anticonvulsants, glomerular filtration rate (GFR) of >60 mL/min, and the absence of metabolic, malabsorption, and liver diseases [14].

Hypercalcemia With Normal PTH/Normohormonal pHPT

The second type of mild disease occurs when the patient has an elevated serum calcium level associated with a normal but nonsuppressed PTH level or normohormonal hyperparathyroidism (NHHPT). The normal physiologic reaction to elevated calcium should be a very low or undetectable PTH level [13].

BACKGROUND

The term “mild primary hyperparathyroidism” has been interpreted in many different ways over the past 30 years and, as such, is not a universal term with clear definition. The literature contains many examples in which it is defined as asymptomatic disease, or pHPT wherein the calcium and/or PTH levels are above normal but are only slightly elevated [15–18]. For the purposes of this review, mild pHPT refers to patients with NCHPT or NHHPT.

Of all patients diagnosed with pHPT, 5%–28% have the mild form of the disease [19–25]. In a large series, the distribution of all patients with mild pHPT was 68.6% NHHPT and 31.4% NCHPT [26]. The NIH has had three international workshops on asymptomatic hyperparathyroidism [10, 27, 28]. Based on these guidelines, one indication for operative intervention in asymptomatic patients is elevated PTH with overt hypercalcemia, defined as calcium at least 1 mg/dL above normal, which is thought of as biochemically classic pHPT. The most recent workshop addressed mild pHPT and recognized it as a distinct disease process with persistently normal calcium and unclear cause of elevated PTH. Recommendations called for further investigation of the natural history and evolution of this disease to appropriately manage these patients [28]. Although many surgeons believe that these patients can benefit from parathyroidectomy, it remains controversial whether they should undergo operative management because the

disease course has not been clearly defined and the benefit questioned.

ETIOLOGY

In an effort to better characterize patients who have persistent NCHPT, Maruani et al. [21] looked at a group of 178 patients with pHPT, 34 of whom had NCHPT. Overall, those with NCHPT had a milder excess of PTH concentration, as well as a lower fasting urinary calcium excretion and renal tubular calcium reabsorption, thereby suggesting a baseline resistance of the bone and kidney to the actions of parathyroid hormone.

Hollenberg and Arnold [29] were among the first to identify NHHPT in a case study in 1991. They discussed potential mechanisms for its unique biochemical profile and encouraged consideration of pHPT in the differential diagnosis of patients with elevated calcium and normal PTH levels. In a larger study in 2011 of 46 patients with NHHPT, Wallace et al. [19] found similar clinical characteristics of abnormal bone density, nephrolithiasis, and neuropsychiatric symptoms when comparing NHHPT patients with those with classic disease and proposed a lower PTH set point in the NHHPT group.

Rao et al. [30] initially suggested that mild pHPT is part of a biphasic disease course that progresses over an unpredictable time period to classic pHPT. There is an initial elevation in PTH (NCHPT), followed by a period of disease stability during which there is no progression of biochemical markers or decline in forearm bone density when compared with age-matched controls. This is followed by a second stage in which the patients become hypercalcemic and establish the biochemical profile of classic disease. The patients who followed up over an 11-year period did not show any disease progression; therefore, it was concluded that surgery should be withheld until symptoms occur or the patient develops overt hypercalcemia. However, 54% of the patients were lost to follow-up, so the true incidence of disease progression remained unclear.

This theory of a biphasic course of pHPT is a point of continued discussion in current literature [9, 11, 23, 31]. In one study, Zhao et al. [17] evaluated three groups of patients: the first group had diagnosed classic pHPT, the second group had pHPT with slightly elevated calcium, and the third group had NCHPT (however, with unknown vitamin D levels). They administered calcium gluconate (4 mg/kg per hour) for 120 minutes to the second and third groups and measured serum calcium, phosphate, and PTH levels at 30, 60, 90, and 120 minutes after the initiation of the infusion. These values were compared with a normal control group. The authors found that the PTH inhibition rate (PTH-IR), which is the suppression rate or reduction of PTH from baseline value, was markedly diminished in group two when compared with the controls (41% vs. 80%), further suggesting that calcium sensing is impaired before calcium becomes overtly elevated. They concluded that in patients with an elevated PTH, a $<73\%$ reduction in serum PTH concentration from baseline to 120 min during the calcium suppression test and a baseline serum calcium level higher than 2.43 mmol/L can be used as thresholds suggestive of primary hyperparathyroidism even in the presence of vitamin D deficiency. As a result, they proposed five hypothetical stages of the continuum of pHPT: Stage 0: Normal serum PTH and calcium concentrations. Stage 1: Elevated PTH concentration with a suppression rate greater than 73% and serum calcium level less than 2.43 mmol/L.

Stage 2: Asymptomatic elevated PTH with PTH-IR less than 73% and a normal but slightly increased serum calcium concentration (≥ 2.43 mmol/L). Stage 3: Mild symptomatic progression with biochemical changes observed in stage 2. Stage 4: Further increase in PTH with serum calcium concentration above normal.

Silverberg et al. [32] conducted a 10-year prospective study of patients diagnosed with pHPT who did not meet the quantitative NIH criteria for an operation, which is marked hypercalcemia at least 1 mg/dL above normal [27]. These patients were followed nonoperatively to monitor for disease progression. Over the course of the study, 27% of patients in the nonoperative group developed an indication for operation. These patients were statistically younger and at baseline had similar serum calcium, PTH, urine calcium, and bone mineral density (BMD) than their counterparts who did not progress. 100% of the symptomatic patients in the nonoperative group either had recurrent symptoms or developed an additional indication for surgery, suggesting that patients with mildly elevated calcium in pHPT can have progression over time if their disease goes untreated, although only 27% will meet quantitative indications for surgery.

Bilezikian and Silverberg [33] found similar results in a group of patients with biochemically mild disease, with 22% of them developing overt hypercalcemia over 4 years of medical management. Unlike the study above by Silverberg et al. [32], the patients who progressed were older and had higher serum calcium levels at baseline.

In NCHPT patients followed over a median of 3 years without an operation, Lowe et al. [11] found that 41% showed evidence of progression. Of these, 19% developed frank hypercalcemia, 29% demonstrated progressive cortical bone loss, and 5% developed marked hypercalciuria. Those who developed hypercalcemia had higher baseline serum calcium levels, higher urinary calcium excretion, and older age. There was no difference in the baseline serum PTH in these patients who progressed to hypercalcemia. There was no uniform time course for progression of disease in this biphasic disease course model, because patients who were followed for NCHPT did not have predictable biochemical progression of disease.

Other studies, however, did not find the same progression of disease and do not support a biphasic course of NCHPT. Tordjman et al. [34] followed 20 NCHPT patients for a mean of 4 years and found that no biochemical markers changed significantly over that time period, nor did any of the patients develop an indication for surgery. It should be noted that this study was over a shorter mean time frame of 4 years versus the study by Silverberg et al. [32], which examined patients over a 10-year time period [32].

Despite the limitations of these studies, it is clear that a certain percentage of patients with mild disease will progress both in terms of symptoms and biochemical indices. The literature lacks clear guidance on the patient or disease features that might predict progression. Although there are various theories on the continuum of parathyroid disease progression, the time course for this progression appears to be variable. Nonetheless, mild pHPT (NCHPT and NHHPT) are likely precursors to more overt hyperparathyroidism, both in terms of symptomatology and biochemical indices.

In a population-based study evaluating women with calcium in the upper range of normal identified at screening mammography, Lundgren et al. [23] found patients with mild disease had the same, but less extensive morphologic and functional histologic derangements of parathyroid tissue on pathologic evaluation when compared with those patients with classic disease, again suggesting that mild pHPT is part of a spectrum that may ultimately progress to classic pHPT.

Presentation

Patients with mild pHPT are often identified during routine laboratory evaluation or when undergoing workup for bone loss. As such, they tend to be postmenopausal women who are at risk for osteoporosis that undergo BMD studies and calciotropic hormone measurements for evaluation [9–11].

In patients with NHHPT, 74% presented after routine laboratory screening identified an incidental elevated calcium level. Upon questioning, 70% of these patients had at least one symptom. Further studies suggested pHPT: 50% had abnormal bone densitometry, 37% had suffered neuropsychiatric symptoms, and 17% had a history of nephrolithiasis [19].

In patients with NCHPT identified while undergoing bone densitometry studies, Lowe et al. [11] found recent fragility fracture in 11%, fracture in adulthood in 46%, osteoporosis in 57%, and a history of kidney stones in 14%. Bone disease in this group was found to be more substantial than that of classic pHPT, and 40% of those patients developed worsening or new symptoms related to their pHPT during the observation period. Although the presence of bone disease in the NCHPT group may reflect a referral bias, the degree of bone loss suggests that selection bias may not entirely account for this finding.

In a retrospective review of 156 patients with pHPT identified at screening for skeletal disease, Marques et al. [35] found that 28.6% of patients with NCHPT had a history of kidney stones compared with 0.7% of patients without primary hyperparathyroidism. Tordjman et al. [34] found that 77% of patients with mild pHPT had lumbar spine osteopenia, and 46% had osteoporosis. These authors also found osteopenia at the hip in 64% of these patients and osteoporosis in 36%. It should be noted, however, that measurements were not taken only at the lumbar spine and hip, so the values do not reflect the distal radius, which is the site most commonly affected by pHPT.

Biochemically mild disease does not necessarily correlate with symptomatically mild disease. For example, Adler et al. [36] showed that 50% of patients with mild pHPT are found to have at least one symptom at presentation, such as nephrolithiasis, osteoporosis, fractures, or neuromuscular symptoms compared with 43% of patients with biochemically classic pHPT. Amaral et al. [14] found that patients with mild disease present with symptoms equally as frequently as those with classic disease. In this study, the frequency of nephrolithiasis (18.2% vs. 18.9%) and fractures (15.2% vs. 10.8%) occurred with equal frequency in patients with both mild and classic disease, and the BMDs were similar at the lumbar spine and the femoral neck for both groups as well. The BMD at the distal radius was significantly higher in the group with NCHPT. Because these are surgical series, there is an inherent selection bias toward those with more symptomatic mild pHPT, so this may not accurately reflect the symptoms of *all* patients with mild pHPT.

Biochemically mild disease does not necessarily correlate with symptomatically mild disease. For example, Adler et al. showed that 50% of patients with mild pHPT are found to have at least one symptom at presentation, such as nephrolithiasis, osteoporosis, fractures, or neuromuscular symptoms compared with 43% of patients with biochemically classic pHPT.

In a study by Bergenfelz et al. [37], of 211 patients operated on for pHPT, 12% had NCHPT, and 9% had NHHPT. When compared with the NHHPT and classic group, the NCHPT group had lower systolic blood pressure (SBP), with no other differences in clinical signs on presentation, symptoms other biochemical markers, bone density, or renal function. The NHHPT group was 10 years younger on average and had lower bone turnover with preserved bone density and GFR but did not differ in presenting signs and 4 symptoms [26]. Amin et al. [38] found that when comparing patients with NHHPT to those with classic disease, those with NHHPT were found to have similar subjective symptoms, bone health, and frequency of single gland disease.

Diagnosis

When diagnosing pHPT, secondary causes must first be ruled out. According to the proceedings of the third international workshop on asymptomatic pHPT [12], multiple etiologies contribute to elevations in PTH. Drugs such as bisphosphonates, anticonvulsants, furosemide, and phosphorus can cause elevated PTH. In addition to drugs, disorders such as renal hypercalciuria, chronic kidney disease (GFR <60 ml/min), malabsorption syndromes (celiac disease and cystic fibrosis), and vitamin D insufficiency with plasma 25-OH vitamin D levels of <50 nmol/L should be ruled out. Other considerations are hypalbuminemia, hypomagnesemia, and elevated calcitonin [39].

If patients are on one of the above listed medications and it is safe to discontinue the medication, they should cease taking them and have serum calcium rechecked after 3 months [40]. In patients with no elevation in total or ionized calcium, an oral calcium-loading test may be helpful to diagnose pHPT. This loading test consists of administering 1g of elemental calcium to the patient and then measuring immunoradiometric PTH at 30, 60, and 120 minutes [41].

In true NCHPT, patients have elevated PTH with normal serum and ionized calcium at all times, not just intermittently. Bone sialoprotein is a phosphorylated glycoprotein making up 5%–10% of the noncollagenous protein of bone and is thought to reflect bone resorption. This is also often found to be elevated in patients with classic pHPT, but there is currently no evidence on its presence in mild disease [42].

Invernizzi et al. [43] performed oral peptone and oral calcium loads in patients with NCHPT. This oral peptone test consisted of taking measuring serum gastrin, PTH, ionized calcium, and phosphate at baseline and then measuring the response to administration of 1 g of oral calcium gluconate with 10 g of meat stock at 15, 30, 45, 60, 90, and 120 minutes. The test was conducted in patients with both classic disease

and NCHPT matched for serum PTH levels. They found that 30 minutes after oral peptone load, the PTH increased significantly in classic pHPT patients for whom there was no significant increase in either the NCHPT or the control groups. After oral calcium load, PTH levels remained constant in patients with classic disease, and they decreased in NCHPT patients. This demonstrated that NCHPT patients had a partially preserved regulatory pathway of calciotropic hormone handling when compared with classic pHPT patients. Invernizzi et al. suggest this may prove these patients do not have autonomously secreting parathyroid glands and, as such, may not benefit from surgery. For these patients, these authors suggest adding the oral peptone test to the diagnostic workup for NCHPT.

Wallace et al. [19] recommend a workup for pHPT that consists of two sets of data confirming elevated calcium and intact parathyroid hormone (iPTH) in addition to 25-OH vitamin D, 1,25-OH vitamin D, 24-hour urine calcium. After that, localization studies (ultrasound and sestamibi) are beneficial because they demonstrate pathology 80% of the time, although positive or negative localization studies do not rule in or out disease.

Mischis-Troussard et al. [44] found 95% of patients with NHHPT had symptoms such as fatigue, polyuria, hypertension, or kidney stones; however, because of the normal intact PTH level, diagnosis was delayed 40% of the time. In cases of NHHPT, authors recommend eliminating other causes of elevated calcium and evaluating the patient with functional tests. Once other causes have been eliminated, then the diagnosis of pHPT can be made and followed by localization studies such as sestamibi scan or ultrasound.

Although eliminating other causes for elevated PTH is important, additional or excessive testing can delay treatment. Wallace et al. [19] noted that additional testing led to a delay in diagnosis in nearly all patients with NHHPT. In this study, imaging located parathyroid disease in 80% of the patients, and at median follow-up of this study, 96% remained cured of their disease with normal iPTH and serum calcium after undergoing parathyroidectomy at follow-up (median 8.9 months).

Sestamibi and cervical ultrasound are less likely to localize disease in patients with mild pHPT compared with their counterparts with classic disease. This could potentially be due to a higher proportion of multigland disease in this cohort [22, 26], although some studies have found the same prevalence of single adenomas as in classic pHPT [19]. Tordjman et al. [34] found that sestamibi positively identified disease in 75% of those with NCHPT, and ultrasound was positive 48% of the time. In one study in which patients got both sestamibi and ultrasound, all of the patients who underwent parathyroidectomy had at least one positive localizing study.

TREATMENT

This section will first address medical management of pHPT. There are few data on the medical management of mild pHPT; however, there are studies that have assessed the medical management and outcomes of patients with asymptomatic pHPT, as well as symptomatic patients who did not undergo operation for other reasons, and those papers will be discussed here. More thorough investigations are needed to determine

whether medical therapy can be safe and efficacious in this group. Also, we will address the surgical treatment of mild pHPT. Operating on patients with mild pHPT is controversial because the biochemical profile of these patients does not correlate with the classic definition of pHPT and the current recommendations for surgery.

Medical

Some suggest that it is reasonable to observe those patients with asymptomatic pHPT who do not meet the NIH guidelines for surgery until they develop an established indication for an operation [30, 32]. This is controversial, because there may be progression of mild disease to classic disease when symptoms may have been avoided with an earlier operation. However, for the patients who either refuse surgery or who are not medically fit for an operation, there are guidelines for surveillance measurements and medical therapy. Current recommendations for nonsurgical management from the third international workshop on asymptomatic pHPT include annual measurement of serum calcium and creatinine as well as measurements of bone densitometry (at three sites) every 1–2 years. Recommendations from previous workshops also included measurement of 24-hour urinary calcium, creatinine clearance from 24-hour urine collection, and abdominal x-ray; however, these procedures are no longer part of the routine medical management of these patients [28].

One of the above studies suggesting that medical management is safe until there is a clear indication for parathyroidectomy per NIH criteria arises was conducted in 1999 by Silverberg et al. [32]. They showed that over a 10-year period of medical management, 27% of patients initially diagnosed with asymptomatic pHPT progressed to develop an indication for operation. Silverberg et al. advise a surveillance schema of following: serum calcium levels twice yearly, urinary calcium excretion yearly, and bone mineral density measurements yearly. On a daily basis, patients are also advised to remain hydrated, to avoid immobilization, and to avoid thiazide diuretics, which can increase serum calcium levels.

When managing patients medically, Farford et al. [45] recommend maintaining vitamin D intake appropriate for their age and sex, as well as limiting daily elemental calcium intake to 800–1,000 mg daily, whereas others have suggested that there is no evidence that restricting dietary calcium intake has any effect on the serum calcium in patients with primary hyperparathyroidism [46].

Aside from monitoring the above parameters and following at-home recommendations, there are also some medications used in the medical management of pHPT. Bisphosphonates inhibit bone resorption by interfering with the destructive properties of osteoclasts and by inducing osteoclast apoptosis [47]. In patients with classic pHPT, the bisphosphonate alendronate treatment was shown to produce short-term fluctuations in serum calcium and PTH that reverted to baseline at 3 months. The same study showed an increase in BMD at the lumbar spine [48], whereas another study demonstrated an increase at the lumbar spine, as well as the femoral neck [49], but these gains peaked at 1 year. Khan et al. [50] also demonstrated improvement in lumbar spine and femoral neck BMD at the 2-year mark.

Although bisphosphonates can increase BMD, they do not have a long-term effect on the serum PTH and calcium levels. Calcimimetics are a drug class that modulate the calcium sensing receptor to increase sensitivity extracellular calcium, thereby reducing the secretion of PTH and serum calcium concentration. Cinacalcet is a second generation calcimimetic that was shown to normalize serum calcium and decrease PTH effectively [51]. There are currently no data to show that cinacalcet increases BMD or has any long-term clinical benefit of cinacalcet in patients with mild pHPT [52].

Raloxifene is an oral selective estrogen modulator that is associated with reductions in serum calcium levels, as well as markers of bone turnover in postmenopausal women with mild pHPT [53]. This medication does, however, have a two- to threefold increased risk of venous thromboembolic events, poses an increased risk of death from stroke in at risk postmenopausal women, and is also associated with leg cramps and hot flashes [54].

Surgical

Surgery is the definitive management of primary hyperparathyroidism and the only curative therapy. Cure rates for classic disease are 95%–98% with complication rates of 1%–2% [55–57]. A study by Sosa et al. [58] demonstrated that surgeon experience determined the length of stay and number of complications and that hospital volume was not consistently associated with outcomes. If undertaken by an experienced endocrine surgeon, minimally invasive parathyroidectomy is an ideal operation if preoperative imaging localizes an adenoma, otherwise bilateral neck exploration is undertaken [59].

The short half-life of PTH (average 1.68 ± 0.94 minutes) [60] allows for intraoperative testing and detection when the abnormal gland has been excised [56]. Determining surgical cure based on the Miami criterion of a 50% decline in intraoperative PTH (ioPTH) from the highest preoperative baseline 10 minutes after excision [61, 62] is of interest in the patients who have a normal preoperative parathyroid hormone level (NHHPT). There are five other criterion for surgical cure of pHPT that have been published [63], including: >50% decline in ioPTH after 10 minutes from preincision level [64], > 50% drop from the highest ioPTH level at 10 minutes after gland excision and a final ioPTH level less than the preincision value [65], >50% drop from the highest ioPTH level at 10 minutes after gland excision and a final ioPTH level within the reference range [66], >50% drop after 5 minutes from highest ioPTH [67], and >50% drop in ioPTH from the pre-excision level after 10 minutes [68]. Alhefdhi et al. [25] did find that a 50% decline of the preincision value even of patients with NHHPT values is reliable 96.5% of the time, although it takes a longer period of time for this decline to occur in these patients, as well as NCHPT patients [26].

The incidence of multigland disease was higher in patients with mild disease when compared with those with classic disease in multiple studies. Mild disease has multigland involvement 26%–50% of the time as compared with classic disease, which has an occurrence of 13%–29% [20, 25, 26]; however, this was not consistent across all studies [19]. Tordjman et al. [34] found 18% of patients were found to have

hyperplasia, and 82% had a single adenoma, although the sample size was quite small (11 patients).

When comparing the pathology, patients with mild pHPT have lower weight adenomas and overall parathyroid tissue than their classic pHPT counterparts [38]. In addition, patients with NCHPT had higher serum PTH per gram of adenomatous tissue and patients with NHHPT had a lower serum PTH per gram of adenomatous tissue when compared with the group with classic pHPT [37].

OUTCOMES

There is no approved medical treatment available for pHPT at this time; however, patients with no clear indication for surgery can be closely monitored [69] according to the guidelines in Table 1, established in the summary statement from the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism [28]. Figure 1 provides a flow-chart for the management of pHPT. Below, we will discuss the outcomes after curative surgical therapy in patients with mild pHPT.

Quality of Life and Mental Health

Patients with both classic and mild pHPT experience more neuropsychiatric symptoms and decreased quality of life when compared with the general population [36], as well as age- and sex-matched controls [71]. Parathyroidectomy has been shown to improve the quality of life of these patients as measured by the SF-36 survey, a health survey that evaluates quality of life measures of bodily pain, general health, vitality, and mental health [15, 16, 18, 36, 70].

A randomized trial of parathyroidectomy versus medical management was conducted in patients with asymptomatic NCHPT and slightly elevated calcium level. Both operative and nonoperative groups had general health evaluated every 6 months for 2 years by the SF-36 health survey. The surgical group had statistically significant improvement in two measured scales: social functioning and emotional role functioning [15]. Patients in the nonoperative group were seen to have a significant decline in five measured scales, including social functioning, physical problem, emotional problem, energy, and health perception. The surgical group declined only in physical function [18]. These results demonstrate that surgery improves the quality of life of people with NCHPT and those with pHPT and slightly elevated calcium; however, not all studies have agreed with these findings. Although those with asymptomatic pHPT were found to have decreased quality of life and more psychological symptoms than the controls at baseline, Bollerslev et al. [71] did not find an improvement in these symptoms after an operation.

In a prospective cohort study, Burney et al. [16] compared functional health status between patients with high normal/slightly elevated (<10.9 mg/dL) or overtly elevated (>10.9 mg/dL) serum calcium levels before and after surgery. Preoperatively, both groups had similarly profound deficits of functional health status when compared with controls, and postoperatively both groups returned to normal in six of eight SF-36 domains. The high calcium group demonstrated less improvement in their degree of pain and had a persistently abnormal pain score when compared with the low calcium

group at 6 months. This showed that the absolute level of serum calcium does not predict disease severity and is a poor predictor of the benefits obtained from operation, suggesting that surgical intervention may benefit patients with mild pHPT.

Cardiovascular/Metabolic Effects

In classic pHPT, even mildly elevated calcium levels are associated with increased cardiovascular abnormalities and dysfunction [72, 73], many of which improved with parathyroidectomy [74, 75]. When comparing operative and nonoperative groups with classic disease, those who were observed were found to have significantly increased left ventricular mass 1 year after surgery. Those who had surgery also were found to have improvement in diastolic function, suggesting that early surgical treatment of pHPT is optimal [76].

Although there are fewer data specifically addressing the cardiovascular benefits for patients with mild disease, there are some small studies that appear promising. Patients with mild pHPT have statistically higher SBP than their classic pHPT counterparts [26] [37]. In a population-based screening of postmenopausal women, Hagström et al. [77] identified that those with only slight elevation of calcium have increased proatherogenic lipoprotein levels and glucose levels compared with age-matched controls. In these patients, parathyroidectomy normalized all lipid variables such that there were no differences when compared with the control group. Those followed conservatively were found to have continued elevation in total triglyceride and atherogenic index with a decrease in HDL levels.

Although there has not been a lot of attention in the literature given to the impact of surgery on cardiovascular disease in patients with mild pHPT, well established studies on classic disease show a clear benefit of parathyroidectomy, suggesting that operating on patients with mild disease could prevent progression of the potential cardiovascular effects of pHPT.

Bone Disease

Parathyroidectomy is shown to improve BMD in patients with asymptomatic classic disease [70, 71, 78]. Many patients with NCHPT or NHHPT are diagnosed at the time of workup for bone disease without overt symptoms [35].

In a prospective, randomized trial, Ambrogini et al. [70] studied the effect of surgery on bone mineral density (BMD) in 50 patients who did not meet any guidelines for parathyroidectomy because of NCHPT or a slightly elevated calcium as recommended by the 2002 NIH consensus guidelines [10]. These patients were randomized to surgery or observation, and BMD was compared both pre- and postoperatively. The surgical group had a significant improvement at the lumbar spine, total hip, femoral neck, and trochanter at 1-year follow-up [70]. In another prospective randomized trial of patients with mild pHPT, Rao et al. [18] found a statistical increase in BMD at the femoral neck and total hip in patients with NCHPT or pHPT with slight calcium elevation who had parathyroidectomy when compared with those who were observed at 1-year follow-up.

In a study evaluating BMD in patients with mild pHPT, a statistical difference between patients with classic and mild

Table 1. Select points summarizing epidemiology, patient population, and outcomes in mild pHPT

Article	Finding
Silverberg et al. [32]	27% of asymptomatic patients with pHPT who did not meet the quantitative NIH criteria for parathyroidectomy (at least 1mg/dL above normal) developed an indication for operation over a 10-year period.
Bilezikian and Silverberg [33]	22% of patients who initially had NCHPT developed overt hypercalcemia over 4 years of medical management.
Lowe et al. [11]	NCHPT patients followed went over 3 years without an operation. 41% showed evidence of progression such as frank hypercalcemia, progressive cortical bone loss, or marked hypercalciuria. There was no uniform time course for progression.
Tordjman et al. [34]	NCHPT patients were followed nonoperatively for a mean of 4 years, and none had a significant change in biochemical markers or developed an indication for surgery.
Wallace et al. [19]	74% of patients with NHHPT presented after routine laboratory screening identified an elevated calcium level. Upon questioning, 70% of these patients had at least one symptom. There was a 96% cure rate approximately 9 months after surgery with normalized biochemical profiles.
Marques et al. [35]	8.9% prevalence of NCHPT was found in a sample of women referred for osteoporosis screening. 28.6% of these patients with NCHPT had a history of kidney stones compared with 0.7% of noncarriers.
Adler et al. [36]	50% of patients with mild pHPT were found to have at least one symptom at presentation compared with 43% of patients with biochemically classic pHPT. After parathyroidectomy, the patients with mild pHPT experienced improved quality of life on all 10 scales of the SF-36 Health Survey.
Mischis-Troussard et al. [44]	95% of patients with NHHPT were symptomatic at the time of presentation; however, because of the normal intact PTH level, diagnosis was delayed 40% of the time.
Rao et al. [18]	At 1-year follow-up, surgery statistically improved bone density (femoral neck and total hip) and quality of life of people in patients with NCHPT and those with pHPT who had only slightly elevated calcium.
Ambrogini et al. [70]	Patients with NCHPT or pHPT with slightly elevated calcium who underwent an operation had significant improvement in bone mineral density (lumbar spine, total hip, femoral neck, and trochanter), as well as quality of life, at 1-year follow-up.
Siperstein et al. [39]	NCHPT, intermittent hypercalcemic pHPT, and classic pHPT patients benefitted equally from surgery when comparing biochemical and symptom profiles.
Alhefdhi et al. [25]	In patients who had NHHPT, a 50% decline in intraoperative PTH is reliable to predict a cure 96.5% of the time. In a series of 142 of these patients, 100% were cured with normal serum calcium 6 months after surgery.

Abbreviations: NCHPT, normocalcemic primary hyperparathyroidism; NHHPT, normohormonal hyperparathyroidism; pHPT, primary hyperparathyroidism.

disease was found only at the site of the distal radius, not in the lumbar spine or femoral neck as was found in the above studies by Ambrogini et al. [70] and Rao et al. [18]. Patients with NCHPT had statistically higher BMD at this site than their overtly hypercalcemic counterparts [14].

In a longitudinal cohort study monitoring disease progression of NCHPT, Lowe et al. [11] identified 57% of referrals for NCHPT had osteoporosis in at least one site at presentation, 19% at two sites, and 8% at three sites. Distribution of these sites was the greatest at the hip (38%), followed by the lumbar spine (34%) and distal third of the radius (28%). After an average 3-year follow-up without surgery, 43% of patients had a 5% decline in bone density at one or more sites, and 40% of patients had a decline of 10%. The decline of BMD loss did not correlate with the degree of PTH excess.

Taken together, the majority of these studies show that patients with mild pHPT will experience loss of BMD if left untreated. Therefore, surgical treatment of mild pHPT appears to provide some benefit for preventing further declines in bone density.

Persistence/Recurrence of Disease

Following parathyroidectomy for mild pHPT, the persistence of disease is defined as elevated calcium (for NHHPT) or PTH (for NCHPT) within 6 months after the operation and recurrent disease is elevated calcium or PTH after 6 months following the

operation. Repeat biochemical markers of calcium, PTH, and vitamin D are evaluated to confirm that the etiology remains pHPT in the postoperative period [26]. For patients with mild disease, the operative failure rate in one initial report was found to be 5% as compared with 1% for classic disease. One potential explanation for this is the incidence of multigland disease, which was statistically higher in those with mild disease [20]. However, in another larger study from a high volume center with greater than 1,400 patients, there was no difference was seen in the rate of recurrence after surgery between mild and classic pHPT patients. Of those who did recur in the mild group, 66% were NCHPT, and 33% were NHHPT [26].

In the hands of experienced surgeons, parathyroidectomy is a safe and curative treatment for pHPT, and this is also shown to be true in patients with mild disease. Comparing biochemical and symptom profiles before and after surgery, it was found that normocalcemic pHPT, intermittent hypercalcemic pHPT, and persistently hypercalcemic pHPT patients benefitted equally from surgery [39]. Preoperatively, the three groups were metabolically indistinguishable from one another with the exception of the calcium level, and postoperatively all had normalization of abnormal laboratory values, demonstrating that removal of the abnormal parathyroid gland(s) is capable of normalizing PTH levels and establishing a biochemical cure in NCHPT patients.

Figure 1. Flowchart for the management of patients with mild primary hyperparathyroidism.
Abbreviation: PTH, parathyroid hormone.

Monchik et al. [79] performed a retrospective analysis of patients with NCHPT found on routine bone densitometry screen. Fifteen patients had documented NCHPT, and each had a bilateral neck exploration from which cures were established in fourteen patients. One patient needed a reoperation with exploration of the mediastinum; however, in all other cases, calcium levels normalized, demonstrating a high cure rate from operation in these patients. Follow-up time was not specified in this retrospective study.

Wallace et al. [19] identified a series of 46 patients with NHHPT, all of whom had histologically confirmed abnormal parathyroid tissue at the time of operation. There was a 96% cure rate approximately 9 months after surgery with normalized biochemical profiles. Similarly, Alhefdhi et al. [25] reported on a series of 142 patients with NHHPT and found that 100% were cured with normal serum calcium after 6 months. Amin et al. [38] demonstrated similar cure rates and complication rates for the classic and NHHPT groups.

DISCUSSION

Mild pHPT is a disease that is being diagnosed with increasing frequency because of the widespread use of laboratory testing of calcium and PTH in diagnosis and screening of bone health. Current NIH guidelines do not recommend parathyroidectomy for these patients if they are asymptomatic. Mild pHPT also has inconsistent definitions in the literature, and this confuses universal identification, research, and communication about this disease entity. In addition, there are very few randomized prospective trials investigating the impact of operative therapy

in comparison with observation. A significant amount of literature reviewed here is retrospective, leaving it vulnerable to selection bias and other intrinsic flaws of that type of data collection. Because many of these studies are surgical series, they probably represent a selection bias for healthy patients, fit for surgery. Patient selection obviously influences these reports of beneficial outcomes.

Despite these flaws, the data summarized here suggest that parathyroidectomy is beneficial for many patients with mild pHPT. Without an operation, 27% of patients with asymptomatic pHPT will progress to symptomatic or classic disease [32]. In addition, many patients with mild disease stated to be asymptomatic do possess the neurocognitive features or more subtle symptoms of pHPT often attributed to other disease processes like depression, fatigue, anxiety, or fibromyalgia. Surgery has shown to provide an improvement in quality of life [15, 36, 71] and bone health [11, 18, 71] for patients with mild pHPT.

One difficult aspect of mild pHPT is how to define a cure. Depending on which criteria the surgeon uses (reviewed in the Treatment: Surgical section), the decline in intraoperative PTH defines operative cure. Perhaps monitoring PTH levels and keeping them in a normal range is appropriate monitoring for patients with NCHPT, whereas following serum calcium levels is more appropriate for the NHHPT patient group. Alternatively, the relationship between the calcium and PTH levels can be used, but this obviously becomes open to interpretation. This is certainly a topic that deserves consideration to appropriately follow these patients in the long term, especially because more of these patients are offered surgery.

The decision to operate on patients with mild disease should involve weighing the benefits with the potential risks [18]. Preoperative imaging is not as sensitive in these patients, possibly because the glands have lower median weight and size or the higher frequency of multigland disease seen in patients with mild disease. Therefore, compared with patients with classic disease, they are more likely to require bilateral neck exploration [22]. A more extensive operation increases the risks inherent to the operation and should therefore be performed by experienced surgeons at high volume centers. When making the decision to operate, each patient should be evaluated individually with respect to potential benefits and morbidity. In cases of significant medical comorbidities and/or advanced age, observation may be the preferred treatment. Observation or medical management might also be the preferred strategy for asymptomatic patients at centers lacking an experienced, high-volume parathyroid surgeon.

Studies examining the cost effectiveness of parathyroidectomy versus medical management for patients with classic but asymptomatic pHPT demonstrate operative intervention in the hands of an experienced surgeon is a more cost-effective treatment and results in a better quality of life in these patients when compared with medical management in the form of cinacalcet or observation alone [80,81]. However, further studies are still needed to determine cost effectiveness of parathyroidectomy in patients with mild disease when compared with medical management. If mild pHPT represents an early form of classic disease, then early intervention could prevent exacerbation of bone, cardiovascular, and psychiatric disorders.

Studies examining the cost effectiveness of parathyroidectomy versus medical management for patients with classic but asymptomatic pHPT demonstrate operative intervention in the hands of an experienced surgeon is a more cost-effective treatment and results in a better quality of life in these patients when compared with medical management in the form of cinacalcet or observation alone.

Although there are certainly patients who do not want or cannot tolerate an operation, there is a growing body of

literature that supports parathyroidectomy for patients with mild pHPT. If the indications for surgery are expanded to include patients with mild disease, determining a long-term cure becomes the next challenge. Traditional indices of cure include normal calcium and normal PTH levels before and 6 months after surgery; however, in patients who have mild disease, one of these values was normal preoperatively. Furthermore, in a review by Olthoff et al. [82], 12%–43% of patients with classic disease have been found to have elevated PTH with eucalcemia after parathyroidectomy. The etiology of this is unclear, but possible explanations include bone hunger, vitamin D deficiency, inadequate calcium intake or absorption, reduced peripheral sensitivity to PTH, underlying chronic kidney disease, or a renal leak of calcium. The presence of this elevated PTH can, but does not necessarily, indicate operative failure or the presence of recurrence [83]. Therefore, it is important to identify and define more advanced definitions of persistence and recurrence for patients with mild biochemical indices. This will require a nuanced examination of PTH and calcium values that accounts for their relationship to each other rather than to normal ranges. Furthermore, the patients' bone health and vitamin D status contribute to the calcium and PTH levels.

CONCLUSION

Although the current body of literature suggests that patients with mild pHPT benefit from parathyroidectomy, careful patient and surgeon selection are critical to ensuring safety and efficacy. Universal acceptance of parathyroidectomy in this subset of patients will require more high quality, prospective studies and improved definitions of long-term cure.

AUTHOR CONTRIBUTIONS

Conception/Design: David F. Schneider

Provision of study materials or patients: David F. Schneider

Collection and/or assembly of data: Megan K. Applewhite

Data analysis and interpretation: Megan K. Applewhite, David F. Schneider

Manuscript writing: Megan K. Applewhite, David F. Schneider

Final approval of manuscript: David F. Schneider

DISCLOSURES

The authors indicated no financial relationships.

REFERENCES

- Adler JT, Sippel RS, Chen H. New trends in parathyroid surgery. *Curr Probl Surg* 2010;47:958–1017.
- Heath H III, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: Incidence, morbidity, and potential economic impact in a community. *N Engl J Med* 1980;302:189–193.
- Lundgren E, Hagström EG, Lundin J et al. Primary hyperparathyroidism revisited in menopausal women with serum calcium in the upper normal range at population-based screening 8 years ago. *World J Surg* 2002;26:931–936.
- Yeh MW, Ituarte PH, Zhou HC et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab* 2013;98:1122–1129.
- Wermers RA, Khosla S, Atkinson EJ et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: An update on the changing epidemiology of the disease. *J Bone Miner Res* 2006;21:171–177.
- Lo CY, Chan WF, Kung AW et al. Surgical treatment for primary hyperparathyroidism in Hong Kong: Changes in clinical pattern over 3 decades. *Arch Surg* 2004;139:77–82.
- Aboud A, Vestergaard P. Increasing incidence of primary hyperparathyroidism in Denmark. *Dan Med J* 2013;60:A4567.
- Zhao L, Liu JM, He XY et al. The changing clinical patterns of primary hyperparathyroidism in Chinese patients: Data from 2000 to 2010 in a single clinical center. *J Clin Endocrinol Metab* 2013;98:721–728.
- Silverberg SJ, Bilezikian JP. “Incipient” primary hyperparathyroidism: A “forme fruste” of an old disease. *J Clin Endocrinol Metab* 2003;88:5348–5352.
- Bilezikian JP, Potts JT Jr., Fuleihan G-H et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: A perspective for the 21st century. *J Clin Endocrinol Metab* 2002;87:5353–5361.
- Lowe H, McMahon DJ, Rubin MR et al. Normocalcemic primary hyperparathyroidism: Further characterization of a new clinical phenotype. *J Clin Endocrinol Metab* 2007;92:3001–3005.
- Eastell R, Arnold A, Brandi ML et al. Diagnosis of asymptomatic primary hyperparathyroidism: Proceedings of the third international workshop. *J Clin Endocrinol Metab* 2009;94:340–350.

13. Chen H. Primary hyperparathyroidism. In: Cameron JL, Cameron AM, eds. *Current Surgical Therapy*. Philadelphia, PA: Elsevier Saunders; 2011.
14. Amaral LM, Queiroz DC, Marques TF et al. Normocalcemic versus hypercalcemic primary hyperparathyroidism: More stone than bone? *J Osteoporos* 2012;2012:128352.
15. Talpos GB, Bone HG III, Kleerekoper M et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: Patient description and effects on the SF-36 health survey. *Surgery* 2000;128:1013–1020; discussion 1020–1021.
16. Burney RE, Jones KR, Christy B et al. Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. *Surgery* 1999;125:608–614.
17. Zhao L, Zhang MJ, Zhao HY et al. PTH inhibition rate is useful in the detection of early-stage primary hyperparathyroidism. *Clin Biochem* 2011;44:844–848.
18. Rao DS, Phillips ER, Divine GW et al. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab* 2004;89:5415–5422.
19. Wallace LB, Parikh RT, Ross LV et al. The phenotype of primary hyperparathyroidism with normal parathyroid hormone levels: How low can parathyroid hormone go? *Surgery* 2011;150:1102–1112.
20. Carneiro-Pla DM, Irvin GL III, Chen H. Consequences of parathyroidectomy in patients with “mild” sporadic primary hyperparathyroidism. *Surgery* 2007;142:795–799.
21. Maruani G, Hertig A, Paillard M et al. Normocalcemic primary hyperparathyroidism: Evidence for a generalized target-tissue resistance to parathyroid hormone. *J Clin Endocrinol Metab* 2003;88:4641–4648.
22. Wade TJ, Yen TW, Amin AL et al. Surgical management of normocalcemic primary hyperparathyroidism. *World J Surg* 2012;36:761–766.
23. Lundgren E, Ridefelt P, Akerström G et al. Parathyroid tissue in normocalcemic and hypercalcemic primary hyperparathyroidism recruited by health screening. *World J Surg* 1996;20:727–735.
24. Lundgren E, Rastad J, Thrujell E et al. Population-based screening for primary hyperparathyroidism with serum calcium and parathyroid hormone values in menopausal women. *Surgery* 1997;121:287–294.
25. Alhefdhi A, Pinchot SN, Davis R et al. The necessity and reliability of intraoperative parathyroid hormone (PTH) testing in patients with mild hyperparathyroidism and PTH levels in the normal range. *World J Surg* 2011;35:2006–2009.
26. Schneider DF, Burke JF, Ojomo KA et al. Multigland disease and slower decline in intraoperative PTH characterize mild primary hyperparathyroidism. *Ann Surg Oncol* 2013;20:4205–4211.
27. NIH conference. NIH conference. Diagnosis and management of asymptomatic primary hyperparathyroidism: Consensus development conference statement. *Ann Intern Med* 1991;114:593–597.
28. Bilezikian JP, Khan AA, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the third international workshop. *J Clin Endocrinol Metab* 2009;94:335–339.
29. Hollenberg AN, Arnold A. Hypercalcemia with low-normal serum intact PTH: A novel presentation of primary hyperparathyroidism. *Am J Med* 1991;91:547–548.
30. Rao DS, Wilson RJ, Kleerekoper M et al. Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: Evidence for biphasic disease course. *J Clin Endocrinol Metab* 1988;67:1294–1298.
31. Cusano NE, Silverberg SJ, Bilezikian JP. Normocalcemic primary hyperparathyroidism. *J Clin Dentom* 2013;16:33–39.
32. Silverberg SJ, Shane E, Jacobs TP et al. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 1999;341:1249–1255.
33. Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism. *Arq Bras Endocrinol Metabol* 2010;54:106–109.
34. Tordjman KM, Greenman Y, Osher E et al. Characterization of normocalcemic primary hyperparathyroidism. *Am J Med* 2004;117:861–863.
35. Marques TF, Vasconcelos R, Diniz E et al. Normocalcemic primary hyperparathyroidism in clinical practice: An indolent condition or a silent threat? *Arq Bras Endocrinol Metabol* 2011;55:314–317.
36. Adler JT, Sippel RS, Schaefer S et al. Surgery improves quality of life in patients with “mild” hyperparathyroidism. *Am J Surg* 2009;197:284–290.
37. Bergenfelz A, Lindblom P, Lindergrård B et al. Preoperative normal level of parathyroid hormone signifies an early and mild form of primary hyperparathyroidism. *World J Surg* 2003;27:481–485.
38. Amin AL, Wang TS, Wade TJ et al. Normal PTH levels in primary hyperparathyroidism: Still the same disease? *Ann Surg Oncol* 2011;18:3437–3442.
39. Siperstein AE, Shen W, Chan AK et al. Normocalcemic hyperparathyroidism. Biochemical and symptom profiles before and after surgery. *Arch Surg* 1992;127:1157–1163.
40. Bilezikian JP, Silverberg SJ. Clinical practice: Asymptomatic primary hyperparathyroidism. *N Engl J Med* 2004;350:1746–1751.
41. Monchik JM, Lamberton RP, Roth U. Role of the oral calcium-loading test with measurement of intact parathyroid hormone in the diagnosis of symptomatic subtle primary hyperparathyroidism. *Surgery* 1992;112:1103–1110.
42. Silverberg SJ. Natural history of primary hyperparathyroidism. *Endocrinol Metab Clin North Am* 2000;29:451–464.
43. Invernizzi M, Carda S, Righini V et al. Different PTH response to oral peptone load and oral calcium load in patients with normocalcemic primary hyperparathyroidism, primary hyperparathyroidism, and healthy subjects. *Eur J Endocrinol* 2012;167:491–497.
44. Mischis-Troussard C, Goudet P, Verges B et al. Primary hyperparathyroidism with normal serum intact parathyroid hormone levels. *QJM* 2000;93:365–367.
45. Farford B, Presutti RJ, Moraghan TJ. Nonsurgical management of primary hyperparathyroidism. *Mayo Clin Proc* 2007;82:351–355.
46. Silverberg SJ, Bilezikian JP, Bone HG et al. Therapeutic controversies in primary hyperparathyroidism. *J Clin Endocrinol Metab* 1999;84:2275–2285.
47. Russell RG. Bisphosphonates: From bench to bedside. *Ann N Y Acad Sci* 2006;1068:367–401.
48. Parker CR, Blackwell PJ, Fairbairn KJ et al. Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: A 2-year study. *J Clin Endocrinol Metab* 2002;87:4482–4489.
49. Chow CC, Chan WB, Li JK et al. Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003;88:581–587.
50. Khan AA, Bilezikian JP, Kung AW et al. Alendronate in primary hyperparathyroidism: A double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004;89:3319–3325.
51. Shoback DM, Bilezikian JP, Turner SA et al. The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003;88:5644–5649.
52. Marcocci C, Cetani F. Update on the use of cinacalcet in the management of primary hyperparathyroidism. *J Endocrinol Invest* 2012;35:90–95.
53. Rubin MR, Lee KH, McMahon DJ et al. Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003;88:1174–1178.
54. Muchmore DB. Raloxifene: A selective estrogen receptor modulator (SERM) with multiple target system effects. *The Oncologist* 2000;5:388–392.
55. AAEC/AAES Task Force on Primary Hyperparathyroidism. The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism. *Endocr Pract* 2005;11:49–54.
56. Udelman R, Pasiaka JL, Sturgeon C et al. Surgery for asymptomatic primary hyperparathyroidism: Proceedings of the third international workshop. *J Clin Endocrinol Metab* 2009;94:366–372.
57. Stavakis AI, Iuarte PH, Ko CY et al. Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery. *Surgery* 2007;142:887–899; discussion 887–899.
58. Sosa JA, Bowman HM, Tielsch JM et al. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg* 1998;228:320–330.
59. Chen H, Mack E, Starling JR. A comprehensive evaluation of perioperative adjuncts during minimally invasive parathyroidectomy: Which is most reliable? *Ann Surg* 2005;242:375–380; discussion 380–383.
60. Libutti SK, Alexander HR, Bartlett DL et al. Kinetic analysis of the rapid intraoperative parathyroid hormone assay in patients during operation for hyperparathyroidism. *Surgery* 1999;126:1145–1151.
61. Irvin GL III, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. *Am J Surg* 1991;162:299–302.
62. Carneiro DM, Solorzano CC, Nader MC et al. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: Which criterion is the most accurate? *Surgery* 2003;134:973–981.
63. Chiu B, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. *Arch Surg* 2006;141:483–488.

64. Gordon LL, Snyder WH III, Wians F Jr. et al. The validity of quick intraoperative parathyroid hormone assay: An evaluation in seventy-two patients based on gross morphologic criteria. *Surgery* 1999; 126:1030–1035.
65. Irvin GL III, Molinari AS, Figueroa C et al. Improved success rate in reoperative parathyroidectomy with intraoperative PTH assay. *Ann Surg* 1999;229:874–879.
66. Yang GP, Levine S, Weigel RJ. A spike in parathyroid hormone during neck exploration may cause a false-negative intraoperative assay result. *Arch Surg* 2001;136:945–949.
67. Irvin GL III, Deriso GT III. A new, practical intraoperative parathyroid hormone assay. *Am J Surg* 1994;168:466–468.
68. Weber CJ, Ritchie JC. Retrospective analysis of sequential changes in serum intact parathyroid hormone levels during conventional parathyroid exploration. *Surgery* 1999;126:1139–1143; discussion 1143–1144.
69. Bilezikian JP, Rubin M, Silverberg SJ. Asymptomatic primary hyperparathyroidism. *Arq Bras Endocrinol Metabol* 2006;50:647–656.
70. Ambrogini E, Cetani F, Cianferotti L et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: A prospective, randomized clinical trial. *J Clin Endocrinol Metab* 2007; 92:3114–3121.
71. Bollerslev J, Jansson S, Mollerup CL et al. Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: A prospective, randomized trial. *J Clin Endocrinol Metab* 2007;92:1687–1692.
72. Smith JC, Page MD, John R et al. Augmentation of central arterial pressure in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 2000;85: 3515–3519.
73. Ringe JD. Reversible hypertension in primary hyperparathyroidism: Pre- and postoperative blood pressure in 75 cases. *Klin Wochenschr* 1984; 62:465–469.
74. Dominiczak AF, Lyall F, Morton JJ et al. Blood pressure, left ventricular mass and intracellular calcium in primary hyperparathyroidism. *Clin Sci (Lond)* 1990;78:127–132.
75. Nilsson IL, Aberg J, Rastad J et al. Circadian cardiac autonomic nerve dysfunction in primary hyperparathyroidism improves after parathyroidectomy. *Surgery* 2003;134:1013–1019.
76. Almqvist EG, Bondeson AG, Bondeson L et al. Cardiac dysfunction in mild primary hyperparathyroidism assessed by radionuclide angiography and echocardiography before and after parathyroidectomy. *Surgery* 2002;132:1126–1132.
77. Hagström E, Lundgren E, Lithell H et al. Normalized dyslipidaemia after parathyroidectomy in mild primary hyperparathyroidism: Population-based study over five years. *Clin Endocrinol (Oxf)* 2002;56:253–260.
78. Almqvist EG, Becker C, Bondeson AG et al. Early parathyroidectomy increases bone mineral density in patients with mild primary hyperparathyroidism: A prospective and randomized study. *Surgery* 2004; 136:1281–1288.
79. Monchik JM, Gorgun E. Normocalcemic hyperparathyroidism in patients with osteoporosis. *Surgery* 2004;136:1242–1246.
80. Zanocco K, Angelos P, Sturgeon C. Cost-effectiveness analysis of parathyroidectomy for asymptomatic primary hyperparathyroidism. *Surgery* 2006;140:874–881; discussion 881–882.
81. Sejean K, Calmus S, Durand-Zaleski I et al. Surgery versus medical follow-up in patients with asymptomatic primary hyperparathyroidism: A decision analysis. *Eur J Endocrinol* 2005;153: 915–927.
82. Oltmann SC, Maalouf NM, Holt S. Significance of elevated parathyroid hormone after parathyroidectomy for primary hyperparathyroidism. *Endocr Pract* 2011;17(Suppl 1):57–62.
83. Ning L, Sippel R, Schaefer S et al. What is the clinical significance of an elevated parathyroid hormone level after curative surgery for primary hyperparathyroidism? *Ann Surg* 2009;249:469–472.

CME

This article is available for continuing medical education credit at CME.TheOncologist.com.