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Review Article

Current Thinking on Primary Hyperparathyroidism

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- Management of primary hyperparathyroidism

Abstract

Primary hyperparathyroidism (PHPT) arises from an unregulated overproduction of PTH from an abnormal parathyroid gland. The majority of patients who have an elevated serum calcium level have a problem in one or more of their parathyroid glands. The only definitive and curative treatment of PHPT is an operation. More than 95% of patients with PHPT are symptomatic and only the minority is truly asymptomatic. Criteria exists for the management of the asymptomatic patient but the trend is shifting towards the surgical management of all patients with this disease independent of symptoms who have a reasonable life expectancy and suitable operative and anesthesia risk. This review paper will focus on the current thinking PHTP which is one of the most common endocrine disorders seen today.

INTRODUCTION

The overproduction of parathyroid hormone (PTH), termed hyperparathyroidism (HPT), can be categorized as primary, secondary, or tertiary. Primary hyperparathyroidism (PHPT) arises from an unregulated overproduction of PTH from an abnormal parathyroid gland. Increased PTH levels may also occur as a compensatory response to hypocalcemic states resulting from chronic renal failure or gastrointestinal (GI) malabsorption of calcium. This secondary HPT can be reversed by correction of the underlying problem (e.g., kidney transplantation for chronic renal failure). However, chronically stimulated parathyroid glands may occasionally become autonomous, resulting in persistence or recurrence of the hypercalcemia after successful renal transplantation, resulting in tertiary HPT. This review paper will focus on PHTP which is one of the most common endocrine disorders [1-3].

EPIDEMIOLOGY AND ETIOLOGY

PHPT is defined as 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 [2,3]. The most common cause of hypercalcemia in the outpatient setting is PHPT [2], with approximately 100,000 new cases per year reported in the United States [4,5]. Since the advent of routine laboratory testing, the prevalence of the disease has increased from 0.1% to 0.4% (one to seven cases per 1000 adults) [4,6-8]. In a study by Yeh et al., [8], the incidence of PHPT fluctuated between 36.3 and 120.2 cases per 100,000 women-years and 13.4 and 35.6 in 100,000 men-year. PHPT may present at any age, with the vast majority of cases occurring in patients older than 45 years of age. The mean age at diagnosis has remained between 52 and 56 years [4]. Women have consistently made up the preponderance of cases, with a female-to-male ratio of 3 to 4:1[5]. Based on a population based study from Rochester Minnesotathe higher incidence of this could be secondary (hypothetically) to estrogen deficiency after menopause that reveals underlying HPT [4]. The precise origin of PHPT is unknown, although exposure to low-dose therapeutic ionizing radiation [9,10] and familial predisposition account for some cases [11]. Irradiation for acne could have accounted for a 2 to 3-fold increase in the incidence of this disease [9] at some point in time, and a 4-fold increase was noted in survivors of the atomic bomb [10]. Schneider et al., [12], in their study of 2555 patients followed for 50 years, even low doses of radiation exposure during the teenage years was associated with a slight risk of developing PHPT. In this study a dose response was documented in people receiving external-beam radiotherapy for benign diseases before their 16th birthday [12].The latency period for the development of PHPT after radiation exposure is longer than that for the development of thyroid tumors, with most cases occurring 30 to 40 years after exposure [13]. Patients who have been radiated have similar clinical manifestations and serum calcium levels when compared to patients without a history of radiation exposure [14]. However, the former tend to have higher PTH levels and a higher incidence of concomitant thyroid neoplasms [14,15]. Certain medications have been implicated in the development of hypercalcemia. Lithium therapy has been known to shift the set point for PTH secretion in parathyroid cells, thereby resulting in elevated PTH levels and mild hypercalcemia [16]. Lithium stimulates the growth of abnormal parathyroid glands in vitro and also in susceptible patients in vivo [16]. Unusual metabolic features associated with lithium use include low urinary calcium excretion, normal

cyclic AMP excretion and lack of calcic nephrolithiasis [17]. The mechanism probably results from lithium linking with the calcium sensing receptor on the parathyroid glands resulting in PTH secretion [17].

Elevated serum calcium levels have been associated with thiazide diuretic [18].The overall annual age- and sex-adjusted (to 2000 U.S. whites) incidence was 7.7 (95% CI, 5.9 to 9.5) per 100,000 individuals [19]. The average 24-hour plasma calcium concentrations are increased with thiazide diuretic use, but the mean 24-hour PTH levels remain unchanged in subjects with normal baseline PTH levels and no evidence of hypercalciuria [20]. Thiazides diuretics have several metabolic effects that may contribute to increased calcium levels. A decrease in urine calcium excretion is the most likely cause [21-23], but in some cases diuretic use has been associates with a metabolic alkalosis that could also because an increase in total serum calcium levels through a pH-dependent increase in protein-bound calcium. Although plasma 1,25 (OH) vitamin D levels are unchanged [24], increased intestinal calcium absorption in response to thiazide diurectic use has been noted and could also contribute to an increase in serum calcium [25,26]. One last possible explanation for the elevated serum calcium levels associated with thiazide diuretic use is hemoconcentration associated with dieresis [27].

Numerous genetic abnormalities have been identified in the development of PHPT, including anomalies in tumor suppressor genes and proto-oncogenes. Specific DNA mutations in a parathyroid cell may confer a proliferative advantage over normal neighboring cells, thus allowing for clonal growth. Large populations of these altered cells containing the same mutation within hyper functioning parathyroid tissue suggest that such glands are a result of clonal expansion [28]. The majority of PHPT cases are sporadic. Nonetheless, PHPT also occurs within the spectrum of a number of inherited disorders such as multiple endocrine neoplasia syndromes (MEN), MEN type 1 (Wermer Syndrome) [29], MEN type 2A (Sipple Syndrome) [30], isolated familial HPT [31,32], and familial HPT with jaw-tumor syndrome [32]. All of these syndromes are inherited in an autosomal dominant fashion.

The earliest and most common presentation of MEN1 [29] is PHPT, and develops in approximately 80% to 100% of patients by age 40 years. These patients also are predisposed to the development of pancreatic neuroendocrine tumors and pituitary adenomas and, less frequently, to skin angiomas, lipomas, adrenocortical tumors, and neuroendocrine tumors of the thymus, bronchus, or stomach. MEN type 1 has been shown to result from a germline mutation in a tumor suppressor gene, called MEN1 gene, located on chromosome 11q12-13 that encodes Menin, a protein that is postulated to interact with the transcription factors JunD and nuclear factor-κB in the nucleus, in addition to replication protein A and other proteins [33]. Pre-symptomatic screening for mutation carriers for MEN type 1 is difficult because generally MEN1 mutations result in a nonfunctional protein and are scattered throughout the translated nine exons of the gene. MEN1 mutations also have been found in kindred's initially suspected to represent isolated familial HPT. Screening for mutation carriers for MEN type 1 has a very high detection rate, greater than 94% [34], and is used in Sweden for patients with PHPT with a first-degree relative with a major endocrine tumor, age of onset is less than 30 years and/or if multiple pancreatic tumors/parathyroid hyperplasia is detected; thus these patients should be screened for MEN1 mutations. Approximately 20% of patients with MEN type 2A (Sipple Syndrome) develop PHPT which is usually less severe. MEN type 2A is caused by a germline mutation of the RET proto-oncogene located on chromosome 10 [30]. Genotype and phenotype correlations have been noted in this syndrome in that individuals with mutations at codon 634 are more likely to develop PHPT [35]. Patients with the familial HPT with jaw-tumor syndrome have an increased predisposition to parathyroid carcinoma [36]. This syndrome maps to a tumor suppressor locus HRPT2 (parafibromin) on chromosome 1 [36-38]. Sporadic parathyroid adenomas and some hyper plastic parathyroid glands have loss of heterozygosity (LOH) at 11q13, the site of the MEN1 gene in approximately 25% to 40% of the cases [39]. Over expression of PRAD1, which encodes cyclin D1, a cell cycle control protein, is found approximately 18% of parathyroid adenomas [40,41]. This was proven to result from a rearrangement on chromosome 11 that places the PRAD1 gene under the control of the PTH promoter [42]. Other chromosomal regions deleted in parathyroid adenomas and possibly reflecting loss of tumor suppressor genes include 1p, 6q, and 15q, whereas amplified regions suggesting on co genes have been identified at 16p and 19p [11,43]. RET mutations are unusual in sporadic parathyroid tumors [44]. Sporadic parathyroid cancers are characterized by uniform loss of the tumor suppressor gene RB [45], which is involved in cell cycle regulation, and 60% have HRPT2 (CDC73) mutations [38]. These alterations are rare in benign parathyroid tumors and may have implications for diagnosis. The p53 tumor suppressor gene is also inactivated in a subset (30%) of parathyroid carcinomas [36]. Single gland adenoma is the most common cause (75-85%), lower pole adenomas (in relation to the thyroid) are more common than are upper pole adenomas [46,47]; sizes range from 1 cm to 3 cm. The normal weight of a parathyroid gland is approximately 40 to 50 mg [36], and the weight of parathyroid adenomas vary between 553.7 +/- 520.5 mg (range, 66-2536) [48]. Ectopic glands can be present (4% to 16% of cases) [49-51]. PHPT is caused by the enlargement of a single parathyroid gland or parathyroid adenoma in approximately 75% to 89% of the cases, multiple adenomas or hyperplasia in 15% to 25% of the cases, and parathyroid carcinoma as the cause of PHPT is extremely rare in most parts of the world (~1%) [2,36,52-54] of patients. Multi-gland adenoma arises in a significant number of patients, double adenomas are seen in approximately 2% to 12% of the cases, triple adenomas in less than 1% the cases, and four adenomas or parathyroid gland hyperplasia in less than 3% to 15% of the cases [2,52,54]. Most parathyroid adenomas consist of parathyroid chief cells. They are usually encapsulated and in 50% of the cases they are surrounded by normal parathyroid tissue. Some adenomas, nevertheless, are composed of oxyphil cells. These adenomas are usually larger than chief cell adenomas [54]. Parathyroid adenomas are sometimes located within the thymus and they express a parathyroid-specific gene, GCMB, Contrasting with the normal thymus, which does not neither PTH nor GCMB [55]. In a study by Ruda et al., [54], 20, 225 patients with PHPT, parathyroid hyperplasia accounted for approximately six percent of cases. In parathyroid hyperplasia all four glands are enlarged,

with the lower glands typically being larger than the upper ones. The glands are usually composed of chief cells. Clear cell hyperplasia is very rare, and is the only form in which the upper glands are larger than the lower ones.

DIAGNOSIS

Clinical manifestations

Despite what most of the literature reports, PHPT is symptomatic in more than 95% of the cases if proper attention is payed to the subtle symptoms and signs that this disease can produce due to the fluctuating calcium levels [56]. 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 [57]. At this point in time most patients present with fatigue (# 1 symptom) [58-61], general malaise [59], decrease levels of energy [58,59], anxiety, irritability leading to decrease social interaction [62], depression (10% of cases) [58], memory loss [59], decrease concentration, decrease ability to learn new things, decrease ability to complete daily tasks at home [61,63], decrease ability to complete daily tasks at work [63], decrease social interaction, insomnia [64], arthralgia's (32% of the cases) [65], myalgia's (14% to 41% of the cases) [65], bone pain [60-62], muscle weakness (specially proximal muscle groups) [60], intermittent headaches, polydipsia, polyuria [66], nocturia, nausea (24% of the cases) [67-69], anorexia (15% of the cases) [67-69], non-specific abdominal pain [68,70], heartburn (30% of the cases) [58,69,70], constipation (33% of the cases) [69], palpitations, arrhythmias (usually atrial fibrillation), elevated blood pressure, thinning of the hair (specially in women in the frontal region), and pruritus [56,71,72]. 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) [73,74] and other specific questionnaires [75]. PHPT that is truly "asymptomatic" is a rare occurrence, seen in less than five percent of patients [57,69], this is important when talking about management based on current guidelines [76]. Patients 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 [66]. Nephrolithiasis was previously reported in approximately40% to 80% of patients [77], but now occur only in about 20% to 25% of the cases [78]. The pathophysiology is thought to be related to the filtered load of calcium in the glomerulus that increases proportionately with the degree of hypocalcaemia [79]. Most renal stones in patients with PHPT are composed of calcium oxalate, although slightly alkaline urine may favor the precipitation of calcium phosphate stones [79,80]. Stone formers are more likely to be hypercalciuric, but less than one-third of the hypercalciuric patients with PHPT actually develop renal stones [80]. Hypercalciuria is not a predictor of nephrolithiasis in patients with PHPT and is no longer considered as an indication for surgery [81]. At the present time, it is almost impossible to securely foresee which patients with PHPT would develop a new onset nephrolithiasis, based on the biochemical measurements in the blood or urine (including hypercalciuria) [66,80].

Nephrocalcinosis, which refers to renal parenchymal calcification, is found in less than five percent of patients and is more likely to lead to renal dysfunction [82]. The incidence of hypertension is variable, anywhere between 30% to 50% of patients with PHPT [83-85]. 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 [84]. Another plausible explanation of the origin of hypertension in patients with PHPT is the synthesis of parathyroid hypertensive factor that triggers an increase in blood pressure [86]. The elevated levels of PTH is also linked with the disruption in the renin-angiotensin-aldosterone system [87]. Skeletal manifestations including osteopenia, osteoporosis, and osteitis fibrosacystica, are found in approximately 15% of patients with PHPT [88,89]. 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 [88,89]. 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 [88-90]. Osteitis fibrosacystica, a skeletal 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 [91]. The radiologic findings seen in patients with PHPT with bone disease are characterized by subperiosteal resorption (most obvious on the radial aspect of the middle phalanx of the second and third fingers), bone cysts, and tufting of the distal phalanges [92], which are best evaluated on plain x-rays of the hands. Brown or osteoclastic tumors (accumulations of osteoclasts and fibrous tissue) and bone cysts also may be present [93]. Brown tumors have a slightly greater incidence in PHPT than in secondary HPT (3% versus 2%) [94]. 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 results in mobilization of calcium from the bones through rapid osteoclastic turnover of bone to maintain normal serum calcium levels [94]. In regions where bone loss is exceptionallyfast, hemorrhage, and reparative granulation tissue, with active, vascular, proliferating fibrous tissue may replace the normal marrow contents, resulting in a brown tumor [94]. Hemosiderin imparts the brown color(hence the name of the lesions) [95]. The skull also may be affected and appears mottled with a loss of definition of the inner and outer cortices [95]. Patients with normal serum alkaline phosphatase levels almost never have clinically apparent osteitis fibrosacystica. Bone disease correlates with serum PTH and vitamin D levels. The most frequent gastrointestinal manifestations of PHPT are constipation, heartburn, nausea and anorexia that occur in 33%, 30%, 24% and 15% of cases, respectively [69]. A significant reduction in patient symptoms is seen after parathyroidectomy. The precise Pathophysiology is not fully known. Variations in gene expression secondary to sustained stimulation of PTH receptors may help explain some of the symptoms [96]. As a

result, gut dysmotility occurs and often leads to constipation and dyspepsia [68]. PHPT has been associated with increased incidence of malignancies, especially of the colon [97].PHPT has been associated with peptic ulcer disease [98-100]. The incidence varies between five percent to 30 % of the cases [96,100]. In animal models, elevated gastric levels have been shown to result from PTH infusion into blood vessels supplying the stomach, independent of its effects on serum calcium [99]. An increased incidence of pancreatitis has been reported in patients with PHPT [101]. PHPT as a cause of acute pancreatitis was first described by Cope et al., [102] in 1957. In retrospective series the incidence of acute pancreatitis in patients with PHPT has varied from 1% [103] to 12% [104]. In a study by Jacob et al., [105] they showed a 28-fold increase in the risk of developing pancreatitis in patients with PHPT compared to the general population. After removing all other causes, the average serum calcium level seems to be the only predictive factor for pancreatitis development [104-106]. In the diagnostic work-up of acute pancreatitis PHPT should be included in the differential diagnosis, although PHPT is found in less than one percent of individuals who present with acute pancreatitis [107]. The mechanism of origin that leads to pancreatitis seems to be related more to the hypercalcemia than to the PHPT [108,109]. Experimental studies have validated that calcium ions cause calculus deposition within the pancreatic ducts, with subsequent obstruction and inflammation [110]. Calcium can also trigger the pancreatitis cascade by promoting conversion of trypsinogen to trypsin [111-113]. Patients with PHPT also have an increased incidence of cholelithiasis [113], presumably due to PTH inhibition of gallbladder wall emptying, hepatic bile secretion and sphincter Oddi dysmotility, as well as modification of bile composition (increase in biliary calcium), which leads to the formation of calcium bilirubinate stones [113]. Subjective neuropsychiatric manifestations have been described with PHPT since the 1940s [114]. Lethargy, drowsiness, anxiety, fatigue, depressed mood, neurasthenia, paranoia, hallucinations, disorientation, confusion, and cognitive (mostly memory) complaints have been documented in a number of studies [115-119]. The exact etiology of these symptoms is not known but some studies have demonstrated that levels of certain neurotransmitters (monoamine metabolites 5-hydroxyindoleacetic acid and homovanillic acid) are reduced in the cerebrospinal fluid of patients with PHPT when compared to controls. Abnormalities in electroencephalogram have been reported in patients with PHPT and tend to normalize following parathyroidectomy [120]. Patients with PHPT may experience subtle cardiovascular manifestations, such as hypertension [121], disturbances in the renin-angiotensin–aldosterone system [122], cardiac arrhythmias (bradycardia, shortened QT interval, atrial fibrillation) [123,124], 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) [125-127]. Several studies suggest that PHPT is associated with increased death rates from cardiovascular disease even in patients with mild PHPT [128-131].

Diagnostic evaluation

The total serum calcium concentration should be used for both the initial and the subsequent serum calcium measurements. Total serum calcium concentration is an appropriate first-line biochemical test for the diagnosis of PHPT [132]. The normal serum calcium concentration varies between laboratories but it is usually between 8.6 mg/dl to 10.2 mg/dl. This reference range is obtained from a patient population that includes infants, children, adolescents, and adults who makes interpretation of the results difficult. Almost all adults live with a serum calcium concentration between 9 mg/dl to 10 mg/dl[3]. It is very unusual for an adult (over 30 years of age) to have persistent calcium levels above 10.1 mg/dl or below 9.2 mg/dl[3]. This is due to the very tight regulation by the parathyroid glands. There is a normal variability in the serum calcium concentration between different calcium results taken at different points in time but if the parathyroid glands are functioning properly the variability between different laboratory results should be minimal, usually less than 0.4 mg/dl (0.19 +/- 0.09 mg/dl variability)[3]. If the variability is equal to or above 0.4 mg/dl in the same patient, we should suspect an abnormally functioning parathyroid gland. 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 red light that the parathyroid glands are not working properly. Norman et al., [133], 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). In this study 85.6% of the patients with PHPT had a serum calcium concentration 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 the point of the variability seen in patients with PHTP with respect to the serum calcium concentration. Only four percent 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 this paragraph is very important to take into account when reviewing the up to date guidelines in the management of this disease [76]. If the serum calcium concentration is found to be elevated it should be repeated to confirm the presence of hypercalcemia or to identify the wide variability that exists in patient with PHPT. A common mistake that some physicians make when they have a patient with a serum calcium concentration that is abnormally high and another one that is normal 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. Previous values for serum calcium concentrations should be reviewed, if available, looking for this wide variability. The presence of longstanding hypocalcaemia or wide variability between different results is more suggestive of PHPT. If the laboratory is known to measure ionized calcium reliably well, some experts 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 [134]. One situation in which the serum ionized calcium concentration is an important adjunct to the diagnosis is in patients with presumed normocalcemic PHPT[3]. In order to make this diagnosis, the ionized serum calcium levels should be normal. In a series by Glendenning et al., [135], 12 out

of 60 patients in whom the diagnosis of normocalcemic PHPT was suspected a raised serum concentration of ionized calcium was found in the presence of a normal total serum calcium concentration. Either an intact PTH (second-generation PTH assay) or PTH 1-84 assays (third-generation) should be used alongside with the serum calcium level to diagnose PHPT [136]. Approximately 80% to 90% of patients with PHPT have serum PTH concentrations above the normal range for the test (10 to 65 pg/ml) [137,138]. Norman et al., [133], in a series of more than 10,000 patients with proven PHPT found that the average serum PTH concentration was 105.8 pg/ml (median 95 pg/ml, and mode 84 pg/dl). Around 10% to 20%of patients had a serum PTH values that were 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) [138]. In the study by Norman et al., [3], 16.5% of the patients kept their 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 hypocalcaemia are inappropriately high; normal subjects given intravenous calcium can suppress the serum PTH concentrations (below 10 pg/mL), and patients with non-parathyroid hypercalcemia virtually always have values below 20 to 25 pg/mL [139,140]. 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 help distinguish PHPT from BFHH, although this is an extremely rare 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, fluctuations in the PTH serum concentration can occur an should be used the help to make the diagnosis [3]. As a general rule, the higher the PTH levels the higher serum calcium levels but we should keep in mind that there is a great deal of variation between serum calcium and PTH levels, with little correlation between the average calcium level compared to the average PTH level [3]. Thus a high PTH level does not necessarily dictate high calcium level and vice versa in any individual patient. The classic patient with PHPT will have a high serum calcium (above 10.2 mg/dl) and a high serum PTH level (above 65 pg/ml) but some patients may have a very elevated serum calcium level (greater 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 (Figure 1). Obtaining measurements of vitamin D metabolites (usually 25 OH Vitamin D) may be useful to distinguish PHPT from other conditions and it can help confirm the diagnosis of PHPT[3]. The vast majority of patients with PHPT will have concomitant vitamin D deficiency. Norman et al [133], 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. In this study they also found an increase conversion of 25 OH Vitamin D to 1-25 OH Vitamin D. A vitamin D deficiency is something to expect in patients with PHPT with an average value of 22.4 ng/ml[3]. Low levels of vitamin D can help with the diagnosis of PHPT.

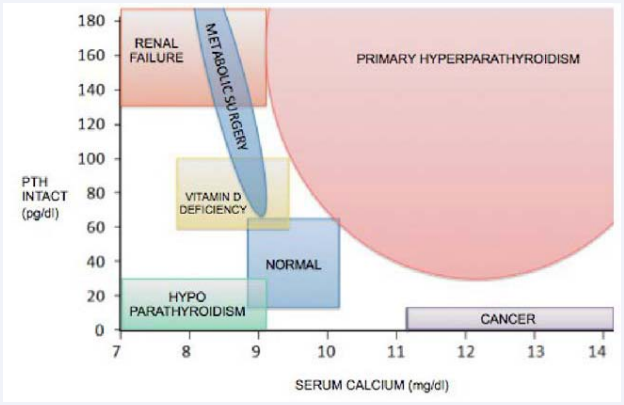

Figure 1 Differential Diagnosis of PHPT Based on Serum Calcium and PTH Levels [3].

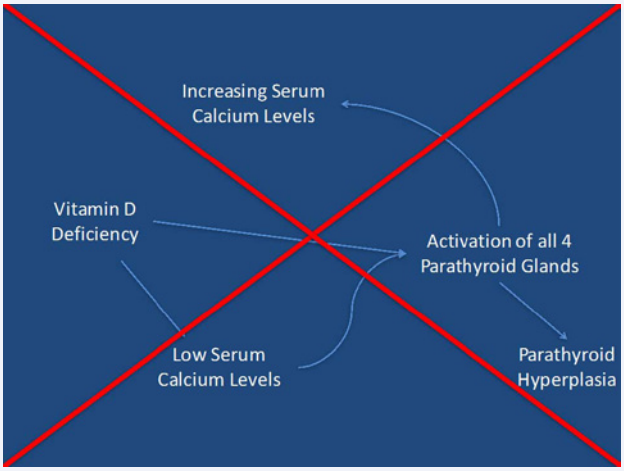

Figure 2 Erroneous Pathophysiology of Secondary Hyperparathyroidism.

Low vitamin D levels do NOT cause high levels of serum calcium. The notion that vitamin D deficiency causes a decrease in the serum calcium levels (because of a decrease intestinal absorption) and that this decrease in serum calcium concentration will lead to an activation of the parathyroid glands, with subsequent parathyroid gland hyperplasia and increase PTH secretion leading to hypocalcaemia should be rethought (Figure 2). Norman et al., [3], showed that 98% of the patients in their study who had PHPT with concomitant vitamin D deficiency had a parathyroid adenoma and only two percent had parathyroid gland hyperplasia refuting the current thinking shown in (Figure 2). Shah et al., [141], performed a meta-analysis of the world literature in 2014 and concluded Vitamin D replacement in subjects with PHPT and coexistent vitamin D deficiency increase 25 (OH) D and reduces serum PTH significantly without causing hypercalcemia and hypercalciuria but mentioned that the finding of there. Study needs to be confirmed by larger randomized control trials in patients with PHPT and coexistent vitamin D deficiency.

Twenty four-hour urinary calcium excretion is not usually required for the diagnosis of PHPT, because of the lack of

Table 1: Differential Diagnosis of Hypercalcemia [153].
Primary Hyperparathyroidism: • Single adenoma • Multiple gland adenoma (double and triple adenoma) • Multiple gland hyperplasia
Tertiary Hyperparathyroidism
Malignancy: • Parathyroid carcinoma • Multiple myeloma • Solid tumors producing PTH-related peptide: o Ovarian tumors o Lung tumors • Acute or chronic leukemia
Drugs / Medications: • Lithium • Thiazide diuretics (hydrochlorothiazide) • Vitamin A intoxication Vitamin D intoxication [155,156]
Endocrine Disorders: • Hyperthyroidism • Addisonian crisis • VIPoma
Granulomatous Disease: • Sarcoidosis • Tuberculosis • Berylliosis • Histoplasmosis
Milk-Alkali Syndrome
Chronic renal failure
Paget's Disease
Immobilization

correlation with the risk of developing renal complications. The current NIH guidelines no longer take into account the 24 hour urinary calcium excretion as criteria for surgery [76]. For patients with hypercalcemia and a PTH that is only slightly elevated or inappropriately normal given the patient's hypercalcemia, the 24-hour urinary calcium also helps to distinguish PHPT from familial benign hypocalciuric hypercalcemia (FHH) [142]. Most patients with PHPT have normal 24-hour urinary calcium excretion with only about 40% of patients been hypercalciuric [143]. An elevated urinary calcium concentration, greater than200 to 300 mg/day, essentially excludes FHH [142]. If the 24-hour urinary calcium excretion is less than 200 mg/day, PHPT with concomitant vitamin D deficiency should be suspected. Patients with PHPT whose calcium intake is extremely low may have low urinary calcium values. Approximately 75% of patients with FHH excrete less than 100 mg of calcium in urine a day [144]. 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) [142,145,146]. 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] ÷ [serum Ca x 24-hour urine Cr]. The data establishing the value of the Ca/Cr clearance ratio in differentiating FHH from PHPT are based primarily on 24-hour urine collections [142]. A 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 [142,145-147].

Approximately 50% of patients with PHPT will have decreased in their serum phosphate concentrations. Hypophosphatemia associated with PHPT is usually of moderate severity; increased urinary phosphate excretion is balanced by 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 [148]. A mild hyperchloremic metabolic acidosis may also is present in patients with PHPT, thereby leading to an elevated chloride-to-phosphate ratio (>33) [149-151]. High concentrations of PTH inhibit proximal tubular bicarbonate reabsorption, which tends to cause a mild metabolic acidosis. However, this effect is usually counterbalanced by the alkali liberated as a result of increases in bone resorption and in tubular reabsorption of bicarbonate caused by hypercalcemia [152]. Thus, metabolic acidosis is unusual in patients PHPT unless serum PTH concentrations are very high or the patient has coexistent renal insufficiency.

Differential diagnosis

The differential diagnosis of hypercalcemia is broad [153], as listed in (Table 1), but the etiology of hypercalcemia that results in a concomitantly elevated PTH level are few BFHH, 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[3]. Conversely, when considering this diagnosis, all potential causes of secondary HPT (low calcium intake, gastrointestinal disorders, renal insufficiency, and hypercalciuria of renal origin) should be excluded [154]. 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 are typically 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. PHPT and malignancy account for more than 90% of all cases of hypercalcemia. PHPT is more common in the outpatient setting, whereas malignancy is the leading cause of hypercalcemia in hospitalized patients. PHPT can virtually always be distinguished from other diseases causing hypercalcemia by a combination of history, physical examination, and appropriate laboratory investigations. It is usually 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 tumors, both solid tumors and leukemia'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 [157]. Production of humoral factors by the primary tumor, collectively known as humoral hypercalcemia of malignancy (HHM), is the mechanism responsible for 80% of the cases [158,159]. The vast majority of HHM is caused by tumor production of PTH-related protein followed by infrequent tumor 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 tumor necrosis factor and interleukin-1 appear to play a role by stimulating the differentiation of osteoclast precursors into mature osteoclasts [157].

Almost 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 in an appropriate manner 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 [154]. Patients with gastrointestinal mal absorption secondary to gastric bypass surgery [160], Celiac disease [161], Crohn disease [162], and small bowel resection will have decrease calcium absorption from the gastrointestinal tract leading to an increase in serum PTH levels secondary to parathyroid gland hyperplasia (normal response). The increase in the PTH level will cause an increase in calcium resorption from 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) [161,162]. 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 [142]. 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 [142,144,145,163].

Immobilization is a rare cause of hypercalcemia. For the diagnosis of immobilization-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 [164].Patients that immobilized with pre-existing conditions of high bone turnover (adolescents and patients with Paget's disease, thyrotoxycosis or PHPT), and / or reduced renal function are at an increased risk of developing severe hypercalcemia [165-167].The exact etiology of immobilization hypercalcemia remains unknown. The loss of mechanical stress (mechanostat theory) has proven critical for bone loss [168]. Another proposed mechanism is the acidic environment created by low blood flow that may impair mineralization of bone and increase PTH activity [169,170]. Overall, increased osteoclastic bone resorption and decreased osteoblastic bone formation are hallmarks in bone biopsy.

Diagnostic imaging

Parathyroid gland localization can be accomplished with the use of 99mTc sestamibi scans. Both thyroid and parathyroid tissues demonstrate radionuclide uptake, but sestamibi washes out of thyroid tissue early after its injection, leaving only parathyroid tissue that demonstrates activity at two to four hours [171-173]. Parathyroid localization studies are not used to confirm the diagnosis of PHPT, but rather to aid in the surgical management of the disease. The 99mTc sestamibiscan cannot be used as a confirmatory test because it is negative in more than 35% of patients with proven PHPT. In some series the sestamibi scan was negative anywhere between 65% to 81% of time [52,174]. Ultrasonography is one of the modalities used to help localize abnormal parathyroid glands but it should not be used to confirm the diagnosis of PHPT [175]. Adenomas appear as well-defined hypoechoic lesions with potential cystic or necrotic areas. Ultrasonography offers the advantage of depicting potential concomitant thyroid disease, which is present in approximately 40% of patients with parathyroid disease [176]. Studies of physician-performed ultrasound show accuracy rates that compare favorably with the accuracy of traditional radiology departments, in the vicinity of 75% to 80% [177-179]. Computed tomography scanning (CT) and magnetic resonance imaging (MRI) have also been used by some centers to help locate abnormal parathyroid glands. Classic CT scanning has a very low sensitivity. CT scanning with dynamic contrast images (4D-CT) has shown promise, with accuracy rates near 88% [180,181]. MRI can be useful, particularly in cases of recurrent or persistent disease and in ectopic locations such as the mediastinum [182]. Our experience and the experience reported by other authors [52], shows that no matter what the imaging techniques utilized, the status of all four glands cannot be known reliable preoperatively. We perform a head and neck ultrasound on all our patients with PHPT to rule out concomitant thyroid pathology and on the day of the operation we perform a 99mTc sestamibi scan.

Management of PHPT

The current management 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 [56]. Some controversy exists regarding the optimal management of asymptomatic patients, which entails the minority of cases of PHPT (less than 5% of the cases) [56]. 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 1) [76, 183]. There is growing consensus that surgery will eventually be appropriate in the vast majority of patients with asymptomatic disease because it is the only definitive therapy [76,184] and the only treatment that can prevent the long-term consequences of having the disease (Table 2). The panel emphasized the need for

the operation to be performed by skilled parathyroid surgeons who are highly experienced and skilled in the procedure [76]. Large population-based studies show that patients with PHPT appear to be at risk for premature death. Most of these deaths were due to cardiovascular disease or cancer. This data included both symptomatic and asymptomatic patients. Leifsson et al., [185], in a study of 33,346 patients with PHPT over an 11-year period, 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 have early surgery for parathyroid disease have improved survival when compared to patients with untreated PHPT [186-190]. Patients with PHPT have a higher incidence of cardiovascular disease (2.5 to 3.0 times that of the general population) such as hypertension [191], left ventricular hypertrophy [191-193], heart failure [193,194], arrhythmias [195,196], stroke [84], and myocardial infarction [197], compared to patients with normal serum calcium levels. Some studies have also shown that the cardiovascular risk returns to normal after a successful surgery which is important for preventing cardiovascular disease in patients with PHPT [131,196]. Patients with PHPT have a higher incidence of developing certain types of malignancies compared to the general population (approximately 2 times higher) [198-200]. The malignancies most commonly associated with PHPT are breast cancer [200-202], renal cancer [200], colorectal cancer [200,203], endocrine tumors (adrenals, thymus, pituitary and pancreas) [198,199], squamous cell carcinoma [200],and prostate cancer [200,204]. The classic bilateral neck exploration (BE) without localizing studies, which had a 95% success rate, was considered the standard of care for the management of PHPT. Dr. John Doppman was quoted on saying that the only localizing study necessary is to locate an experienced parathyroid surgeon [205]. Technological advances from the late 1970s and early 1990s have gradually contributed the transformation of parathyroid surgery. Parathyroid surgery now relies more on a number of localizing studies and perioperative adjuncts such as the sestamibi scan and ultrasound [206,207]. Elaboration of the rapid intraoperative PTH (IOPTH) assays has had a very strong impact on parathyroid surgery [208,209]. The surgical management of PHPT has undergone a major paradigm shift turning away from the classic BE (once considered the standard of care) to the more limited parathyroid explorations (LE). Greene et al., [210], studied the national trends in parathyroid surgery in the United States from 1998 to 2008 and found that currently 10% of surgeons practice BE, 68% practice LE, and 22% have a mixed practice. Five years ago, these percentages were, respectively, 26%, 43%, and 31%; and 10 years ago they were 74%, 11%, and 15%. The shift to LE was greatest among endocrine surgeons, high-volume surgeons (such a head and neck surgeons), and surgeons trained by mentors who practiced LE. Strict criteria must be met in order to perform a LE for the treatment of PHPT (Table 3). We believe as well as other authors that the quest for a ''mini'' unilateral parathyroid operation has gone too far [211]. Many surgeons and endocrinologists have come to believe that only patients with a localized parathyroid tumor can have a mini- parathyroid operation (or any parathyroid operation at all). They have been led to understand that exploring both sides of the neck can be dangerous and fraught with potential problems. Nearly a third of patients with PHPT are not being referred to a surgeon because the endocrinologist has not been able to localize the tumor on a scan [211]. A negative sestamibi scan delays the referral for definitive management of patients with PHPT by an average of 2.7 years [212]. Experts in the field of PHPT should remind everyone involved in the care of patients with this disease that localizing scans should not play a role in the diagnosis or treatment and, therefore, should not be used to classify surgical from nonsurgical candidates. A LE has two major benefits that cannot be denied. First, any patient who is not cured after a LE can undergo a simple, noncomplex second operation that is performed in virgin tissues. Second, the LE allows many surgeons who do not have the training in parathyroid surgery to take care of a vast number of patients without the need for referring them to a more specialized center. Physicians using the LE to treat PHPT (regardless of the adjuncts used intraoperatively) must realize that the long-term cure rate from this operation will rarely exceed 95% and that five percent of patients who are believed to be cured at the time of surgery will have a recurrence in within the next ten years [52]. Based on the available medical literature the functional status of all four parathyroid glands

Table 2: Fourth International Workshop on Asymptomatic PHPT [76].
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-scoreless than-2.5) and/or previous asymptomatic vertebral fracture (by radiograph, CT, MRI, or vertebral fracture assessment.
Twenty-four-hour urinary calcium 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.
Shorter life span
Increase risk of developing cardiovascular disease
Increase risk of developing a malignancy
Increase risk of developing bone disease
Increase risk of developing renal disease
Decrease quality of life

Table 4: Criteria for Performing a Limited Parathyroid Exploration.
Sestamibi characteristics: • Radioactive uptake by the adenoma should be different from the thyroid gland • Rest of the study should not have any abnormality
Patients great that 25 years of age
No family history of PHPT or multiple endocrine neoplasia
Absence of goiter
No history of lithium intake
No history of radiation to the neck
No history of diseases of the pancreas, adrenal gland and pituitary gland

cannot be known preoperatively no matter what the imaging modality used (and the expertise of the team performing the scans) [52,174,211,213], and no intraoperative test, short of examining all four parathyroid glands, can assure that no other abnormal parathyroid gland is present. The experience of our group, along with the first-hand experience of many others [52,179,214-216], has shown that IOPTH assays cannot be used to definitively determine the status of other parathyroid glands and therefore, cannot guarantee cure from the disease. In a study by Norman et al., [52], a total of 233 patients were referred for a second operation following the removal of one parathyroid adenoma that had a greater than 50% drop in PTH levels at 20 minutes post adenoma resection. The fall in PTH values of 50% or greater during the first operation did not prove that there were no other glands that were abnormally functioning; even patients with IOPTH levels falling greater than 90% had missed second adenomas. In 25% or more of the cases more than one parathyroid gland is removed when all four parathyroid glands are examined [52,179,214]. Our group performs a BE through a 2 cm incision using a radio-guided technique previously described in the literature [174,217]. We evaluated the functional status of each parathyroid gland and only remove the gland or glands that are hyper-functioning. Cure rates of greater than 95% have been reported with this technique [52]. Thanks to this technique we do not have to depend on intraoperative pathology making the case much shorter. One important principle is that we do not use de gamma probe as a localizing instrument, we utilize the gamma probe de determine the physiologic activity all the parathyroid glands in order to identify which one needs to be removed. Our patients due to issues with insurance companies in our country are usually discharged home the following day but outpatient surgery has been proven to be a save and cost effective alternative [218,219].

CONCLUSIONS

The vast majority (99.8 %) of patients who have an elevated serum calcium level have a problem in one or more of their parathyroid glands. More than 95% of patients with PHPT are symptomatic and only the minority is truly asymptomatic. Criteria exists for the surgical management of the asymptomatic patient but the trend is shifting towards the surgical treatment of all patients with this disease independent of symptoms who have a reasonable life expectancy and suitable operative and anesthesia risk. The only definitive and curative treatment of PHPT is an operation.

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