

Review Article

Current Thinking on Primary Hyperparathyroidism

Arrangoiz R^{1*}, Cordera F¹, Lamberton F², Luque-de-Leon E³, Muñoz-Juárez M⁴, and Moreno E⁵

¹Department of Surgery, Centro Médico ABC, Mexico

²Cermep - Imagery Du Vivant, France

³Bariatric Surgery, Mexican Institute of Social Security, Mexico

⁴Department of General Surgery, American British Cowdray Medical Center, Mexico

⁵Institute for cell Biology, University of Bern, Switzerland

***Corresponding author**

Arrangoiz R, Department of Surgery, Centro Médico ABC, Av. Carlos Graeffernández #154 Consultorio 515 Col. Tlaxcala, Delg. Cuajimalpa, México, D.F. 05300, Tel: 1103-1600 Extension 4515 a la 4517; Fax: 1664-7164; Email: rodrigo.arrangoiz@gmail.com

Submitted: 30 June 2016

Accepted: 03 August 2016

Published: 05 August 2016

Copyright

© 2016 Arrangoiz et al.

OPEN ACCESS**Keywords**

- Primary hyperparathyroidism
- Clinical manifestations of primary hyperparathyroidism
- Diagnosis and differential diagnosis of primary hyperparathyroidism
- 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 PHPT 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 PHPT 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 Minnesota the 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 associated with a metabolic alkalosis that could also be 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 diuretic 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 diuresis [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- κ B 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 hyperplastic 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 onco 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 paid 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 excretion of magnesium [66]. Nephrolithiasis was previously reported in approximately 40% 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 exceptionally fast, 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/dl³. 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/dl³. 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 PHPT 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 PHPT³. 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 and 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 PHPT³. 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

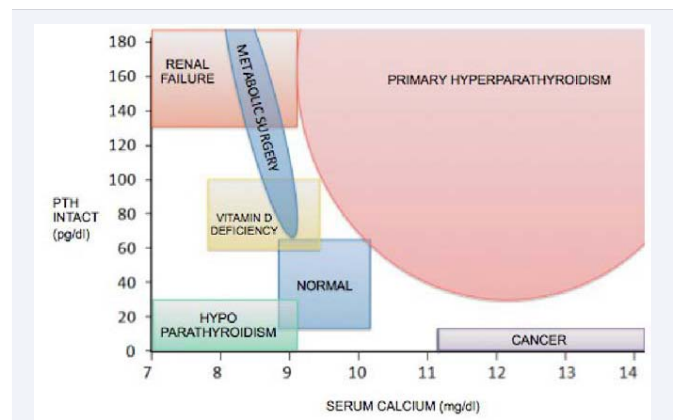


Figure 1 Differential Diagnosis of PHPT Based on Serum Calcium and PTH Levels [3].

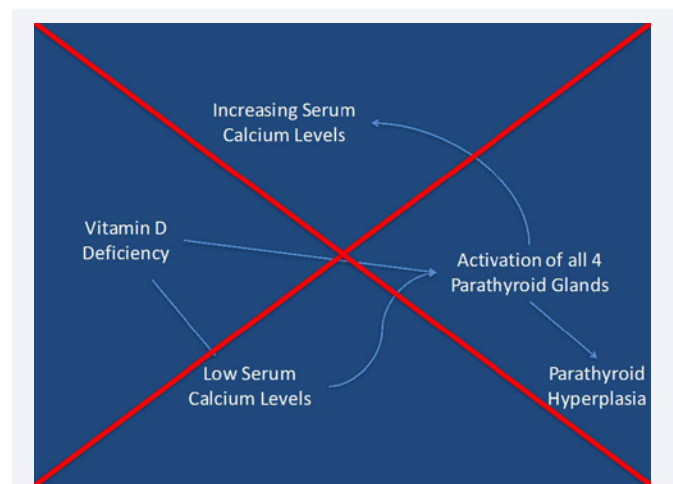


Figure 2 Erroneous Pathophysiology of Secondary Hyperparathyroidism.

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/ml³. Low levels of vitamin D can help with the diagnosis of PHPT.

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

Table 1: Differential Diagnosis of Hypercalcemia [153].
Primary Hyperparathyroidism: <ul style="list-style-type: none"> • Single adenoma • Multiple gland adenoma (double and triple adenoma) • Multiple gland hyperplasia
Tertiary Hyperparathyroidism
Malignancy: <ul style="list-style-type: none"> • Parathyroid carcinoma • Multiple myeloma • Solid tumors producing PTH-related peptide: <ul style="list-style-type: none"> ○ Ovarian tumors ○ Lung tumors • Acute or chronic leukemia
Drugs / Medications: <ul style="list-style-type: none"> • Lithium • Thiazide diuretics (hydrochlorothiazide) • Vitamin A intoxication Vitamin D intoxication [155,156]
Endocrine Disorders: <ul style="list-style-type: none"> • Hyperthyroidism • Addisonian crisis • VIPoma
Granulomatous Disease: <ul style="list-style-type: none"> • Sarcoidosis • Tuberculosis • Berylliosis • Histoplasmosis
Milk-Alkali Syndrome
Chronic renal failure
Paget's Disease
Immobilization

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 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 than 200 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: $\text{Ca/Cr clearance ratio} = \frac{[24\text{-hour urine Ca} \times \text{serum Cr}]}{[\text{serum Ca} \times 24\text{-hour urine Cr}]}$. 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 be 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 PHPT³. 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, thyrotoxicosis 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

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-score less 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 than 400 mg/d, but there are limited 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:
<ul style="list-style-type: none"> 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

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 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.

REFERENCES

1. Surgeons AAoCEaAAoE. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Position Statement on the Diagnosis and Management of Primary Hyperparathyroidism. *Endocr Pract.* 2005; 11: 50-54.
2. Fraser WD. Hyperparathyroidism. *Lancet.* 2009; 374: 145-158.
3. Norman J, Goodman A, Politz D. Calcium, parathyroid hormone, and vitamin D in patients with primary hyperparathyroidism: normograms developed from 10,000 cases. *Endocr Pract.* 2011; 17: 384-394.
4. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res.* 2006; 21: 171-177.
5. Ching BWFC. *The M.D. Anderson Surgical Oncology Handbook: Fifth Edition.* Philadelphia: Wolters Kluwer / Lippincott Williams and Wilkins. 2014.
6. Adami S, Marcocci C, Gatti D. Epidemiology of primary hyperparathyroidism in Europe. *J Bone Miner Res.* 2002; 17: 18-23.
7. Christensson T, Hellström K, Wengle B, Alverdy A, Wikland B. Prevalence of hypercalcaemia in a health screening in Stockholm. *Acta Med Scand.* 1976; 200: 131-137.
8. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab.* 2013; 98: 1122-1129.
9. Beard CM, Heath H 3rd, O'Fallon WM, Anderson JA, Earle JD, Melton LJ 3rd. Therapeutic radiation and hyperparathyroidism. A case-control study in Rochester, Minn. *Arch Intern Med.* 1989; 149: 1887-1890.
10. Fujiwara S, Spoto R, Ezaki H, Akiba S, Neriishi K, Kodama K, et al. Hyperparathyroidism among atomic bomb survivors in Hiroshima. *Radiat Res.* 1992; 130: 372-378.
11. Arnold A, Shattuck TM, Mallya SM, Krebs LJ, Costa J, Gallagher J, et al. Molecular pathogenesis of primary hyperparathyroidism. *J Bone Miner Res.* 2002; 17: 30-36.
12. Schneider AB, Gierlowski TC, Shore-Freedman E, Stovall M, Ron E, Lubin J. Dose-response relationships for radiation-induced hyperparathyroidism. *J Clin Endocrinol Metab.* 1995; 80: 254-257.
13. Stephen AE, Chen KT, Milas M, Siperstein AE. The coming of age of radiation-induced hyperparathyroidism: evolving patterns of thyroid and parathyroid disease after head and neck irradiation. *Surgery.* 2004; 136: 1143-1153.
14. Tezelman S, Rodriguez JM, Shen W, Siperstein AE, Duh QY, Clark OH. Primary hyperparathyroidism in patients who have received radiation therapy and in patients who have not received radiation therapy. *J Am Coll Surg.* 1995; 180: 81-87.
15. Kalaghchi B, Brietzke SA, Drake AJ 3rd. Effects of prior neck radiation therapy on clinical features of primary hyperparathyroidism and associated thyroid tumors. *Endocr Pract.* 2003; 9: 353-362.
16. Saunders BD, Saunders EF, Gauger PG. Lithium therapy and hyperparathyroidism: an evidence-based assessment. *World J Surg.* 2009; 33: 2314-2323.
17. Pieri-Balandraud N, Huguency P, Henry JF, Tournebise H, Dupont C. [Hyperparathyroidism induced by lithium. A new case]. *Rev Med Interne.* 2001; 22: 460-464.
18. Silverberg SB. *Clinical course of primary hyperparathyroidism.* San Diego: Academic Press. 2001.
19. Wermers RA, Kearns AE, Jenkins GD. Incidence and clinical spectrum of thiazide-associated hypercalcemia. *Am J Med.* 2007; 120: 911-915.
20. Rejnmark L, Vestergaard P, Heickendorff L, Andreasen F, Mosekilde L. Loop diuretics alter the diurnal rhythm of endogenous parathyroid hormone secretion. A randomized-controlled study on the effects of loop- and thiazide-diuretics on the diurnal rhythms of calcitropic

- hormones and biochemical bone markers in postmenopausal women. *Eur J Clin Invest.* 2001; 31: 764-772.
21. Coe FL, Canterbury J, Reiss E. Hyperparathyroidism in idiopathic hypercalciuria: primary or secondary? *Trans Assoc Am Physicians.* 1971; 84: 152-161.
 22. Brickman AS, Massry SG, Coburn JW. Changes in serum and urinary calcium during treatment with hydrochlorothiazide: studies on mechanisms. *J Clin Invest.* 1972; 51: 945-954.
 23. Middler S, Pak CY, Murad F, Bartter FC. Thiazide diuretics and calcium metabolism. *Metabolism.* 1973; 22: 139-146.
 24. Riis B, Christiansen C. Actions of thiazide on vitamin D metabolism: a controlled therapeutic trial in normal women early in the postmenopause. *Metabolism.* 1985; 34: 421-424.
 25. Jorgensen FS, Transbol I. The effect of bendroflumethiazide on the intestinal absorption of calcium in normocalcaemic renal stone formers and in hyperparathyroidism. *Acta Med Scand.* 1974; 195: 33-36.
 26. Bazzini C, Vezzoli V, Sironi C, Dossena S, Ravasio A, De Biasi S, et al. Thiazide-sensitive NaCl-cotransporter in the intestine: possible role of hydrochlorothiazide in the intestinal Ca²⁺ uptake. *J Biol Chem.* 2005; 280: 19902-19910.
 27. Heath H 3rd. Postural and venous stasis-induced changes in total calcium. *Mayo Clin Proc.* 2005; 80: 1101.
 28. Arnold A, Staunton CE, Kim HG, Gaz RD, Kronenberg HM. Monoclonality and abnormal parathyroid hormone genes in parathyroid adenomas. *N Engl J Med.* 1988; 318: 658-662.
 29. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. *J Clin Endocrinol Metab.* 2012; 97: 2990-3011.
 30. Calmettes C, Ponder BA, Fischer JA, Raue F. Early diagnosis of the multiple endocrine neoplasia type 2 syndrome: consensus statement. European Community Concerted Action: Medullary Thyroid Carcinoma. *Eur J Clin Invest.* 1992; 22: 755-760.
 31. Hannan FM, Nesbit MA, Christie PT, Fratter C, Dudley NE, Sadler GP, et al. Familial isolated primary hyperparathyroidism caused by mutations of the MEN1 gene. *Nat Clin Pract Endocrinol Metab.* 2008; 4: 53-58.
 32. Simonds WF, Robbins CM, Agarwal SK, Hendy GN, Carpten JD, Marx SJ. Familial isolated hyperparathyroidism is rarely caused by germline mutation in HRPT2, the gene for the hyperparathyroidism-jaw tumor syndrome. *J Clin Endocrinol Metab.* 2004; 89: 96-102.
 33. Balogh K, Rácz K, Patócs A, Hunyady L. Menin and its interacting proteins: elucidation of menin function. *Trends Endocrinol Metab.* 2006; 17: 357-364.
 34. Tham E, Grandell U, Lindgren E, Toss G, Skogseid B, Nordenskjöld M. Clinical testing for mutations in the MEN1 gene in Sweden: a report on 200 unrelated cases. *J Clin Endocrinol Metab.* 2007; 92: 3389-3395.
 35. Schuffenecker I, Virally-Monod M, Brohet R, Goldgar D, Conte-Devolx B, Leclerc L, et al. Risk and penetrance of primary hyperparathyroidism in multiple endocrine neoplasia type 2A families with mutations at codon 634 of the RET proto-oncogene. *Groupe D'etude des Tumeurs a Calcitonine. J Clin Endocrinol Metab.* 1998; 83: 487-491.
 36. Arrangoiz RaR, J. A. Parathyroid Carcinoma, in *Textbook of Uncommon Cancer.* NJ, USA. John Wiley & Sons, Inc, Hoboken. 2012.
 37. Haven CJ, van Puijenbroek M, Tan MH, Teh BT, Fleuren GJ, van Wezel T, et al. Identification of MEN1 and HRPT2 somatic mutations in paraffin-embedded (sporadic) parathyroid carcinomas. *Clin Endocrinol (Oxf).* 2007; 67: 370-376.
 38. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. *Nat Genet.* 2002; 32: 676-680.
 39. Agarwal SK, Kester MB, Debelenko LV, Heppner C, Emmert-Buck MR, Skarulis MC, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet.* 1997; 6: 1169-1175.
 40. Hsi ED, Zukerberg LR, Yang WJ, Arnold A. Cyclin D1/PRAD1 expression in parathyroid adenomas: an immunohistochemical study. *J Clin Endocrinol Metab.* 1996; 81: 1736-1739.
 41. Arnold A, Motokura T, Bloom T, Rosenberg C, Bale A, Kronenberg H, et al. PRAD1 (cyclin D1): a parathyroid neoplasia gene on 11q13. *Henry Ford Hosp Med J.* 1992; 40: 177-180.
 42. Imanishi Y, Hosokawa Y, Yoshimoto K, Schipani E, Mallya S, Papanikolaou A, et al. Primary hyperparathyroidism caused by parathyroid-targeted overexpression of cyclin D1 in transgenic mice. *J Clin Invest.* 2001; 107: 1093-1102.
 43. Agarwal SK, Schröck E, Kester MB, Burns AL, Heffess CS, Ried T, et al. Comparative genomic hybridization analysis of human parathyroid tumors. *Cancer Genet Cytogenet.* 1998; 106: 30-36.
 44. Uchino S, Noguchi S, Nagatomo M, Sato M, Yamashita H, Yamashita H, et al. Absence of somatic RET gene mutation in sporadic parathyroid tumors and hyperplasia secondary to uremia, and absence of somatic Men1 gene mutation in MEN2A-associated hyperplasia. *Biomed Pharmacother.* 2000; 54: 100-103.
 45. Cryns VL, Thor A, Xu HJ, Hu SX, Wierman ME, Vickery AL Jr, et al. Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. *N Engl J Med.* 1994; 330: 757-761.
 46. Marzouki HZ, Chavannes M, Tamilia M, Hier MP, Black MJ, Levental M, et al. Location of parathyroid adenomas: 7-year experience. *J Otolaryngol Head Neck Surg.* 2010; 39: 551-554.
 47. Yazıcı P, Demir U, Bozdağ E, Bozkurt E, Işıl G, Bostancı Ö, et al. What is the effect of treatment modality on red blood cell distribution width in patients with acute cholecystitis? *Ulus Cerrahi Derg.* 2015; 31: 1-4.
 48. Yao K, Singer FR, Roth SI, Sassoon A, Ye C, Giuliano AE. Weight of normal parathyroid glands in patients with parathyroid adenomas. *J Clin Endocrinol Metab.* 2004; 89: 3208-3213.
 49. Hooghe L, Kinnaert P, Van Geertruyden J. Surgical anatomy of hyperparathyroidism. *Acta Chir Belg.* 1992; 92: 1-9.
 50. Vail AD, Coller FC. The parathyroid glands: clinicopathologic correlation of parathyroid disease as found in 200 unselected autopsies. *Mo Med.* 1967; 64: 234-238.
 51. Peeler BB, Martin WH, Sandler MP, Goldstein RE. Sestamibi parathyroid scanning and preoperative localization studies for patients with recurrent/persistent hyperparathyroidism or significant comorbid conditions: development of an optimal localization strategy. *Am Surg.* 1997; 63: 37-46.
 52. Norman J, Lopez J, Politz D. Abandoning unilateral parathyroidectomy: why we reversed our position after 15,000 parathyroid operations. *J Am Coll Surg.* 2012; 214: 260-269.
 53. Bartsch D, Nies C, Hasse C, Willuhn J, Rothmund M. Clinical and surgical aspects of double adenoma in patients with primary hyperparathyroidism. *Br J Surg.* 1995; 82: 926-929.
 54. Ruda JM, Hollenbeak CS, Stack BC Jr. *Otolaryngol Head Neck Surg.* 2005; 132: 359-372.
 55. Maret A, Bourdeau I, Ding C, Kadkol SS, Westra WH, Levine MA. Expression of GCMB by intrathyroid parathyroid hormone-secreting

- adenomas indicates their parathyroid cell origin. *J Clin Endocrinol Metab.* 2004; 89: 8-12.
56. Perrier ND. Asymptomatic hyperparathyroidism: a medical misnomer? *Surgery.* 2005; 137: 127-131.
 57. Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. *N Engl J Med.* 2004; 350: 1746-1751.
 58. Wilhelm SM, Lee J, Prinz RA. Major depression due to primary hyperparathyroidism: a frequent and correctable disorder. *Am Surg.* 2004; 70: 175-179.
 59. Walker MD, McMahon DJ, Inabnet WB, Lazar RM, Brown I, Vardy S, et al. Neuropsychological features in primary hyperparathyroidism: a prospective study. *J Clin Endocrinol Metab.* 2009; 94: 1951-1958.
 60. Pasięka JL, Parsons LL. Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. *World J Surg.* 1998; 22: 513-519.
 61. Sheldon DG, Lee FT, Neil NJ, Ryan JA Jr. Surgical treatment of hyperparathyroidism improves health-related quality of life. *Arch Surg.* 2002; 137: 1022-1026.
 62. Okamoto T, Kamo T, Obara T. Outcome study of psychological distress and nonspecific symptoms in patients with mild primary hyperparathyroidism. *Arch Surg.* 2002; 137: 779-783.
 63. Lundgren E, Szabo E, Ljunghall S, Bergström R, Holmberg L, Rastad J. Population based case-control study of sick leave in postmenopausal women before diagnosis of hyperparathyroidism. *BMJ.* 1998; 317: 848-851.
 64. Joborn C, Hetta J, Johansson H, Rastad J, Agren H, Akerström G, et al. Psychiatric morbidity in primary hyperparathyroidism. *World J Surg.* 1988; 12: 476-481.
 65. Helliwell M. [Rheumatic symptoms in primary hyperparathyroidism]. *Postgrad Med J.* 1983; 59: 236-240.
 66. Peacock M. Primary hyperparathyroidism and the kidney: biochemical and clinical spectrum. *J Bone Miner Res.* 2002; 17: 87-94.
 67. Gasparoni P, Caroli A, Sardeo G, Maschio S, Lo Giudice C, Fioretti D. [Primary hyperparathyroidism and peptic ulcer]. *Minerva Med.* 1989; 80: 1327-1330.
 68. Gardner EC Jr, Hersh T. Primary hyperparathyroidism and the gastrointestinal tract. *South Med J.* 1981; 74: 197-199.
 69. Chan AK, Duh QY, Katz MH. Clinical manifestations of primary hyperparathyroidism before and after parathyroidectomy. A case-control study. *Ann Surg.* 1995; 222: 402-414.
 70. Reiher AE, Mazeh H, Schaefer S, Gould J, Chen H, Sippel RS. Symptoms of gastroesophageal reflux disease improve after parathyroidectomy. *Surgery.* 2012; 152: 1232-1237.
 71. Bargren AE, Replinger D, Chen H. Can biochemical abnormalities predict symptomatology in patients with primary hyperparathyroidism? *J Am Coll Surg.* 2011; 213: 410-414.
 72. Eigelberger MS, Cheah WK, Ituarte PH, Streja L, Duh QY, Clark OH. The NIH criteria for parathyroidectomy in asymptomatic primary hyperparathyroidism: are they too limited? *Ann Surg.* 2004; 239: 528-535.
 73. Burney RE, Jones KR, Christy B. Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. *Surgery.* 1999; 125: 608-614.
 74. Talpos GB, Bone HG 3rd, Kleerekoper M, Phillips ER, Alam M, Honasoge M, et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. *Surgery.* 2000; 128: 1013-1020
 75. Prager G, Kalaschek A, Kaczirek K, Passler C, Scheuba C, Sonneck G, et al. Parathyroidectomy improves concentration and retentiveness in patients with primary hyperparathyroidism. *Surgery.* 2002; 132: 930-935.
 76. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014; 99: 3561-3569.
 77. Pak CY, Nicar MJ, Peterson R, Zerwekh JE, Snyder W. A lack of unique pathophysiologic background for nephrolithiasis of primary hyperparathyroidism. *J Clin Endocrinol Metab.* 1981; 53: 536-542.
 78. Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. *J Intern Med.* 2005; 257: 6-17.
 79. Frokjaer VG, Mollerup CL. Primary hyperparathyroidism: renal calcium excretion in patients with and without renal stone disease before and after parathyroidectomy. *World J Surg.* 2002; 26: 532-535.
 80. Corbetta S, Baccarelli A, Aroldi A, Vicentini L, Fogazzi GB, Eller-Vainicher C, et al. Risk factors associated to kidney stones in primary hyperparathyroidism. *J Endocrinol Invest.* 2005; 28: 122-128.
 81. Silverberg SJ, Lewiecki EM, Mosekilde L, Peacock M, Rubin MR. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab.* 2009; 94: 351-365.
 82. Monk RD BD. Nephrolithiasis and nephrocalcinosis. *Comprehensive Clinical Nephrology*: 2nd edition. Mosby. 2003.
 83. Rosenthal FD, Roy S. Hypertension and hyperparathyroidism. *Br Med J.* 1972; 4: 396-397.
 84. Walker MD, Fleischer J, Rundek T, McMahon DJ, Homma S, Sacco R, et al. Carotid vascular abnormalities in primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2009; 94: 3849-3856.
 85. Rubin MR, Maurer MS, McMahon DJ, Bilezikian JP, Silverberg SJ. Arterial stiffness in mild primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2005; 90: 3326-3330.
 86. Lewanczuk RZ, Pang PK. Expression of parathyroid hypertensive factor in hypertensive primary hyperparathyroid patients. *Blood Press.* 1993; 2: 22-27.
 87. Gennari C, Nami R, Gonnelli S. Hypertension and primary hyperparathyroidism: the role of adrenergic and renin-angiotensin-aldosterone systems. *Miner Electrolyte Metab.* 1995; 21: 77-81.
 88. Seeman E, Wahner HW, Offord KP, Kumar R, Johnson WJ, Riggs BL. Differential effects of endocrine dysfunction on the axial and the appendicular skeleton. *J Clin Invest.* 1982; 69: 1302-1309.
 89. Larsson K, Lindh E, Lind L, Persson I, Ljunghall S. Increased fracture risk in hypercalcemia. Bone mineral content measured in hyperparathyroidism. *Acta Orthop Scand.* 1989; 60: 268-270.
 90. Silverberg SJ, Shane E, de la Cruz L, Dempster DW, Feldman F, Seldin D, et al. Skeletal disease in primary hyperparathyroidism. *J Bone Miner Res.* 1989; 4: 283-291.
 91. Agarwal G, Mishra SK, Kar DK, Singh AK, Arya V, Gupta SK, et al. Recovery pattern of patients with osteitis fibrosa cystica in primary hyperparathyroidism after successful parathyroidectomy. *Surgery.* 2002; 132: 1075-1083.

92. Hayes CW, Conway WF. Hyperparathyroidism. *Radiol Clin North Am*. 1991; 29: 85-96.
93. DG G. Metabolic bone diseases in *Musculoskeletal Radiology*: Mosby 2002.
94. Chew FS, Huang-Hellinger F. Brown tumor. *AJR Am J Roentgenol*. 1993; 160: 752.
95. Khan A, Bilezikian J. Primary hyperparathyroidism: pathophysiology and impact on bone. *CMAJ*. 2000; 163: 184-187.
96. Ellis C, Nicoloff DM. Hyperparathyroidism and peptic ulcer disease. *Arch Surg*. 1968; 96: 114-118.
97. Sharma S, Longo WE, Baniadam B. Colorectal manifestations of endocrine disease. *Dis Colon Rectum*. 1995; 38: 318-323.
98. Efremidou EI, Liratzopoulos N, Papageorgiou MS. Peptic ulcer perforation as the first manifestation of previously unknown primary hyperparathyroidism. *Case Rep Gastroenterol*. 2007; 1: 21-26.
99. Wise SR, Quigley M, Saxe AW, Zdon MJ. Hyperparathyroidism and cellular mechanisms of gastric acid secretion. *Surgery*. 1990; 108: 1058-1063.
100. Ellison EH, Abrams JS, Smith DJ. A postmortem analysis of 812 gastroduodenal ulcers found in 20,000 consecutive autopsies, with emphasis on associated endocrine disease. *Am J Surg*. 1959; 97: 17-30.
101. Banks PA, Freeman ML. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006; 101: 2379-2400.
102. Cope O, Culver PJ, Mixer CG. Pancreatitis, a diagnostic clue to hyperparathyroidism. *Ann Surg*. 1957; 145: 857-863.
103. Bess MA, Edis AJ, van Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association? *JAMA*. 1980; 243: 246-247.
104. Carnaille B, Oudar C, Pattou F, Combemale F, Rocha J, Proye C. Pancreatitis and primary hyperparathyroidism: forty cases. *Aust N Z J Surg*. 1998; 68: 117-119.
105. Jacob JJ, John M, Thomas N, Chacko A, Cherian R, Selvan B, et al. Does hyperparathyroidism cause pancreatitis? A South Indian experience and a review of published work. *ANZ J Surg*. 2006; 76: 740-744.
106. Curto C, Caillard C, Desurmont T, Sebag F, Brunaud L, Kraimps JL, et al. [Acute pancreatitis and primary hyperparathyroidism: a multicentric study by the Francophone Association of Endocrine Surgeons]. *J Chir (Paris)*. 2009; 146: 270-274.
107. Prinz RA, Aranha GV. The association of primary hyperparathyroidism and pancreatitis. *Am Surg*. 1985; 51: 325-329.
108. Gafter U, Mandel EM, Har-Zahav L, Weiss S. Acute pancreatitis secondary to hypercalcemia. Occurrence in a patient with breast carcinoma. *JAMA*. 1976; 235: 2004-2005.
109. Hochgelerent EL, David DS. Acute pancreatitis secondary to calcium infusion in a dialysis patient. *Arch Surg*. 1974; 108: 218-219.
110. Ward JB, Petersen OH, Jenkins SA. Is an elevated concentration of acinar cytosolic free ionised calcium the trigger for acute pancreatitis? *Lancet*. 1995; 346: 1016-1019.
111. Mithöfer K, Fernández-del Castillo C, Frick TW, Lewandrowski KB, Rattner DW, Warshaw AL. Acute hypercalcemia causes acute pancreatitis and ectopic trypsinogen activation in the rat. *Gastroenterology*. 1995; 109: 239-246.
112. Frick TW, Fernández-del Castillo C, Bimmler D, Warshaw AL. Elevated calcium and activation of trypsinogen in rat pancreatic acini. *Gut*. 1997; 41: 339-343.
113. Broulik PD, Haas T, Adámek S. Analysis of 645 patients with primary hyperparathyroidism with special references to cholelithiasis. *Intern Med*. 2005; 44: 917-921.
114. Nielsen H. Familial occurrence, gastro-intestinal symptoms and mental disturbances in hyperparathyroidism. *Acta Med Scand*. 1955; 151: 359-366.
115. Fitz TE, Hallman BL. Mental changes associated with hyperparathyroidism; report of two cases. *AMA Arch Intern Med*. 1952; 89: 547-551.
116. Reinfrank RF. Primary hyperparathyroidism with depression. *Arch Intern Med*. 1961; 108: 606-610.
117. Agras S, Oliveau DC. Primary Hyperparathyroidism and Psychosis. *Can Med Assoc J*. 1964; 91: 1366-1367.
118. Flanagan TA, Goodwin DW, Alderson P. Psychiatric illness in a large family with familial hyperparathyroidism. *Br J Psychiatry*. 1970; 117: 693-698.
119. Gatewood JW, Organ CH Jr, Mead BT. Mental changes associated with hyperparathyroidism. *Am J Psychiatry*. 1975; 132: 129-132.
120. Cogan MG, Covey CM, Arief AI, Wisniewski A, Clark OH, Lazarowitz V, et al. Central nervous system manifestations of hyperparathyroidism. *Am J Med*. 1978; 65: 963-970.
121. Lafferty FW. Primary hyperparathyroidism. Changing clinical spectrum, prevalence of hypertension, and discriminant analysis of laboratory tests. *Arch Intern Med*. 1981; 141: 1761-1766.
122. Kovács L, Góth MI, Szabolcs I, Dohán O, Ferencz A, Szilágyi G. The effect of surgical treatment on secondary hyperaldosteronism and relative hyperinsulinemia in primary hyperparathyroidism. *Eur J Endocrinol*. 1998; 138: 543-547.
123. Rayner HC, Hasking DJ. Hyperparathyroidism associated with severe hypercalcaemia and myocardial calcification despite minimal bone disease. *Br Med J (Clin Res Ed)*. 1986; 293: 1277-1278.
124. Stefanelli T, Wikman-Coffelt J, Wu ST, Parmley WW. Calcium-dependent fluorescence transients during ventricular fibrillation. *Am Heart J*. 1990; 120: 590-597.
125. Nuzzo V, Tauchmanová L, Fonderico F, Trotta R, Fittipaldi MR, Fontana D, et al. Increased intima-media thickness of the carotid artery wall, normal blood pressure profile and normal left ventricular mass in subjects with primary hyperparathyroidism. *Eur J Endocrinol*. 2002; 147: 453-459.
126. Bukoski RD, Ishibashi K, Bian K. Vascular actions of the calcium-regulating hormones. *Semin Nephrol*. 1995; 15: 536-549.
127. Isales CM, Sumpio B, Bollag RJ, Zhong Q, Ding KH, Du W, et al. Functional parathyroid hormone receptors are present in an umbilical vein endothelial cell line. *Am J Physiol Endocrinol Metab*. 2000; 279: 654-662.
128. Lundgren E, Lind L, Palmér M, Jakobsson S, Ljunghall S, Rastad J. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. *Surgery*. 2001; 130: 978-985.
129. Palmer M, Adami HO, Bergström R, Jakobsson S, Akerström G, Ljunghall S. Survival and renal function in untreated hypercalcaemia. Population-based cohort study with 14 years of follow-up. *Lancet*. 1987; 1: 59-62.
130. Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, O'Fallon WM, et al. Survival after the diagnosis of hyperparathyroidism: a population-based study. *Am J Med*. 1998; 104: 115-122.
131. Vestergaard P, Mollerup CL, Frøkjær VG, Christiansen P, Blichert-

- Toft M, Mosekilde L. Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg.* 2003; 27: 216-222.
132. Tee MC, Holmes DT, Wiseman SM. Ionized vs serum calcium in the diagnosis and management of primary hyperparathyroidism: which is superior? *Am J Surg.* 2013; 205: 591-596.
 133. Norman J. Increased calcium intake may reduce risk of primary hyperparathyroidism. *BMJ.* 2012; 345.
 134. Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. *J Clin Endocrinol Metab.* 1996; 81: 2036-2040.
 135. Glendenning P, Gutteridge DH, Retallack RW, Stuckey BG, Kermod DG, Kent GN. High prevalence of normal total calcium and intact PTH in 60 patients with proven primary hyperparathyroidism: a challenge to current diagnostic criteria. *Aust N Z J Med.* 1998; 28: 173-178.
 136. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014; 99: 3570-3579.
 137. Endres DB, Villanueva R, Sharp CF Jr, Singer FR. Immunochemiluminometric and immunoradiometric determinations of intact and total immunoreactive parathyrin: performance in the differential diagnosis of hypercalcemia and hypoparathyroidism. *Clin Chem.* 1991; 37: 162-168.
 138. Nussbaum SR, Zahradnik RJ, Lavigne JR, Brennan GL, Nozawa-Ung K, Kim LY, et al. Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. *Clin Chem.* 1987; 33: 1364-1367.
 139. Fuleihan GE, Gundberg CM, Gleason R, Brown EM, Stromski ME, Grant FD, et al. *J Clin Endocrinol Metab.* 1994; 79: 1642-1647.
 140. Grant FD, Conlin PR, Brown EM. Rate and concentration dependence of parathyroid hormone dynamics during stepwise changes in serum ionized calcium in normal humans. *J Clin Endocrinol Metab.* 1990; 71: 370-378.
 141. Shah VN, Shah CS, Bhadada SK, Rao DS. Effect of 25 (OH) D replacements in patients with primary hyperparathyroidism (PHPT) and coexistent vitamin D deficiency on serum 25(OH) D, calcium and PTH levels: a meta-analysis and review of literature. *Clin Endocrinol (Oxf).* 2014; 80: 797-803.
 142. Fuleihan Gel-H. Familial benign hypocalciuric hypercalcemia. *J Bone Miner Res.* 2002; 17: 51-56.
 143. Silverberg SJ, Shane E, Jacobs TP, Siris ES, Gartenberg F, Seldin D, et al. Nephrolithiasis and bone involvement in primary hyperparathyroidism. *Am J Med.* 1990; 89: 327-334.
 144. El-Hajj Fuleihan G BE. Familial Hypocalciuric Hypercalcemia and Neonatal Severe Hyperparathyroidism. In: *The Parathyroids*, 3rd edition. London: Elsevier. 2014.
 145. Marx SJ, Stock JL, Attie MF, Downs RW Jr, Gardner DG, Brown EM, et al. Familial hypocalciuric hypercalcemia: recognition among patients referred after unsuccessful parathyroid exploration. *Ann Intern Med.* 1980; 92: 351-356.
 146. Marx SJ. Letter to the editor: Distinguishing typical primary hyperparathyroidism from familial hypocalciuric hypercalcemia by using an index of urinary calcium. *J Clin Endocrinol Metab.* 2015; 100: 29-30.
 147. Christensen SE, Nissen PH, Vestergaard P, Heickendorff L, Brixen K, Mosekilde L. Discriminative power of three indices of renal calcium excretion for the distinction between familial hypocalciuric hypercalcemia and primary hyperparathyroidism: a follow-up study on methods. *Clin Endocrinol (Oxf).* 2008; 69: 713-720.
 148. JP K. Clinical and physiologic phosphate disturbances. In *The Kidney Physiology and Pathophysiology*. Philadelphia: Lippincott, Williams and Wilkins. 2000.
 149. Boughey JC, Ewart CJ, Yost MJ, Nottingham JM, Brown JJ. Chloride/phosphate ratio in primary hyperparathyroidism. *Am Surg.* 2004; 70: 25-28.
 150. Broulík PD, Pacovský V. The chloride phosphate ratio as the screening test for primary hyperparathyroidism. *Horm Metab Res.* 1979; 11: 577-579.
 151. Higashi K, Morita M, Tajiri J, Sato T, Okazaki K, Arai S. Clinical usefulness of the (chloride-90)/phosphate ratio for distinguishing primary hyperparathyroidism from hypercalcemia due to other causes. *Endocrinol Jpn.* 1985; 32: 421-426.
 152. Hulter HN, Peterson JC. Acid-base homeostasis during chronic PTH excess in humans. *Kidney Int.* 1985; 28: 187-192.
 153. E. S. Hypercalcemia: pathogenesis, clinical manifestations, differential diagnosis, and management. In: Favus MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. Philadelphia: Lippincott, Williams & Wilkins. 1999.
 154. Felsenfeld AJ. Considerations for the treatment of secondary hyperparathyroidism in renal failure. *J Am Soc Nephrol.* 1997; 8: 993-1004.
 155. Koul PA, Ahmad SH, Ahmad F, Jan RA, Shah SU, Khan UH. Vitamin d toxicity in adults: a case series from an area with endemic hypovitaminosis d. *Oman Med J.* 2011; 26: 201-204.
 156. Ragavan VV, Smith JE, Bilezikian JP. Vitamin A toxicity and hypercalcemia. *Am J Med Sci.* 1982; 283: 161-164.
 157. Clines GA. Mechanisms and treatment of hypercalcemia of malignancy. *Curr Opin Endocrinol Diabetes Obes.* 2011; 18: 339-346.
 158. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* 2005; 352: 373-379.
 159. Mirrakhimov AE. Hypercalcemia of Malignancy: An Update on Pathogenesis and Management. *N Am J Med Sci.* 2015; 7: 483-493.
 160. Sinha N, Shieh A, Stein EM, Strain G, Schulman A, Pomp A, et al. Increased PTH and 1.25(OH)(2)D levels associated with increased markers of bone turnover following bariatric surgery. *Obesity (Silver Spring).* 2011; 19: 2388-2393.
 161. Lemieux B, Boivin M, Brossard JH, Lepage R, Picard D, Rousseau L, et al. Normal parathyroid function with decreased bone mineral density in treated celiac disease. *Can J Gastroenterol.* 2001; 15: 302-307.
 162. Prosnitz AR, Leonard MB, Shults J, Zemel BS, Hollis BW, Denson LA, et al. Changes in vitamin D and parathyroid hormone metabolism in incident pediatric Crohn's disease. *Inflamm Bowel Dis.* 2013; 19: 45-53.
 163. Nissen PH, Christensen SE, Heickendorff L, Brixen K, Mosekilde L. Molecular genetic analysis of the calcium sensing receptor gene in patients clinically suspected to have familial hypocalciuric hypercalcemia: phenotypic variation and mutation spectrum in a Danish population. *J Clin Endocrinol Metab.* 2007; 92: 4373-4379.
 164. Tori JA, Hill LL. Hypercalcemia in children with spinal cord injury. *Arch Phys Med Rehabil.* 1978; 59: 443-446.
 165. Meythaler JM, Korkor AB, Nanda T, Kumar NA, Fallon M. Immobilization hypercalcemia associated with Landry-Guillain-

- Barre syndrome. Successful therapy with combined calcitonin and etidronate. *Arch Intern Med.* 1986; 146: 1567-1571.
166. Massagli TL, Cardenas DD. Immobilization hypercalcemia treatment with pamidronate disodium after spinal cord injury. *Arch Phys Med Rehabil.* 1999; 80: 998-1000.
 167. Gopal H, Sklar AH, Sherrard DJ. Symptomatic hypercalcemia of immobilization in a patient with end-stage renal disease. *Am J Kidney Dis.* 2000; 35: 969-972.
 168. Bikle DD, Halloran BP. The response of bone to unloading. *J Bone Miner Metab.* 1999; 17: 233-244.
 169. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. *Am J Physiol.* 1992; 262: 442-448.
 170. Raisz IG. Bone Resorption in Tissue Culture. Factors Influencing the Response to Parathyroid Hormone
 171. *J Clin Invest.* 1965; 44: 103-116.
 172. Martínez-Rodríguez I, Martínez-Amador N, de Arcocha-Torres M, Quirce R, Ortega-Nava F, Ibáñez-Bravo S, et al. Comparison of 99mTc-sestamibi and 11C-methionine PET/CT in the localization of parathyroid adenomas in primary hyperparathyroidism. *Rev Esp Med Nucl Imagen Mol.* 2014; 33: 93-98.
 173. Shafiei B, Hoseinzadeh S, Fotouhi F, Malek H, Azizi F, Jahed A. et al. Preoperative 99mTc-sestamibi scintigraphy in patients with primary hyperparathyroidism and concomitant nodular goiter: comparison of SPECT-CT, SPECT, and planar imaging. *Nucl Med Commun.* 2012; 33: 1070-1076.
 174. Griffith B, Chaudhary H, Mahmood G. Accuracy of 2-Phase Parathyroid CT for the Preoperative Localization of Parathyroid Adenomas in Primary Hyperparathyroidism. *AJNR Am J Neuroradiol.* 2015; 36: 2373-2379.
 175. Norman J, Politz D. 5,000 parathyroid operations without frozen section or PTH assays: measuring individual parathyroid gland hormone production in real time. *Ann Surg Oncol.* 2009; 16: 656-666.
 176. Tee MC, Chan SK, Nguyen V, Strugnell SS, Yang J, Jones S, et al. Incremental value and clinical impact of neck sonography for primary hyperparathyroidism: a risk-adjusted analysis. *Can J Surg.* 2013; 56: 325-331.
 177. Bentrem DJ, Angelos P, Talamonti MS, Nayar R. Is preoperative investigation of the thyroid justified in patients undergoing parathyroidectomy for hyperparathyroidism? *Thyroid.* 2002; 12: 1109-1112.
 178. Van Husen R, Kim LT. Accuracy of surgeon-performed ultrasound in parathyroid localization. *World J Surg.* 2004; 28: 1122-1126.
 179. Solorzano CC, Carneiro-Pla DM, Irvin GL 3rd. Surgeon-performed ultrasonography as the initial and only localizing study in sporadic primary hyperparathyroidism. *J Am Coll Surg.* 2006; 202: 18-24.
 180. Siperstein A, Berber E, Barbosa GF, Tsinberg M, Greene AB, Mitchell J, et al. Predicting the success of limited exploration for primary hyperparathyroidism using ultrasound, sestamibi, and intraoperative parathyroid hormone: analysis of 1158 cases. *Ann Surg.* 2008; 248: 420-428.
 181. Rodgers SE, Hunter GJ, Hamberg LM, Schellingerhout D, Doherty DB, Ayers GD, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. *Surgery.* 2006; 140: 932-940.
 182. Eichhorn-Wharry LI, Carlin AM, Talpos GB. Mild hypercalcemia: an indication to select 4-dimensional computed tomography scan for preoperative localization of parathyroid adenomas. *Am J Surg.* 2011; 201: 334-338.
 183. Shah S, Win Z, Al-Nahhas A. Multimodality imaging of the parathyroid glands in primary hyperparathyroidism. *Minerva Endocrinol.* 2008; 33: 193-202.
 184. Silverberg SJ, Clarke BL, Peacock M, Bandeira F, Boutroy S, Cusano NE, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014; 99: 3580-3594.
 185. Bilezikian JP, Khan AA, Potts JT. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab.* 2009; 94: 335-339.
 186. Leifsson BG, Ahrén B. Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab.* 1996; 81: 2149-2153.
 187. Hedbäck G, Odén A, Tisell LE. The influence of surgery on the risk of death in patients with primary hyperparathyroidism. *World J Surg.* 1991; 15: 399-405.
 188. Hedbäck G, Odén A. Increased risk of death from primary hyperparathyroidism--an update. *Eur J Clin Invest.* 1998; 28: 271-276.
 189. Hedbäck G, Tisell LE, Bengtsson BA, Hedman I, Oden A. Premature death in patients operated on for primary hyperparathyroidism. *World J Surg.* 1990; 14: 829-835.
 190. Palmér M, Adami HO, Bergström R, Akerström G, Ljunghall S. Mortality after surgery for primary hyperparathyroidism: a follow-up of 441 patients operated on from 1956 to 1979. *Surgery.* 1987; 102: 1-7.
 191. Sivula A, Ronni-Sivula H. Natural history of treated primary hyperparathyroidism. *Surg Clin North Am.* 1987; 67: 329-341.
 192. Dominiczak AF, Lyall F, Morton JJ, Dargie HJ, Boyle IT, Tune TT, et al. Blood pressure, left ventricular mass and intracellular calcium in primary hyperparathyroidism. *Clin Sci (Lond).* 1990; 78: 127-132.
 193. Piovesan A, Molineri N, Casasso F, Emmolo I, Ugliengo G, Cesario F, et al. Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. *Clin Endocrinol (Oxf).* 1999; 50: 321-328.
 194. Nilsson IL, Aberg J, Rastad J. Left ventricular systolic and diastolic function and exercise testing in primary hyperparathyroidism--effects of parathyroidectomy. *Surgery.* 2000; 128: 895-902.
 195. Symons C, Fortune F, Greenbaum RA, Dandona P. Cardiac hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism--an association. *Br Heart J.* 1985; 54: 539-542.
 196. Pepe J, Curione M, Morelli S, Colotto M, Varrenti M, Castro C, et al. Arrhythmias in primary hyperparathyroidism evaluated by exercise test. *Eur J Clin Invest.* 2013; 43: 208-214.
 197. Pepe J, Curione M, Morelli S, Varrenti M, Cammarota C, Cilli M, et al. Parathyroidectomy eliminates arrhythmic risk in primary hyperparathyroidism, as evaluated by exercise test. *Eur J Endocrinol.* 2013; 169: 255-261.
 198. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease--a review. *Eur Heart J.* 2004; 25: 1776-1787.
 199. Palmér M, Adami HO, Krusemo UB, Ljunghall S. Increased risk of malignant diseases after surgery for primary hyperparathyroidism. A nationwide cohort study. *Am J Epidemiol.* 1988; 127: 1031-1040.
 200. Pickard AL, Gridley G, Mellemkjæ L, Johansen C, Kofoed-Enevoldsen

- A, Cantor KP, et al. Hyperparathyroidism and subsequent cancer risk in Denmark. *Cancer*. 2002; 95: 1611-1617.
201. Nilsson IL, Zedenius J, Yin L. The association between primary hyperparathyroidism and malignancy: nationwide cohort analysis on cancer incidence after parathyroidectomy. *Endocr Relat Cancer*. 2007; 14: 135-140.
 202. Almquist M, Manjer J, Bondeson L, Bondeson AG. Serum calcium and breast cancer risk: results from a prospective cohort study of 7,847 women. *Cancer Causes Control*. 2007; 18: 595-602.
 203. Almquist M, Bondeson AG, Bondeson L, Malm J, Manjer J. Serum levels of vitamin D, PTH and calcium and breast cancer risk—a prospective nested case-control study. *Int J Cancer*. 2010; 127: 2159-2168.
 204. Enblad P, Adami HO, Glimelius B, Krusemo U, Pählman L. The risk of subsequent primary malignant diseases after cancers of the colon and rectum. A nationwide cohort study. *Cancer*. 1990; 65: 2091-2100.
 205. Skinner HG, Schwartz GG. Serum calcium and incident and fatal prostate cancer in the National Health and Nutrition Examination Survey. *Cancer Epidemiol Biomarkers Prev*. 2008; 17: 2302-2305.
 206. Doppman JL, Miller DL. Localization of parathyroid tumors in patients with asymptomatic hyperparathyroidism and no previous surgery. *J Bone Miner Res*. 1991; 6: 153-159.
 207. Sample WF, Mitchell SP, Bledsoe RC. Parathyroid ultrasonography. *Radiology*. 1978; 127: 485-490.
 208. Edis AJ, Evans TC Jr. High-resolution, real-time ultrasonography in the preoperative location of parathyroid tumors. Pilot study. *N Engl J Med*. 1979; 301: 532-534.
 209. Nussbaum SR, Thompson AR, Hutcheson KA. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. *Surgery*. 1988; 104: 1121-1127.
 210. Irvin GL 3rd, Prudhomme DL, Deriso GT, Sfakianakis G, Chandarlapaty SK. A new approach to parathyroidectomy. *Ann Surg*. 1994; 219: 574-581.
 211. Greene AB, Butler RS, McIntyre S, Barbosa GF, Mitchell J, Berber E, et al. National trends in parathyroid surgery from 1998 to 2008: a decade of change. *J Am Coll Surg*. 2009; 209: 332-343.
 212. Norman J. Controversies in parathyroid surgery: The quest for a “mini” unilateral parathyroid operation seems to have gone too far. *J Surg Oncol*. 2012; 105: 1-3.
 213. Gallagher SF, Denham DW, Murr MM. The impact of minimally invasive parathyroidectomy on the way endocrinologists treat primary hyperparathyroidism. *Surgery*. 2003; 134: 910-917.
 214. Norman J, Politz D. Prospective study in 3,000 consecutive parathyroid operations demonstrates 18 objective factors that influence the decision for unilateral versus bilateral surgical approach. *J Am Coll Surg*. 2010; 211: 244-249.
 215. Siperstein A, Berber E, Mackey R. Prospective evaluation of sestamibi scan, ultrasonography, and rapid PTH to predict the success of limited exploration for sporadic primary hyperparathyroidism. *Surgery*. 2004; 136: 872-880.
 216. Chiu B, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. *Arch Surg*. 2006; 141: 483-487; discussion 487-488.
 217. Karakousis GC, Han D, Kelz RR, Nemani D, Karamacharya J, Roses R, et al. Interpretation of intra-operative PTH changes in patients with multi-glandular primary hyperparathyroidism (pHPT). *Surgery*. 2007; 142: 845-850.
 218. Murphy C. Minimally Invasive radioguided parathyroidectomy (MIRP). In: E. Whitman (Ed.) *Operative Techniques in General Surgery*. New York; 2001.
 219. Norman J, Aronson K. Outpatient parathyroid surgery and the differences seen in the morbidly obese. *Otolaryngol Head Neck Surg*. 2007; 136: 282-286.
 220. Norman JG, Politz DE. Safety of immediate discharge after parathyroidectomy: a prospective study of 3,000 consecutive patients. *Endocr Pract*. 2007; 13: 105-113.

Cite this article

Arrangoiz R, Cordera F, Lamberton F, Luque-de-Leon E, Muñoz-Juárez M, et al. (2016) Current Thinking on Primary Hyperparathyroidism. *JSM Head Neck Cancer Cases Rev* 1(1): 1002.