The Appropriate Diagnosis of Primary Hyperparathyroidism

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ABSTRACT Primary hyperparathyroidism (PHPT) is both underdiagnosed and undertreated. The most common causes for delayed diagnosis include failure to note hypercalcemia, poor workup for hypercalcemia, or not contemplating a diagnosis of HPT. The majority (99.8%) of patients who have an elevated serum calcium level have a problem in one or more of their parathyroid glands. Any serum calcium concentration above 10.2 mg/dl should alert the health care provider of the possibility of PHPT. This paper is intended to contribute to the education of health care providers and patients about the importance of early diagnosis and about the more subtle complications of PHTP to create a sense of urgency for management and appropriate referral of the patient to a specialist. The only definitive and curative treatment of PHPT is an operation that can prevent all the deleterious consequences of the disease.

KEYWORDS Primary Hyperparathyroidism, Diagnosis of Primary Hyperparathyroidism, Differential Diagnosis of Primary Hyperparathyroidism, differential diagnosis of hypercalcemia, hypercalcemia, complications of parathyroidectomy

INTRODUCTION

Primary hyperparathyroidism (PHPT) is both underdiagnosed and undertreated. The most common causes for delayed diagnosis include failure to note hypercalcemia, poor workup for hypercalcemia, or not contemplating a diagnosis of HPT. Asban A, et al. [1] identified that health care providers appear to overestimate the benefits of medical therapy and/or observation and underestimate the potential benefits of parathyroidectomy, as indicated by low rates of surgical referral relative to medical management [1]. The purpose of this review is to help physicians identify, adequately diagnose, and appropriately refer the patient for surgical evaluation.

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DEFINITION OF PHPT

The term hyperparathyroidism (HPT) represents the overproduction of parathyroid hormone (PTH) and can be categorized as primary, secondary, or tertiary. PHPT arises from an unregulated overproduction of PTH from an abnormal parathyroid gland [2]. Increased PTH levels may also arise as a compensatory response to hypocalcemic states resulting from chronic renal failure or gastrointestinal (GI) malabsorption of calcium. This secondary HPT can be undone by rectification of the underlying problem (e.g., kidney transplantation for chronic renal failure). However, chronically stimulated parathyroid glands may sometimes become autonomous, resulting in persistence or recurrence of the hypercalcemia after successful renal transplantation, resulting in tertiary HPT.

The definition of PHPT is hypercalcemia or widely fluctuating levels of serum calcium resulting from the inappropriate or autogenous secretion of PTH by one or more parathyroid glands in the absence of a known or recognized stimulus [2-4].

EPIDEMIOLOGY OF PHPT

The most common aetiology of hypercalcemia in the outpatient setting is PHPT [3, 4], with roughly 100,000 new cases per year recorded in the United States [3]. Since the introduction of routine laboratory testing, the prevalence of PHPT has increased

from 0.1% to 0.4% (one to seven cases per 1000 adults) [3, 5, 6]. Yeh et al. [6] reported that the incidence of PHPT fluctuated between 36.3 and 120.2 cases per 100,000 women-year and 13.4 and 35.6 in 100,000 men-year. The vast majority of cases of PHPT occur in patients older than 45 years of age, with a mean age at diagnosis between 52 and 56 years, but it may present at any age [7]. Women have always made up the majority of cases, with a female-to-male ratio of 3 to 4:1 [2, 3, 8].

HOW TO IMPROVE THE FAILURE TO RECOGNIZE HYPERCALCEMIA AND OTHER LABORATORY ABNORMALITIES SEEN IN PHPT?

In a study by Asban A, et al., 15% of patients had at least one elevated serum calcium concentration that was not recognized by their health care provider, and 12% of patients with an elevated calcium level did not have there PTH checked as part of the initial workup for hypercalcemia [1]. There are several possible explanations for why health care providers may miss elevated calcium on laboratory testing or ascribe the hypercalcemia to other causes. A busy practice was hundreds of laboratory values are processed in any given week, making it fairly easy to miss any single abnormality. Because elevated serum calcium may be deemed of lesser importance than laboratory values related to kidney disease, or diabetes, or liver dysfunction, providers may not feel a sense of urgency related to diagnosis or further workup. Moreover, a tendency to assess an elevated serum calcium level by repeating the calcium measurement without checking a PTH level is a common practice [1]. Repeating the serum calcium without checking the PTH does not provide sufficient information to diagnose the origin of the hypercalcemia because a seemingly normal calcium level may be indicative of PHPT if the PTH is inadequately normal (normocalcemic hyperparathyroidism) [1, 4]. A considerable percentage of patients may have their elevated calcium levels identified in the hospital (inpatient or in emergency room) making it a relatively easy way miss an additional laboratory abnormality [1].

It is very important to look for abnormal calcium levels when checking routine laboratory test; the following section is intended to help health care providers identify abnormal serum calcium levels and to learn which additional test will help them make the diagnosis of PHPT and exclude other causes of hypercalcemia.

The normal serum calcium levels vary between laboratories, but it is typically found to be between 8.6 mg/dl to 10.2 mg/dl. This reference range is attained from a patient population that includes infants, children, adolescents, and adults who make interpretation of the results difficult. Practically all adults live with a serum calcium concentration between 9 mg/dl to 10 mg/dl [4]. It is very uncommon for an adult (over 25 to 30 years of age) to have persistent calcium levels above 10.2 mg/dl or below 9.2 mg/dl [4]. This is secondary to the very strict regulation by the parathyroid glands. Normal variability in the serum calcium concentration is expected between different calcium results taken at different points in time, but the variability should be minimal, usually less than 0.4 mg/dl (0.19 +/- 0.09 mg/dl) [4]. If the variability is equal to or above 0.4 mg/dl in the same patient, we should suspect an abnormally functioning parathyroid gland [4]. Calcium levels may vary more than 1 mg/dL from day to day, month to month in patients with PHPT and this fluctuation in the serum calcium concentration should be used as a warning sign that the parathyroid glands are not working properly. Norman et al., [4], in a series of more than 10,000 patients with proven PHPT found that the average serum calcium concentration was 10.9 ± 0.6 mg/dl (median 10.9 mg/dl, mode 10.8 mg/dl) (Figure 1).

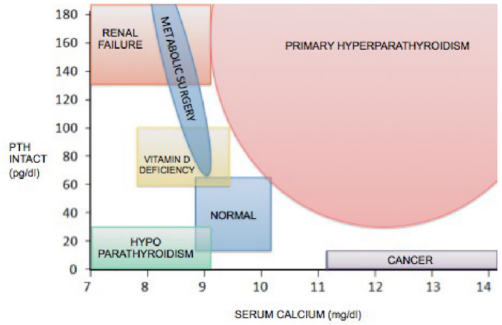

Figure 1. Differential Diagnosis of PHPT Based on Serum Calcium and PTH Levels [2, 4].

In this study, 85.6% of the patients with PHPT had serum calcium concentrations below 11.5 mg/dl, 69% of the patients never had serum calcium concentrations above 11.4 mg/dl. They also found that 74% of the patients with PHPT had at least one serum calcium concentration within the normal reference range, again making a point of the variability seen in patients with PHTP concerning the serum calcium concentration. Only 4% of the patients in this study had an average serum calcium concentration of 12.0 mg/dl or above, and 93% of the patients never had a single serum calcium level this high. The information in the previous paragraph is essential to take into account when reviewing the up to date guidelines in the management of this disease [9, 10]. If the serum calcium levels are found to be elevated, they should be repeated to confirm the presence of hypercalcemia or to identify the variability that exists inpatient with PHPT [2]. A frequent mistake that some physicians make when they have a patient with a serum calcium concentration that is abnormally high and another normal one is to assume that the first result was a laboratory error instead of taking into account the variability that could exist if the parathyroid glands are not functioning properly. If available, previous values for serum calcium concentrations should be reviewed, looking for this variability. The presence of longstanding hypercalcemia or variability between different results is more suggestive of PHPT. If the laboratory is known to measure ionized calcium reliably well, some specialists prefer to measure the ionized calcium although this usually adds little to the diagnosis PHPT in patients with normal serum albumin concentrations and no abnormalities in acid-base balance [11]. One situation in which the serum ionized calcium concentration is an essential adjunct to the diagnosis is in patients with presumed normocalcemic PHPT [4]. In normocalcemic PHPT, the ionized serum calcium levels should be within normal range. In a study by Glendenning et al [12], 12 out of 60 patients in whom the diagnosis of normocalcemic PHPT was presumed a raised serum ionized calcium was identified in the presence of a normal total serum calcium concentration. After abnormal serum calcium is identified in a patient suspected of having PHPT or as an isolated finding, the next test that should be ordered is either an intact PTH (second-generation PTH assay) or PTH 1-84 assays (third-generation) (Figure 1). This test should be ordered alongside a new serum calcium level to help diagnose PHPT [13]. Roughly 80% to 90% of patients with PHPT have serum PTH levels above

Table 1 Differential Diagnosis of Hypercalcemia [18]

Primary Hyperparathyroidism: • Single adenoma • Multiple gland adenoma: – Double adenoma – Triple adenoma • Multiple gland hyperplasia
Tertiary Hyperparathyroidism
Malignancy: • Parathyroid carcinoma • Multiple myeloma • Acute or chronic leukemia • Solid tumors producing PTH-related peptide: – Ovarian tumors – Lung tumors
Drugs / Medications: • Lithium • Thiazide diuretics (hydrochlorothiazide) [19] • Vitamin A intoxication [20] • Vitamin D intoxication [20, 21]
Endocrine Disorders: • Hyperthyroidism • Addisonian crisis • VIPoma
Granulomatous Disease: • Sarcoidosis • Tuberculosis • Berylliosis • Histoplasmosis
Milk-Alkali Syndrome
Chronic renal failure
Paget's Disease
Immobilization

the normal range for the test (10 to 65 pg/ml) [14, 15]. In a series of more than 10,000 patients with proven PHPT, Norman et al. [4], found that the average serum PTH concentration was 105.8 pg/ml (median 95 pg/ml, and mode 84 pg/dl). Approximately 10% to 20% of patients with PHPT have a serum PTH that was only minimally elevated or within the normal range (ranging from 35 to 65 pg/mL in an assay whose normal range is 10 to 60 pg/mL)[15]. In the study by Norman et al. [4], 16.5% of the patients kept there PTH levels within the normal range, and 10.5% of the patients never had even one value above 65 pg/ml. These "normal" values in the presence of hypercalcemia are inappropriately high; normal subjects given intravenous calcium can suppress the serum PTH concentrations (below ten pg/mL), and patients with non-parathyroid hypercalcemia virtually always have values below 20 to 25 pg/mL [16, 17]. When the PTH is within normal limits, or it is only minimally elevated (but inappropriately normal given the patient's hypercalcemia), measurement of 24-hour urinary calcium excretion may assist in discriminating PHPT from familial hypercalcemic hypocalciuria (FHH), though this is a sporadic disease. When the PTH is below or in the lower end of the normal range, non-PTH-mediated causes of hypercalcemia should be investigated (Table 1). As with the serum calcium, variations in the PTH serum concentration can arise an should be used the help to make the diagnosis [4].

As a rule, the higher the PTH levels the higher serum calcium levels, but we should keep in mind that there is a great deal of disparity between serum calcium and PTH levels, with little correlation between the average calcium level compared to the average PTH level [4]. Consequently, a high PTH level does not necessarily determine a high calcium level, and vice versa in any individual patient. The classic PHPT patient will have an elevated serum calcium (above 10.2 mg/dl) and an elevated serum PTH level (above 65 pg/ml) but some patients may have a very elevated serum calcium levels (higher than 11.5 mg/dl) with normal serum PTH levels, or some patients may have normal or only slightly elevated serum calcium levels with elevated serum PTH levels. Acquiring of vitamin D levels (usually 25 OH Vitamin D) may help differentiate PHPT from other conditions, and it can help confirm the diagnosis of PHPT [4]. This is because the majority of patients with PHPT will have coexistent vitamin D deficiency [4, 22]. Norman et al. [4, 22], in a series of more than 10,000 patients with proven PHPT found that 77% of patients had 25 OH Vitamin D levels below 30 ng/ml (normal range above 35 ng/ml), 36% had levels below 20 ng/ml, and none of the patients had elevated 25 OH Vitamin D levels. The authors also found an increase conversion of 25 OH Vitamin D to 1-25 OH Vitamin D. Vitamin D deficiency is something to anticipate in patients with PHPT with an average value of 22.4 ng/ml [4]. Vitamin D deficiency can help with the diagnosis of PHPT [22].

Twenty-four-hour urinary calcium excretion is typically not needed to make the diagnosis of PHPT because of the lack of correlation with the risk of developing renal complications. The current NIH guidelines no longer take into account the 24-hour urinary calcium excretion as a criterion for surgery [9]. The 24-hour urinary calcium can be helpful in patients with hypercalcemia and a minimally elevated PTH or an inappropriately normal PTH given the patient's hypercalcemia, as it helps distinguish PHPT from FHH [23]. The majority of patients with PHPT have normal 24-hour urinary calcium excretion, with only 40% of patients being hypercalciuric [24]. A urinary calcium concentration, greater than 200 to 300 mg/day, basically excludes the diagnosis of FHH [23]. If the 24-hour urinary calcium excretion is below 200 mg/day, PHPT with concomitant vitamin D deficiency should be suspected. Low urinary calcium values can be seen in patients with PHPT whose calcium intake is extremely low. Roughly 75% of patients with FHH excrete less than 100 mg of calcium in urine a day [25]. A calcium/creatinine (Ca/Cr) clearance ratio below 0.01 in a vitamin D-replete individual is highly suggestive of FHH rather than PHPT (ratio usually greater 0.02) [23, 26, 27]. The ratio is calculated using 24-hour urinary calcium and creatinine concentrations, and total serum calcium and creatinine concentrations using the following formula: Ca/Cr clearance ratio = [24-hour urine Ca X serum Cr] ÷ [24-hour urine Cr X serum Ca].

The data establishing the value of the Ca/Cr clearance ratio in differentiating FHH from PHPT are based primarily on 24-hour urine collections [23]. The Ca/Cr clearance ratio less than 0.01 has a sensitivity for FHH of 85%, a specificity of 88%, and a positive predictive value of 85%; a value greater than 0.02 essentially excluded FHH [23, 26-28].

Roughly 50% of patients with PHPT will have decreased in their serum phosphate concentrations. The severity of the hypophosphatemia associated with PHPT is usually moderate; increased urinary phosphate excretion is balanced by the mobilization of phosphate from bone and enhanced intestinal absorption. Serum phosphorus concentrations are seldom less than 2.0 mg/dl unless patients' phosphorus intake is low, or they concurrently ingest phosphate-binding antacids [29]. A mild hyperchloremic metabolic acidosis may also is present in patients with PHPT, thereby leading to an elevated chloride-to-phosphate ratio (> 33) [30-32]. Proximal tubular bicarbonate reabsorption is inhibited by elevated concentrations of PTH, which tends to cause a mild metabolic acidosis. However, this effect is usually offset by the alkali liberated as a result of increases in bone resorption and tubular reabsorption of bicarbonate caused by hypercalcemia [33]. Consequently, metabolic acidosis is uncommon in patients with PHPT unless serum PTH concentrations are very high, or the patient has coexistent renal insufficiency.

LOOKING FOR POSSIBLE CLINICAL FEATURES OF PHPT IN PATIENT WITH HYPERCALCEMIA.

Patients with an elevated serum calcium concentration, an elevated PTH or inappropriately normal PTH in the presence of elevated calcium levels, and signs and symptoms that could be attributed to PHPT, the diagnosis of PHPT should be relatively straight forward. No confirmatory imaging study is required to make the diagnosis, and the patient should be referred for a surgical evaluation. The following section will describe the signs and symptoms health care providers should be looking for in patients with an elevated serum calcium concentration.

PHPT is symptomatic in more than 95% of the cases if proper attention is paid to the subtle symptoms and signs that the disease can produce due to the fluctuating calcium levels [34], regardless of what most of the literature states. The "classic" pentad of kidney stones, painful bones, abdominal groans, psychic moans, and fatigue overtones are rarely seen today since the advent and general use of automated blood analyzers in the early 1970s [35].

Most patients present with fatigue (# 1 symptom) [36-39], decrease levels of energy [36, 37], general malaise [37], anxiety, irritability leading to decrease social interaction [40], depression (10% of cases) [36], memory loss [37], decrease concentration,

Table 2 Fourth International Workshop on Asymptomatic PHPT Clinical Guidelines.

Serum calcium concentration of 1.0 mg/dL or more above the upper limit of normal.
Estimated glomerular filtration rate (eGFR) less than 60 ml/min.
Bone density at the hip, lumbar spine, or distal radius that is more than 2.5 standard deviations below peak bone mass (T-score less than-2.5) and previous asymptomatic vertebral fracture (by radiograph, CT, MRI, or vertebral fracture assessment.
Twenty-four-hour urinary calcium is greater than 400 mg/day. Some experts suggest that a stone risk profile is a useful adjunct for making a decision about surgery in those with urinary calcium excretion greater 400 mg/d, but there are limited to data to support this.
Nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT.
Age less than 50 years.

Table 3 Long-term Consequences of PHPT.

Shorter life span
Increase the risk of developing cardiovascular disease
Increase the risk of developing a malignancy
Increase risk of developing bone disease
Increase the risk of developing renal disease
Decrease quality of life

decrease ability to learn new things, decrease ability to complete daily tasks at home [39, 41], decrease ability to complete daily tasks at work [41], decrease social interaction, insomnia [42], arthralgia's (32% of the cases) [43], myalgia's (14% to 41% of the cases) [43], bone pain [38-40], muscle weakness (specially proximal muscle groups) [38], intermittent headaches, polydipsia, polyuria [44], nocturia, nausea (24% of the cases) [45-47], anorexia (15% of the cases) [45-47], non-specific abdominal pain [46, 48], heartburn (30% of the cases) [36, 47, 48], constipation (33% of the cases) [47], palpitations, arrhythmias (usually atrial fibrillation), elevated blood pressure, thinning of the hair (specially in women in the frontal region), and pruritus [34, 49, 50]. Patients with PHPT also tend to score lower than healthy controls when evaluated by general multidimensional health assessment tools such as the Medical Outcomes Study Short-Form Health Survey (SF-36) [51, 52] and other specific questionnaires [53]. PHPT that is truly "asymptomatic" is a rare occurrence, seen in less than five percent of patients [35, 47], this is important when talking about management based on current guidelines[9].

DIFFERENTIAL DIAGNOSIS OF PHPT

The differential diagnosis of hypercalcemia is extensive [18], as listed in Table 1, but the aetiology of hypercalcemia that results in a concomitantly elevated PTH level are few: FHH, lithium-induced hypercalcemia, and tertiary HPT. A minority of patients (10% to 15%) with PHPT have PTH levels at the high end of the normal reference range (10 to 65 pg/dl), though inappropriately high in the presence of elevated serum calcium concentrations. A group of the patients (2.5% of the cases) have serum calcium levels within the reference range with elevated PTH hormone, so-called normocalcemic PHPT (Figure 1) [4]. On the other hand, when considering this diagnosis, all potential causes of secondary HPT, low calcium intake, gastrointestinal disorders, renal insufficiency, and hypercalciuria of renal origin, should be eliminated [54]. It is often not very difficult to differentiate hypercalcemia caused by PHPT from other causes because in almost all other etiologies of hypercalcemia the serum PTH is in the low normal range.

Secondary and tertiary hyperparathyroidism is usually diagnosed based on their clinical context. Cancer-induced hypercalcemia is usually associated with a low parathyroid hormone level but possibly a high parathyroid hormone-related peptide level (Figure 1). PHPT and malignancy account for more than 90% of all cases of hypercalcemia. Malignancy is the leading cause of hypercalcemia in hospitalized patients comparted to the outpatient setting, where PHPT is the most common cause of the hypercalcemia. PHPT can virtually always be distinguished from other diseases causing hypercalcemia by a combination of history, physical examination, and appropriate laboratory investigations.

It is commonly not difficult to differentiate hypercalcemia secondary to PHPT from hypercalcemia due to malignancy. Malignancy is often evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy have higher calcium concentrations and are more symptomatic from the hypercalcemia than individuals with PHPT. Hypercalcemia may occur in patients with many different types of tumours, both solid tumours and leukaemia's. Serum calcium concentrations above 13 mg/dL are less commonly seen in PHPT and, in the absence of another apparent cause, are more likely due to malignancy. Usually, these patients will have very low PTH levels (between 6 to 12 pg/ml) because their parathyroid glands will be functioning properly [55].

The elaboration of humoral factors by the primary tumour,

collectively known as humoral hypercalcemia of malignancy (HHM), is the mechanism responsible for 80% of the cases [56, 57]. The majority of HHM is caused by tumour production of PTH-related protein followed by infrequent tumour production of 1,25-dihydroxyvitamin D and PTH. The remaining 20% of the cases are caused by bone metastasis with consequent bone osteolysis and release of skeletal calcium. Cytokines such as tumour necrosis factor and interleukin-1 appear to play a role by stimulating the differentiation of osteoclast precursors into mature osteoclasts [55].

Practically all patients with chronic renal failure develop secondary HPT. These patients usually have normal or low normal serum calcium concentrations with very elevated serum PTH levels (between 250 to 4000 pg/ml) (Figure 1). These patients are responding appropriately to very elevated phosphate levels. Patients with high serum calcium concentrations, high PTH levels, modest elevations of serum creatinine, and diminished glomerular filtration rate have PHPT [54].

Patients with gastrointestinal malabsorption secondary to gastric bypass surgery [58], Celiac disease [59], Crohn disease [60], and small bowel resection will have decreased calcium absorption from the gastrointestinal tract leading to an increase in serum PTH levels secondary to parathyroid gland hyperplasia (normal response) (Figure 1). The increase in the PTH level will cause an increase in calcium resorption from the bone, leading to significant osteoporosis. These patients maintain their serum calcium levels between 8.2 mg/dl to 9.2 mg/dl (could drop up to 7 mg/dl) [59, 60].

FHH is a rare autosomal dominant disorder characterized by longstanding, mild hypercalcemia, normal PTH levels, and low urinary calcium excretion. In most instances, it is caused by an inactivating mutation in the calcium-sensing receptor in the parathyroid glands and the kidneys [23]. A family history of mild hypercalcemia, especially in young children, and the absence of symptoms and signs of hypercalcemia (such as fatigue, memory loss, anorexia, neuromuscular symptoms, nephrolithiasis, gastroesophageal reflux disease, hair loss in women, heart abnormalities, osteoporosis, and polyuria) are characteristic of this disorder. Fifteen to 20 percent of patients with FHH may have a mildly elevated PTH concentration [23, 25, 26, 61].

Immobilization is a rare cause of hypercalcemia. For the diagnosis of immobilisation-related hypercalcemia, all the other causes of PTH and vitamin D-dependent hypercalcemia should be carefully excluded (Table 1). Immobilization hypercalcemia results from rapid bone turnover and has been seen after spinal cord injury or long bone fracture in children and adolescents [62]. Patients that immobilized with pre-existing conditions of high bone turnover (adolescents and patients with Paget's disease, thyrotoxicosis or PHPT) and reduced renal function are at an increased risk of developing severe hypercalcemia [63-65]. The exact aetiology of immobilization hypercalcemia remains unknown. The loss of mechanical stress (mechanostat theory) has proven critical for bone loss [66]. An additional suggested mechanism is the acidic environment created by low blood flow that may impair mineralization of bone and increase PTH activity [67, 68]. Overall, increased osteoclastic bone resorption and decreased osteoblastic bone formation are hallmarks in the bone biopsy.

WHY OUR PATIENTS NOT REFERRED FOR SURGICAL EVALUATION?

Asban A et al. [1], identified that the bulk of patients (61%) who were not referred to a surgeon were either told that they would not benefit from an operation or never even had surgery considered as a management option. This may be due to health care providers been confused by the various guidelines related to treatment recommendations for the so-called "asymptomatic" PHPT. There may also be a mistaken sense that PHTP does not have a substantial impact on health in the absence of significant bone disease or development of kidney stones. There also appears to be a belief among some physicians that either medical management or just observing patients with PHTP is preferable to surgery. In a recently published cost-effectiveness study that compared parathyroidectomy with observation for patients with "asymptomatic" HPTP, Zanocco et al. [69], found that parathyroidectomy is a less costly and more effective treatment strategy that leads to a considerably greater quality-adjusted life expectancy. There is currently no medical management that treats the underlying parathyroid dysfunction that causes hyperparathyroidism, and it is entirely unclear whether "medical management" does more than expose patients to the side effects and costs of medication [9, 10, 35]. Another plausible reason for health care providers seen patients with PHPT and not referring them for surgical evaluation is that physicians who do not perform parathyroidectomy likely have little sense of what the operation entails or the ratio of risks and benefits [2]. This may lead them to overestimate the potential risks of surgery and to underappreciate the benefits for patients with PHTP [1, 70]. Minimally invasive parathyroidectomy has been shown to reduce operative time, decrease morbidity, and have a higher cure rate [39, 70-77].

Though not all patients with PHTP will be candidates for surgery, the ideal person to have a conversation about the risks and benefits of parathyroidectomy is a surgeon who regularly operates [1]. Recognition of this fact has prompted the American Association of Endocrine Surgeons to recommend that patients with PHPT at a minimum have the opportunity to discuss management options with a surgeon, irrespective of whether they ultimately undergo surgery [10]. This would permit all patients with HPTP to make informed decisions about their care.

WHAT ARE THE BENEFITS OF PARATHYROIDECTOMY IN PATIENTS WITH PHPT?

The contemporary treatment of symptomatic PHPT is the surgical excision of the abnormal parathyroid glands because it is the only permanent and curative treatment for the disease. There is a universal agreement that surgical treatment should be offered to all patients with symptomatic disease, as mentioned previously, more than 95% of patients with PHPT will have symptoms attributable the disease if properly interrogated [34].

Some controversy exists regarding the optimal management of asymptomatic patients, which entails the minority of cases of PHPT (less than 5% of the cases) [34]. For the minority of patients that fall into the category of asymptomatic PHPT, the Fourth International Workshop on Asymptomatic PHPT published clinical guidelines to help in the management decisions (Table 2) [9, 78].

There is increasing consensus among experts that surgery will eventually be appropriate in the vast majority of patients with asymptomatic disease because it is the only definitive therapy

[9, 79] and the only treatment that can prevent the long-term consequences of having the disease (Table 3). Large population-based studies show that patients with PHPT appear to be at risk for premature death. Most of these deaths were secondary to cardiovascular disease or cancer. This data included both symptomatic and asymptomatic patients. In a study by Leifsson et al. [80], of 33,346 patients with PHPT over 11 years, noted a 20% to 58% higher mortality often of cardiovascular disease in patients with PHPT compared to patients with normal serum calcium levels. Patients who had early surgery for parathyroid disease have improved survival when compared to patients with untreated PHPT [35, 81-84].

Individuals with PHPT have higher incidence of cardiovascular disease (2.5 to 3.0 times that of the general population) such as hypertension [85], disturbances in the renin-angiotensin-aldosterone system [86], heart failure [87, 88], arrhythmias (bradycardia, shortened QT interval, atrial fibrillation) [89, 90], stroke [91], and myocardial infarction [92], as well as structural and functional alterations in the vascular wall (such as changes in endothelial function, increased vascular stiffness leading to subtle diastolic dysfunction, left ventricular hypertrophy) [93-95], compared to patients with normal serum calcium levels. Several studies suggest that PHPT is associated with increased death rates from cardiovascular disease even in patients with mild PHPT [96-99].

Certain studies have also shown that cardiovascular risk returns to normal after a successful surgery, which is important for preventing cardiovascular disease in patients with PHPT [90, 99]. Patients with PHPT have a higher incidence of developing certain types of malignancies compared to the general population (approximately two times higher) [100-102]. The malignancies most commonly associated with PHPT are breast cancer [102-104], renal cancer [102], colorectal cancer [102, 105], endocrine tumors (adrenals, thymus, pituitary and pancreas) [100, 101], squamous cell carcinoma [102],and prostate cancer [102, 106].

Individuals with PHPT have some degree of renal dysfunction or symptoms in approximately 80% of the cases. The renal manifestations implicated with PHPT are decreased glomerular filtration rate, hypercalciuria, nephrolithiasis, nephrocalcinosis, impaired urinary concentrating ability sometimes leading to polyuria, polydipsia, and nocturia, reduced fractional phosphate reabsorption leading to hypophosphatemia, and increased urinary exertion of magnesium [44].

In the past nephrolithiasis was reported in approximately 40% to 80% of patients with PHPT [107], but now occur only in roughly 20% to 25% of the cases [108]. The pathophysiology is thought to be related to the filtered load of calcium in the glomerulus that increases proportionately with the degree of hypercalcemia [109]. The most common type of kidney stones found in patients with PHPT is composed of calcium oxalate, although slightly alkaline urine may favour the precipitation of calcium phosphate stones [109, 110].

Hypercalciuric patients are more likely to be stone formers, but less than one-third of the hypercalciuric patients with PHPT develop renal stones [110].

Hypercalciuria is not a predictor of nephrolithiasis in patients with PHPT and is no longer considered as an indication for surgery [111]. It is almost impossible to predict which patients with PHPT would develop new-onset nephrolithiasis, based on the biochemical measurements in the blood or urine (including hypercalciuria) [44, 110].

Nephrocalcinosis, which refers to renal parenchymal calcification, is identified in less than five per cent of patients with PHPT and is more likely to lead to renal dysfunction [112]. The incidence of hypertension is variable, anywhere between 30% to 50% of patients with PHPT [91, 113]. Hypertension appears to be more common in older patients and correlates with the magnitude of renal dysfunction and, in contrast to other symptoms, is least likely to improve after parathyroidectomy [91]. Another reasonable explanation of the origin of hypertension in patients with PHPT is the secretion of the hypertensive parathyroid factor that triggers an increase in blood pressure [114]. The high levels of PTH are also linked with the disruption in the renin-angiotensin-aldosterone system [115].

Bone manifestations, including osteopenia, osteoporosis, and osteitis fibrosa cystica, are found in approximately 15% of patients with PHPT [116, 117]. PHPT is linked with a reduction in bone mineral density (BMD), particularly in the cortical bone, such as in the distal third of the radius [116, 117]. In the lumbar region, composed all most exclusively by trabecular bone, and in the femoral region, composed by cortical and trabecular bone, the decrease in BMD is less severe [116-118].

Osteitis fibrosa cystica, a bone manifestation that is rarely seen today (seen in less than five percent of patients with PHPT), is caused by an increase in bone turnover and can be determined by finding an elevated serum alkaline phosphatase level [119]. The imaging findings seen in patients with PHPT with the bone disease are characterized by subperiosteal resorption (most apparent on the radial aspect of the middle phalanx of the second and third fingers), bone cysts, and tufting of the distal phalanges [120], which are best evaluated on plain x-rays of the hands. Brown or osteoclastic tumours (accumulations of osteoclasts and fibrous tissue) and bone cysts also may be present [121]. Brown tumours have a somewhat greater incidence in PHPT than in secondary HPT (3% versus 2%) [122]. In patients with chronic kidney disease, persistent and excessive urinary calcium elimination can lower serum calcium level and lead to an increase in PTH secretion. This leads to mobilization of calcium from the bones through rapid osteoclastic turnover of bone to maintain normal serum calcium levels [122]. In areas where bone loss is exceptionally fast, haemorrhage, and reparative granulation tissue, with active, vascular, proliferating fibrous tissue may replace the normal marrow contents, resulting in a brown tumour [122]. The brown colour is the result of hemosiderin (hence, the name of the lesions) [123]. The skull also may be affected and appears mottled with a loss of definition of the inner and outer cortices [123]. A normal serum alkaline phosphatase level virtually rules out clinically apparent osteitis fibrosa cystica. The bone disease is linked with the serum PTH and vitamin D levels.

Subjective neuropsychiatric manifestations have been described with PHPT since the 1940s and have been associated with a decrease in the quality of life of patients [124, 125]. Lethargy, drowsiness, anxiety, fatigue, depressed mood, neurasthenia, paranoia, hallucinations, disorientation, confusion, and cognitive (mostly memory) complaints have been documented in several studies [125-129]. The precise aetiology of these symptoms is not known, but some studies have demonstrated that levels of certain neurotransmitters (monoamine metabolites 5-hydroxy indole acetic acid and homovanillic acid) are reduced in the cerebrospinal fluid of patients with PHPT when compared to controls. Irregularities in electroencephalogram have been reported in patients with PHPT and tend to normalize following parathyroidectomy [130].

WHAT ARE THE COMPLICATIONS OF PARATHYROID SURGERY?

The complication rates of primary parathyroidectomy are extremely low, especially in expert hands [9]. While transient hypocalcemia is common (19% to 38% of the patients), the risk of permanent hypocalcemia is only 0.1% (range less than 1% to 3%) [131]. Likewise, most studies report an incidence of permanent recurrent laryngeal nerve (RLN) injury below 1%, but it can be as high as 9% in the context of re-operative surgery [132]. Approximately 1% to 6% of the patients fail to achieve a biochemical cure [70]. Invariably, surgical failure is due to a "missed" adenoma or the presence of undiagnosed multiglandular disease [70]. Some studies have inversely correlated the risk of failure with the surgeon's case-volume, highlighting the technical aspects of parathyroid surgery [132]. The capsular rupture of an adenoma can lead to parathyromatosis, a rare condition defined by the implantation of hyperfunctioning parathyroid cells in normal tissue [132]. Hungry bone syndrome, characterized by profound hypocalcemia, is seen in patients with severe PHTP and high bone turnover, rarely in the context of primary parathyroid disease [133]. The reported procedure-specific, long-term morbidity rate associated with primary parathyroidectomy is only 1% [134]. The morbidity of parathyroidectomy is higher in the re-operative setting and among the elderly, where it reaches 4% to 10% and carries a 1% mortality rate [132].

CONCLUSIONS

The majority (99.8%) of patients who have an elevated serum calcium level have a problem in one or more of their parathyroid glands. Any serum calcium concentration above 10.2 mg/dl should alert the health care provider of the possibility of PHPT. This paper is intended to contribute to the education of health care providers and patients about the importance of early diagnosis and about the more subtle complications of PHTP to create a sense of urgency for management and appropriate referral of the patient to a specialist. The only definitive and curative treatment of PHPT is an operation that can prevent all the deleterious consequences of the disease.

Competing Interests

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

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