PRIMARY HYPERPARATHYROIDISM

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Revised: January 3, 2017

ABSTRACT

Primary Hyperparathyroidism is a common endocrine disease characterized by excessive secretion of parathyroid hormone from one or more of the 4 parathyroid glands. In most patients, a single, benign adenoma is responsible for the disease, but in a small percentage of subjects 4-gland hyperplasia is evident. Most patients present with sporadic disease but familial multiple endocrine gland syndromes are well known, with genetic bases that have been characterized. The clinical presentation of primary hyperparathyroidism has changed by virtue of the use of automated biochemical screening, in which the serum calcium is routinely measured as well as by a proactive approach to the investigation of known or suspected metabolic bone disease. As a result, three phenotypes of primary hyperparathyroidism are seen throughout the world. Symptomatic disease with skeletal and renal involvement is limited primarily to countries in which biochemical screening is not used and where vitamin D deficiency is endemic. Mild hypercalcemia is the most common biochemical presentation in subjects who are discovered incidentally. The normocalcemic variant of primary hyperparathyroidism is recognized in patients whose disease is manifest by elevated levels of parathyroid hormone in the absence of secondary causes. With recent advances in our ability to investigate in detail the two major target organs of primary hyperparathyroidism, namely bone and kidney, a more complete assessment of patients with this disease is now possible. Knowledge of these different presentations, greater understanding of the disease itself, and information about natural history with or without successful parathyroid surgey have all led to revised guidelines for the management of primary hyperparathyroidism. In those who are not candidates for or refuse parathyrioid surgery, monitoring is recommended, In some individuals, pharmacological agents may be helpful.

INTRODUCTION

In the past 4 decades, our views of Primary Hyperparathyroidism have changed in terms of diagnosis, management, and course. These changes in the clinical phenotypes of primary hyperparathyroidism and resultant modifications in guidelines for management are summarized in publications that resulted from The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism was held in Florence, Italy, 2013 (1-5). This chapter has been completely updated to include the key features of that International Conference as well as developments in the field since.

DIAGNOSIS

In the differential diagnosis of hypercalcemia, primary hyperparathyroidism is the most common cause. It is important and rather straightforward to distinguish between primary hyperparathyroidism and other causes of hypercalcemia. The biochemical distinction between primary hyperparathyroidism and malignancy-associated hypercalcemia, the second most common cause of hypercalcemia, is firmly established by measuring the parathyroid hormone (PTH) level. The second generation immunoassay for PTH is also known as 'intact' PTH and utilizes a more specific technology. While this assay has served with great utility over several decades, it is important to note that this assay cross-reacts with large fragments of PTH truncated at the amino terminal end. With this assay, PTH levels are frankly elevated 75%-80% of the time. When the PTH level is normal, it tends to be in the upper range of normal and, thus, clearly "abnormal" when hypercalcemia is simultaneously present. In the context of hypercalcemia of malignancy and virtually all other causes of hypercalcemia (with the exceptions being those related to thiazide diuretics, lithium, and Familial Hypocalciuric Hypercalcemia), the PTH level will

be suppressed. Thus, when PTH is in the upper range of normal and hypercalcemia is present, abnormal regulation of serum calcium by the parathyroid gland(s) is most likely.

A third generation assay is known as 'whole' PTH because it is more specific for the 1-84 molecule (6-7). Thus, cross-reactivity with large amino terminal truncated fragments does not occur. However, this assay detects a post-translational form of PTH that is characterized by a phosphorylated serine reside in the 15-20 region of the molecule. This posttranslational form of PTH makes up 10% of the circulating form of PTH and is a somewhat higher percentage in individuals in renal failure. This form of PTH has been shown to be overproduced in special situations such as parathyroid cancer and severe hyperparathyroidism (3).

The reference range for the second generation assay is typically given as 10-65 pg/mL. In individuals under the age of 45, the upper limit of normal for PTH should be regarded to be closer to 45 pg/mL. This is because PTH levels normally rise with age and the laboratory reference range doesn't make a distinction on the basis of age. For example, in a 32 year old woman with hypercalcemia, a PTH level of 50 pg/mL should be regarded as frankly elevated, even though technically it is still within normal limits for the assay. However, even if one were to consider the posted normal range, the value of 50 pg/mL would still be distinctly abnormal for someone with hypercalcemia. The typical normal range for the third generation assay for PTH is about half that of the second generation assay, namely about 5-35 pg/mL.

Silverberg et al. applied this "whole" assay to a group of subjects with surgically proved primary hyperparathyroidism. In comparison to the intact assay and the older radioimmunoassay for mid-molecule PTH, the whole assay performed somewhat better with respect to a higher percentage of patients with frankly elevated levels (96%) in comparison to the intact (73%) and mid-molecule assays (63%) (8). Subsequent experience, however, has given the general sense that in subjects without renal failure, the intact assay and the "whole" assay are equivalently useful (9-10). In subjects with renal compromise, however, mid-molecule and the larger aminoterminally truncated forms of PTH do build up. While it may be expected that the "whole" assay would give a more accurate depiction of PTH in these situations, this has not always been appreciated (11). The diagnostic sensitivity between the second and third generation assays for PTH is considered to be similar and for most clinical purposes the second generation assay is more widely used.

The recent controversy over normal reference ranges for 25-hydroxyvitamin D (12-13) has stimulated discussion about normal reference ranges for PTH. The generally accepted reference ranges for PTH, as noted above, do not take into account the levels of 25-hydroxyvitamin D. Since there is a linear, inverse relationship between 25-hydroxyvitamin D levels and PTH (14), the reference range for PTH may well be lower in a vitamin D replete population (15).

As noted, exceptions to the rule that patients with hypercalcemia and elevated PTH levels have primary hyperparathyroidism include two medications, lithium (16) and thiazide diuretics. Actually, many of these patients do have primary hyperparathyroidism but the only way to be sure is to withdraw the medication and to monitor the serum calcium over the next 3-6 months. In those who are dependent upon lithium therapy for their mental well-being, withdrawal may be difficult or unwise, although newer psychotropic agents- effective in bipolar disease, can effect this change more safely than in the past. Recent experience has shown that primary hyperparathyroidism should be seriously considered in someone on lithium because it is unlikely that lithium alone would be responsible for the hypercalcemia. Another exception is tertiary hyperparathyroidism, an end result of longstanding, poorly controlled renal insufficiency. Hypercalcemia in this setting usually does not present a problem in differential diagnosis because the advanced renal failure is clearly evident. In these cases, there is a change from mechanisms of parathyroid gland compensation (i.e., to normalize the tendency for hypocalcemia to develop; a secondary hyperparathyroidism) to mechanisms of parathyroid gland autonomy with attendant hypercalcemia. It is of interest that when surgery is performed, some of these patients are actually found to have primary hyperparathyroidism, that is a single adenomatous gland superimposed upon a background of parathyroid hyperplasia (17).

Another exception to the rule that patients with elevated levels of calcium and PTH have primary hyperparathyroidism is the rare disorder, Familial Hypocalciuric Hypercalcemia (FHH). It is due to an inactivating mutation of the calcium sensing receptor (CASR) gene resulting in an increase in the set point for serum calcium suppression of PTH secretion (18). These individuals tend to be younger than the average patient with primary hyperparathyroidism. In fact the clinical expression of FHH with mild hypercalcemia typically can be traced to childhood or the young adult years. There is also usually a family history of asymptomatic hypercalcemia. The inactivating mutation of the CASR gene also affects the kidney, enhancing calcium reabsorption, resulting in hypocalciuria, with a calcium clearance to creatinine clearance ratio (Ca/Cr) typically less than 0.01, on a normal calcium diet. It is important to distinguish between primary hyperparathyroidism and FHH because surgery is never indicated in FHH, Because of its high penetrance, FHH becomes a particularly important consideration in children and young adults. When the diagnosis is in doubt, CASR gene sequence testing can be obtained (19). It should be emphasized that FHH is a very rare disease.

True Ectopic Parathyroid Hormone Production.

Very rarely, non-parathyroid malignancies have been described in which authentic PTH is produced (19-20). In a patient with a known malignancy, hypercalcemia and elevated parathyroid hormone levels, it is actually more common for that patient to have concomitant primary hyperparathyroidism because ectopic parathyroid hormone production by malignant tumors is so rare. Far more common, in the setting of malignancy-associated hypercalcemia, is the production of parathyroid hormone-related protein (PTHrP). This latter situation does not present a problem *vis a vis* the measurement of PTH since the modern immunoassays do not have any cross reactivity between the two molecules.

Normocalcemic Primary Hyperparathyroidism.

The diagnosis of primary hyperparathyroidism can be made at times in subjects whose total and ionized serum calcium are completely normal but in whom the PTH evel is persistently elevated (21). In order to make the diagnosis of normocalcemic primary hyperparathyroidism, all causes for a secondary hyperparathyroid state must be considered and ruled out. It is essential to recognize the presence of coexisting vitamin D insufficiency which may well be the most common cause for an elevated PTH level. Replacing these patients with vitamin D to reach levels now considered to be clearly normal (i.e., 25-hydroxyvitamin D >30 ng/mL) may return the PTH to normal. The recent recommendations for a revision downward of the normal range of 25-hydroxyvitammin D to 20 ng/mL (22) has not changed the opinion of this author that for the diagnosis of normocalcemic primary hyperparathyroidism, levels of 25-hydroxyvitamin D should be > 30 ng/mL Occasionally, however, these patients will become hypercalcemic with vitamin D replacement thus unmasking more typical hypercalcemic primary hyperparathyroidism. Following vitamin D repletion, if the PTH remains elevated and the serum calcium remains normal, and other causes of an elevated PTH such as renal insufficiency have been excluded, then the diagnosis of normocalcemic PHPT can be strongly suspected.

A large population based study of over 5,000 postmenopausal women who were screened and then retested 8 yrs later provides evidence for the development of hypercalcemia in some of these subjects (23-24). Two observational studies of normocalcemic PHPT have followed patients longitudinally. In one study (25), 37 patients were followed for a mean of 3 yrs (range 1-9). Typical hypercalcemic primary hyperparathyroidism emerged in 7 (19%) individuals. However, a more impressive 40% developed evidence of disease progression with development of kidney stones, fractures, marked hypercalciuria or greater than a 10% decline in bone mineral density (BMD). Seven patients had successful parathyroidectomy of whom three were hypercalcemic and the rest met other criteria for surgery.

The cumulative experience with these individuals by us and others has established this variant of primary hyperparathyroidism as a real clinical entity (21, 25-29). While the initial studies identified these patients from referral populations, and thus not unexpectedly, had more symptomatic disease despite their normal calcium levels, it remained to be seen whether from non-selected populations, normocalcemic primary hyperparathyroidism could be identified. Two large epidemiological studies in which parathyroid disease was not initiailly sought formed the source material to address this question. In both the Mr Os study and the Dallas Heart Study, patients were idenfitied with normocalcemic primary

hyperparathyroidism with prevalence rates of 0.4% in the Mr. Os study and 3.1% in the Dallas Heart Study (30). Other studies have confirmed these results (31). At the 4rd International Workshop on the Management of Asymptomatic PHPT, normocalcemic primary hyperparathyroidism was recognized, for the first time, as a form of primary hyperparathyroidism. The Workshop also suggested, for the first time, a management protocol that can be followed for these patients. If such individuals develop hypercalcemia, then guidelines for the management of the disease would be pertinent. If such individuals do not develop hypercalcemia but classical complications of primary hyperparathyroidism, such as kidney stones, reduced bone mineral density, fractures, they would also become candidates for parathyroidectomy.

Acute primary hyperparathyroidism.

This form of primary hyperparathyroidism often occurs against a backdrop of mild disease. Markedly elevated levels of calcium develop, often > 15 mg/dL associated with symptomatic hypercalcemia.The risk of developing acute primary hyperparathyroidism is very low, < 1%, among patients with mild disease (32-34). Information about the preceding history is often helpful in making the diagnosis of this unusual form of primary hyperparathyroidism. What triggers an abrupt rise in the calcium is rarely clear but an intervening illness during which the patient has become non-ambulatory or dehydrated could be etiological factors (35). At operation, there is rarely any evidence that the parathyroid gland has become infarcted or has hemorrhaged. The diagnosis is readily made by markedly elevated levels of calcium and PTH. Sometimes, a patient without an antecedent history of mild hypercalcemia will present de novo with life-threatening hypercalcemia. While hypercalcemia associated with malignancy is important to consider in this context, it is just as likely to be due to a form fruste presentation of primary hyperparathyroidism. Once the diagnosis is made and the patient is stabilized, parathyroid surgery should be planned without much delay.

Parathyroid carcinoma.

The vast majority of patients with primary hyperparathyroidism have benign disease. The incidence of malignancy of the parathyroids is well under 0.5% of all patients with primary hyperparathyroidism. The typical presentation is quite different from the usual patient with mild disease in that the serum calcium is usually very high, > 14 mg/dL, and the parathyroid hormone level is markedly elevated, up to 20 times normal. Virtually all patients are symptomatic of hypercalcemia. Non-functional parathyroid cancers are exceedingly rare. Along with these features, a neck mass can be present along with the co-presence of bone and stone disease. The genetic aspects are covered elsewhere in this chapter. While parathyroid cancer is typically a sporadic disease, it has seen in association with the hyperparathyroid-jaw tumor syndrome (36). Patients are usually about a decade younger than the typical patient with benign disease (40-50 vs 50-60) and harbor these other features (37). Since parathyroid carcinoma is so rare, the statistics always favor a benign disease even in subjects who present with these features. The management of parathyroid cancer involves total removal of the parathyroid cancer and local neck dissection, when indicated. This is one of the rare cancers in which distant metastases, if present, should be considered for surgical removal (38-39). Typically patients with parathyroid cancer demonstrate an indolent clinical course with disease-free intervals as long as 20 years (40).

Parathyromatosis

. Perhaps the rarest form of hyperparathyroidism presents with scattered foci of parathyroid tissue throughout the neck (40a). Histologically, the parathyroid cells are benign and typically chief cells. Reddick et al. classically described two forms of parathyromatosis (40b). Type 1 is considered to be embryologic in orgin with nests of parathyroid tissue scattered throughout neck and mediastinum during ontogenesis. Type 2 is considered to be a consequence of initial parathyroid surgery, either for primary or secondary/tertiary hyperparathyroidism, in which cells are “spilled” into the surrounding tissues, only to resurface years later as recurrent hyperparathyroidism. Very rarely, parathyromatosis has been reported following fine-needle aspiration of the neck (40b, 40c). Jain et al. have provided recently a very thorough review of this rare form of hyperparathyroidism (40a).

EPIDEMIOLOGY

Primary hyperparathyroidism has become a common endocrine disorder, due in large part to the widespread use of the multichannel autoanalyzer that was introduced in the early 1970s (41). Prior to that time, however, primary hyperparathyroidism was not a common endocrine disease (42). Despite its rarity, as described in older reports, the frequency with which it was diagnosed was, in large measure, a function of one's index of suspicion. For example, Raymond Keating, whose work at the Mayo Clinic helped to establish modern concepts of the disease, began to recognize primary hyperparathyroidism with regularity, only after he was made more acutely aware of it by Aub, Bauer and Albright (43). This experience was the clue that primary hyperparathyroidism was much more prevalent in the population at large than its reported incidence would have suggested it to be. Then, with the advent of the autoanalyzer, in the 1970's, it was rather quickly apparent that there were many individuals with primary hyperparathyroidism whose disease was not being recognized simply because calcium determinations were not being routinely obtained. Incidence figures rose dramatically when calcium determinations were obtained in the context of the multichannel biochemistry profile. Reporting its experience before and after the introduction of the autoanalyzer, the Mayo Clinic saw a 4-5-fold increase in the incidence of primary hyperparathyroidism to approximately 100,000 new cases per year or about 22 cases per 100,000 person years (41, 44). It might be expected that with the 'mining' of the unsuspected population through multichannel screening, the incidence of primary hyperparathyroidism would decline, at least initiatlly (45). However, using a closed health care system database, Yeh et al. noted that during the study period, 1995-2010, well after biochemical screnning became routine in the United States, the prevalence of PHPT tripled. Moreover, they confirmed the prevalence of primary hyperparathyroidism to be 3-4 times more common in women than men with incidence figures of 80 and 36 per 100,000 in women and men respectively during the most common decade of its appearance, namely in those between 50 and 59 years old (46). It was more common in African Americans followed by Caucasian and Asian individuals. These results underscore the point that primary hyperparathyroidism is a common endocrine disorder (47). Moreover, its incidence does not appear to be declining.

A history of childhood irradiation to the face or neck is obtained in a small number of individuals (48). One can summarize this discussion by recognizing three generational phenotypes of primary hyperparathyroidism: prior to the advent of the multichannel screening test; after the advent of the multichannel screening test; and more recently the discovery of normocalcemic individuals in the context of a proactive search to determine etiologies for individuals who present with low bone mass. Which form of primary hyperparathyroidism is more likely to be present in a given country depends upon a number of factors (e.g., utilizatization of multichannel screening, prevalence of vitamin D deficiency in the population; routine use of PTH assays in the evaluation of suspected metabolic bone disease).

HEREDITARY HYPERPARATHYROID STATES

Multiple Endocrine Neoplasia (MEN), both type 1 and type II, is inherited in an autosomal dominant manner. Primary hyperparathyroidism is often the first and is the most common of the endocrinopathies in MEN1, reaching nearly 100% penetrance by the age of 50 (49). In MEN 1, tumors of pancreas and anterior pituitary are seen along with parathyroid disease. In MEN 2, medullary thyroid cancer and pheochromocytoma constitute the syndrome with primary hyperparathyroidism. MEN 3 (also referred to as MEN 2B) is usually not associated with parathyroid disease but with the other tumors associated with MEN 2 along with a marfanoid habitus, mucosal neuromas, and autonomic ganglionic dysfunction of the gastrointestinal tract. Primary hyperparathyroidism is also part of other syndromic complexes such as MEN4 in which parathyroid tumors are found in association with anterior pituitary, gonadal, adrenal, and renal tumors as well as the hyperparathyroidism-jaw tumor (HPT-JT) syndrome.

While these genetic disorders are of great interest, they are vey uncommon causes of primary hyperparathyroidism. Situations in which one would suspect a genetic etiology of the hyperparathyroid state are young adults, because the penetrance of these variants is so complete by the age of 30. A family history of other endocrine neoplasms would be another important clue to the possible existence of one of these genetic syndromes.

Genetic Bases Of The Hereditary Hyperparathyroid States.

The tumor suppressor gene which is inactivated in MEN I encodes menin, the product of the MENIN gene (51-52).

MEN2 and MEN 3 are due to mutations of the RET proto-oncogene (53). MEN 4 is due to mutations of CDNK1B which encodes the cyclin-dependent kinase inhibitor p27kip1. The HPT-JT syndrome is due to mutations of the HRPT2 gene (also known as CDC73) which encodes parafibromin a gene involved in cell cycle division (54). As noted above, the HPT-JT syndrome can be associated with parathyroid cancinoma.
Familial isolated hyperparathyroidism (FIH) includes familial syndromes that do not clearly meet the diagnostic classification of the previous genetically transmitted categories (55). In some kindreds characterized by FIH, genes associated with the multiglandular syndromes describe above have been reported (55-56). It is likely that these families harbor genetic abnormalities that are distinctly different from what are commonly associated with the well known MEN syndromes. HRPT3, for example, has been implicated in 10 families with FIH (57).

Familial hypocalciuric hypercalcemia (FHH).
This presentation that can be confused with the most common form of primary hyperparathyroidism, namely the sporadic isolated disorder, is considered above in the discussion of the differential diagnosis of primary hyperparathyroidism.

Neonatal severe primary hyperparathyroidism (NSHPT).

The recognition of these syndromes, which can alter medical or surgical management, can now be aided by genetic testing. Depending upon the presenation and the index of suspicion, the genes mentoned in this section as well as others can be readily identified. The approach to such decision making is well outlined by Thakker et al. (50).

Molecular Pathogenesis Of Hpt
In primary hyperparathyroidism, clones of abnormal parathyroid cells emerge that dominate and shift the usual steep inverse relationship between PTH release and calcium ion “to the right”. For a given extracellular calcium concentration, PTH is higher. Although in large measure, the defect is altered sensitivity of a clone of parathyroid cells to calcium, increases in the mass of abnormal parathyroid tissue also contribute to excessive secretion of PTH (59). No specific mutations of the calcium sensing receptor have been described in primary hyperparathyroidism. Other genes such as the vitamin D receptor gene, the proto-oncogene RET have also not been demonstrated to be abnormal in primary hyperparathyroidism.

The clonal origin of most parathyroid adenomas implies that defects in specific genes, such as those capable of controlling parathyroid cell growth, were acquired in tumor development and conferred a selective advantage upon an original cell and its progeny. Interestingly, in a model of experimental hyperparathyroidism, the altered sensitivity to calcium, and hypercalcemia, are a secondary consequence of the primary disturbance in parathyroid cell growth (60). The pathogenetic abnormalities in primary hyperparathyroidism involve several genes that have variably been implicated as causal in the disorder. At this time, two genes have been most solidly established as etiologically related to sporadic (non-familial) primary hyperparathyroidism. *Cyclin D1* is likely to be involved, although not commonly, in the context of DNA rearrangements such that tumor-specific juxtaposition of proto-oncogenes lead to the activation of other genes so as to be oncogenic (61-62).

The second genetic abnormality that has been described as etiologically important in primary hyperparathyroidism is the gene associated with multiple endocrine neoplasia, type 1 (MEN1; 63-64). The MEN1 gene product is a tumor suppressor. In primary hyperparathyroidism, or in any mechanism of tumorigenesis due to a tumor suppressor gene, complete inactivation (biallelic dysfunction) is required. Some parathyroid tumors from patients with sporadic primary hyperparathyroidism, that is those who do not have the multiple endocrine neoplasia syndrome, have been shown to involve the MEN 1 gene. As many as 25-40% of sporadic adenomas were shown to be due to allelic loss of chromosome 11 markers (65-66).

The cell division cycle 73 gene (HRPT2, CDC73) shown to be abnormal in parathyroid cancer and in autosomal dominant hyperparathyroidism-jaw tumor syndrome does not seem to be abnormal in benign, sporadic parathyroid adenomas (59).

Although, much more information is needed about the molecular pathogenesis of primary hyperparathyroidism, the implication of several genes so far suggests that perhaps most patients with this order will ultimately be shown to have some underlying molecular defect that leads to the abnormal set point for calcium in this disorder. A number of other candidate gene defects have been described (Arnold chapter in The Parathyroids).

PATHOLOGY

By far the most common lesion found in patients with primary hyperparathyroidism is the solitary, benign parathyroid adenoma, occurring in 80-85% of patients. While in most cases, a single adenoma is found, multiple parathyroid adenomas have been reported in 2-4% of cases (67-69). The diagnosis of double adenomas requires the identification of two enlarged glands in association with at least one other normal parathyroid gland (70). Some of these patients actually have 4-gland disease but its clinical presentation has a dysynchrony such that the other glands become abnormal in time but not when the two 'adenomas' are discovered. Parathyroid adenomas can be discovered in many unexpected anatomic locations. Embryonal migration patterns of parathyroid tissue account for a plethora of possible sites for ectopic parathyroid adenomas. The most common sites for ectopic adenomas are within the thyroid gland, the superior mediastinum, and within the thymus. Occasionally, the adenoma may ultimately be identified in the retroesophageal space, the pharynx, the lateral neck, and even the alimentary submucosa of the esophagus.

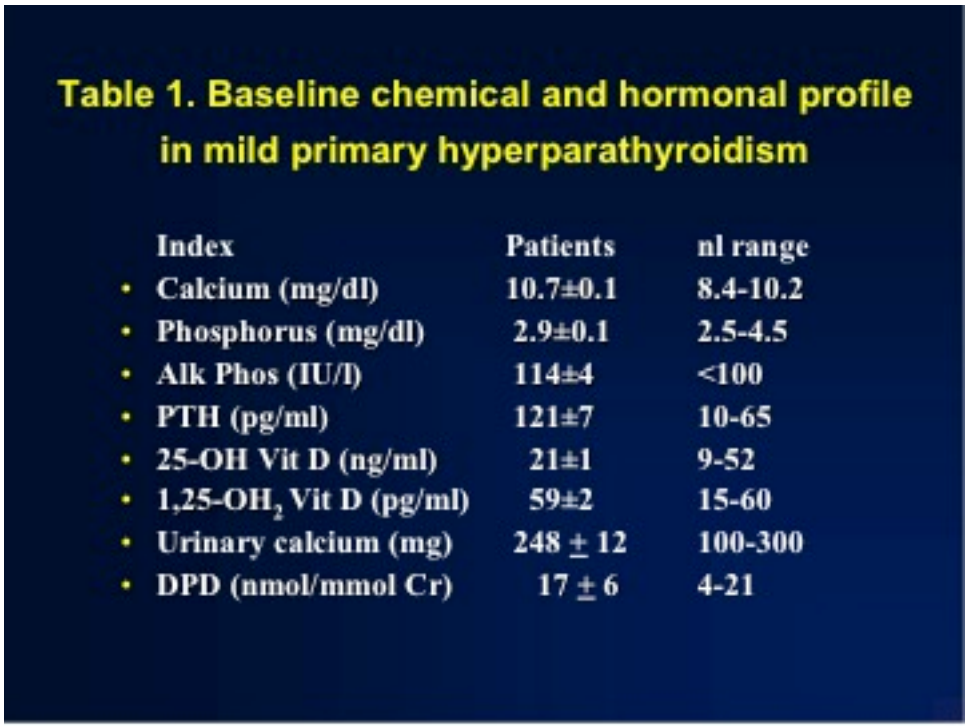
In approximately 15% of patients with primary hyperparathyroidism, all four parathyroid glands are involved. About 30% of patients with multigland disease have a familial syndrome (71-72). There are no clinical features that differentiate single versus multiglandular disease. The etiology of 4-gland parathyroid hyperplasia is multi-factorial. It may be associated with a familial hereditary syndrome, such as MEN, Types 1 and 2. As in the case of parathyroid adenomas, underlying molecular mechanisms are heterogeneous. Very rarely, in fewer than 0.5% of patients with primary hyperparathyroidism, the parathyroid disease will be malignant. They tend to be large tumors with evidence for invasion of surrounding neck structures. However, some parathyroid cancers can appear to be completely encapsulated and resemble benign tissue. It virtually always involves only one gland. It's association with the PHPT-JT syndrome has been described earlier. The key indicators of malignancy are tissue invasion and local or distant metastases. Mitotic activity and nuclear atypia are not sufficient by themselves to make the diagnosis of parathyroid cancer. Virtually all parathyroid cancers are functional and secrete parathyroid hormone, and often have the clinical features of those of advanced, severe, and symptomatic primary hyperparathyroidism (see above).

BIOCHEMICAL FEATURES

Typical biochemical indices associated with primary hyperparathyroidism are shown in Table 1. The serum calcium determination is generally not greater than 1 mg/dL above the upper limits of normal. The serum phosphorus is in the lower range of normal with only approximately 25% of patients showing phosphorus levels that are frankly low (73). Total alkaline phosphatase activity is in the high normal range as is the case also for more specific markers of bone turnover, bone-specific alkaline phosphatase activity, osteocalcin, or collagen breakdown products (N-telopeptide, deoxypyridinoline; 74). If the normal concentration of 25-hydroxyvitamin D level is taken to be >30 ng/mL, then most patients with primary hyperparathyroidism will have low levels. In contrast, the 1,25-dihydroxyvitamin D level tends to be in the upper range of normal and, in fact, frankly elevated in 25% of patients with primary hyperparathyroidism (75). The pattern of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in primary hyperparathyroidism is due to the property of parathyroid hormone to facilitate the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Urinary calcium excretion is typically in the upper range of normal with as many as 40% of individuals showing frank hypercalciuria. Curiously,

the presence of hypercalciuria in those without a history of kidney stones does not have predictive value for the development of nephrolithiasis (76).

Table 1. Biochemical indices in primary hyperparathyroidism. The values for this table are obtained from the cohort of patients followed by Silverberg, Bilezikian et al. over the past 15 years.



CLINICAL FEATURES

It is not surprising that with more widespread recognition of primary hyperparathyroidism, the classical signs and symptoms of the disease would change (77-78).

The Skeleton.

The frequency of specific radiological manifestations of primary hyperparathyroidism has fallen from 23% in the Cope Series (42) to less than 2% in the experience of Silverberg et al. (79). In fact, overt skeletal disease in primary hyperparathyroidism is so infrequent that skeletal X-rays are rarely indicated. Although *osteitis fibrosa cystica* is distinctly unusual in patients who present with primary hyperparathyroidism in the United States, this does not imply that the skeleton is unaffected in those with asymptomatic disease. The availability of sensitive techniques to monitor the skeleton has given us an opportunity to address these issues in patients who have asymptomatic primary hyperparathyroidism.

*Bone Densitometry***.** The advent of bone mineral densitometry as a major diagnostic tool for osteoporosis occurred at a time when the clinical profile of primary hyperparathyroidism was changing from a symptomatic to an asymptomatic disease. Questions about skeletal involvement in primary hyperparathyroidism could be addressed, therefore, despite the absence of overt radiological features. Bone mass measurement, now an integral element of the evaluation of all patients with primary hyperparathyroidism, typically shows evidence for skeletal involvement (80). In its catabolic mode PTH appears to have a proclivity for cortical bone. The distal 1/3 site of the radius provides a convenient cortical site for bone density evaluation in primary hyperparathyroidism to investigate the possibility that this site would be preferentially affected. In primary hyperparathyroidism, as expected from physiological considerations, BMD at the distal 1/3 radius site is diminished (81). The common observation that the cortical compartment is reduced in primary hyperparathyroidism has been seen also with the newer non-invasive technology, high resolution peripheral computed tomography (HRpQCT) (82). Another physiological property of PTH is an osteoanabolic one, at cancellous sites such as the lumbar spine. Bone density at the lumbar spine is only minimally reduced, typically within 5% of age matched mean values. The hip region, containing a relatively equal admixture of cortical and cancellous elements,

shows bone density that is intermediate between the cortical and cancellous sites (figure 1). The results support not only the notion that PTH is catabolic in cortical bone, but also the view that PTH can be, under certain circumstances, anabolic for cancellous bone (83-84). In postmenopausal women, the same pattern is observed (80). Postmenopausal women with primary hyperparathyroidism, therefore, show a reversal of the pattern typically associated with postmenopausal estrogen deficiency, namely preferential loss of cancellous bone. These observations suggest that primary hyperparathyroidism may help to protect postmenopausal women from bone loss due to estrogen deficiency.

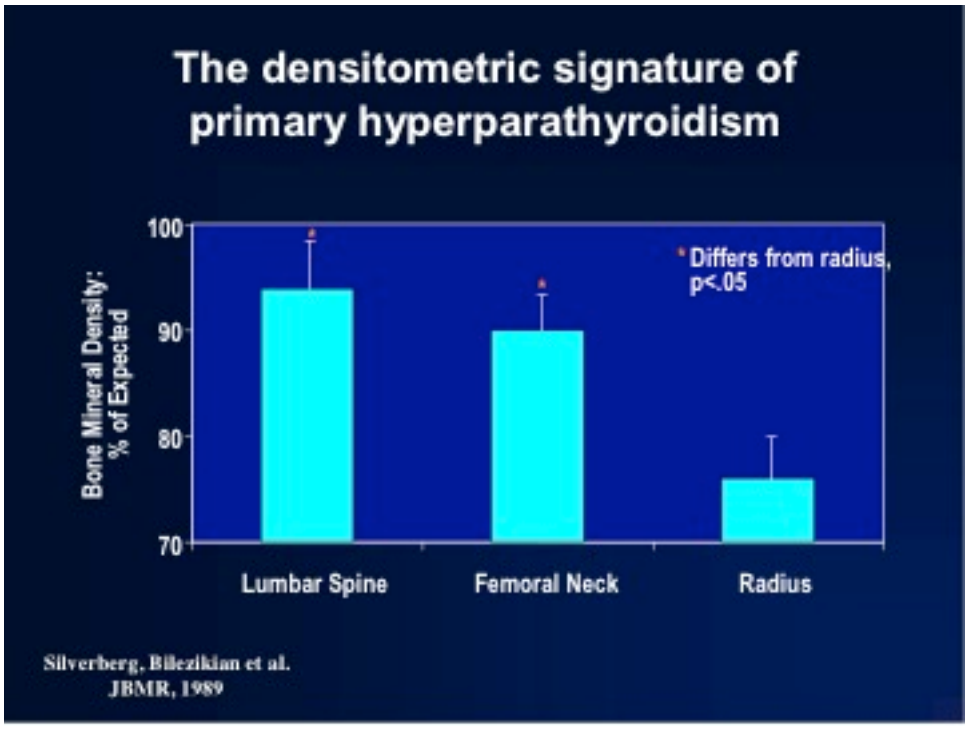


Figure 1. The pattern of bone loss in primary hyperparathyroidism. A typical pattern of bone loss is seen in asymptomatic patients with primary hyperparathyroidism. The lumbar spine is relatively well preserved while the distal radius (1/3 site) is preferentially affected. (Reprinted with permission from reference #80).

The densitometric profile in which there is relative preservation of skeletal mass at the spine and diminution at the more cortical radial site is not always seen in primary hyperparathyroidism. About 15% of patients with primary hyperparathyroidism will be shown to have evidence of vertebral osteopenia at the time of presentation (85).

Histomorphometric analysis of the bone biopsy specimen in primary hyperparathyroidism demonstrates cortical thinning, maintenance of cancellous bone volume and a very dynamic process associated with high turnover and accelerated bone remodeling. Confirming the results by bone densitometry, cancellous bone volume appears to be well preserved. This is seen in the group of all subjects we studied as well as among the subcohort of postmenopausal women with primary hyperparathyroidism. Several studies have shown that cancellous bone is actually increased in primary hyperparathyroidism as compared to normal subjects (86-87). Preservation of cancellous bone volume even extends to comparisons with the expected losses associated with the effects of aging on cancellous bone physiology. In patients with primary hyperparathyroidism, there is no relationship between trabecular number or separation and age, suggesting that the actual trabecular plates and their connections are maintained over time more effectively than in normal aging individuals. Thus, primary hyperparathyroidism seems to retard the normal age-related processes associated with trabecular loss. One of the mechanisms by which cancellous bone is preserved in primary hyperparathyroidism is through the maintenance of inter-connected trabecular plates. Further studies confirmed the salutary effects of PTH on cancellous elements in primary hyperparathyroidism (88-89).

Fracture risk.
Since BMD is an important predictor of fracture risk, the densitometric data in primary hyperparathyroidism suggest certain expectations about fracture incidence. One would expect, for example, that fracture incidence would be increased in the forearm and reduced, or at least unchanged, in the lumbar spine as compared to control subjects without primary hyperparathyoidism. Although some studies were consistent with this expectation (90-92), Dauphine et al. and Khosla et al. (93-94) reported that vertebral fractures were increased. The study of Khosla et al. analyzed retrospectively the incidence of fractures in primary hyperparathyroidism over a 28-year period, 1965-1992. Fracture rate was increased not only at the forearm but also at central, vertebral sites (94). More recently, Vignali et al. reported an increase in vertebral fractures, as determined by X-rays and vertebral fracture assessment by DXA in postmenopausal women with primary hyperparathyroidism (95).

Expectations of fracture risk in primary hyperparathyroidism have to take into account other skeletal effects of PTH that contribute to bone quality. It is clear that BMD is only one of a number of factors that account for bone strength (96). As noted above, the effects of PTH to preserve cancellous microarchitecture may tend to counteract the cortical thinning for which PTH is also responsible. Another important point is the effect of PTH on bone size. Cortical thinning tends to be compensated by the actions of PTH to increase periosteal apposition, thus leading to an increase in cross sectional diameter (97-98). The increase in cross-sectional diameter will tend to increase bone strength independent of the PTH effect to thin the cortices. Thus, in primary hyperparathyroidism, certain skeletal features tend to compete with each other: cortical thinning favoring an increase in fracture risk; increased bone size and preserved skeletal microarchitecture favoring a reduction in fracture risk. These considerations suggest the need for access to other modalties in which to gain insight in skeletal microstructure in primary hyperparathyroidism at both cortical and trabecular compartments, as well as prospective clinical studies of site-specific fracture incidence in primary hyperparathyroidism.

A relatively new approach to gaining greater understanding of bone quality in primary hyperparathyroidism is to utlize HRpQCT in which the highly resolved image can be studied with regard to the cortical and cancellous compartments of bone (99). While one could assume that the classic histomorphometric studies of Dempster et al. are sufficient in this regard, reservations have been expressed if only because the representativeness of the iliac crest- a non weght bearing site relative to the entire skeleton- could be doubted. To this end, HRpQCT analyzes the compartments of bone in the non-vertebral skeleton at both weight bearing (distal tibia) and non-weight bearing (distal radius) sites (100). Using this technology, it has been shown that both cortical and trabecular compartments of bone are adversely affected in primary hyperparathyroidism (101-103). In the study of Stein et al. further insight was gained into trabecular microstructure by applying to the resolved image, individual trabecular segmentation analysis by which the topology of the orientation of the trabecular compartment into plates and rods could be quantitated. In this study, the orientation of the trabecular indices favored the vertically oriented rods, a spatial disposition that is suboptimal for bone strength (figure 2).

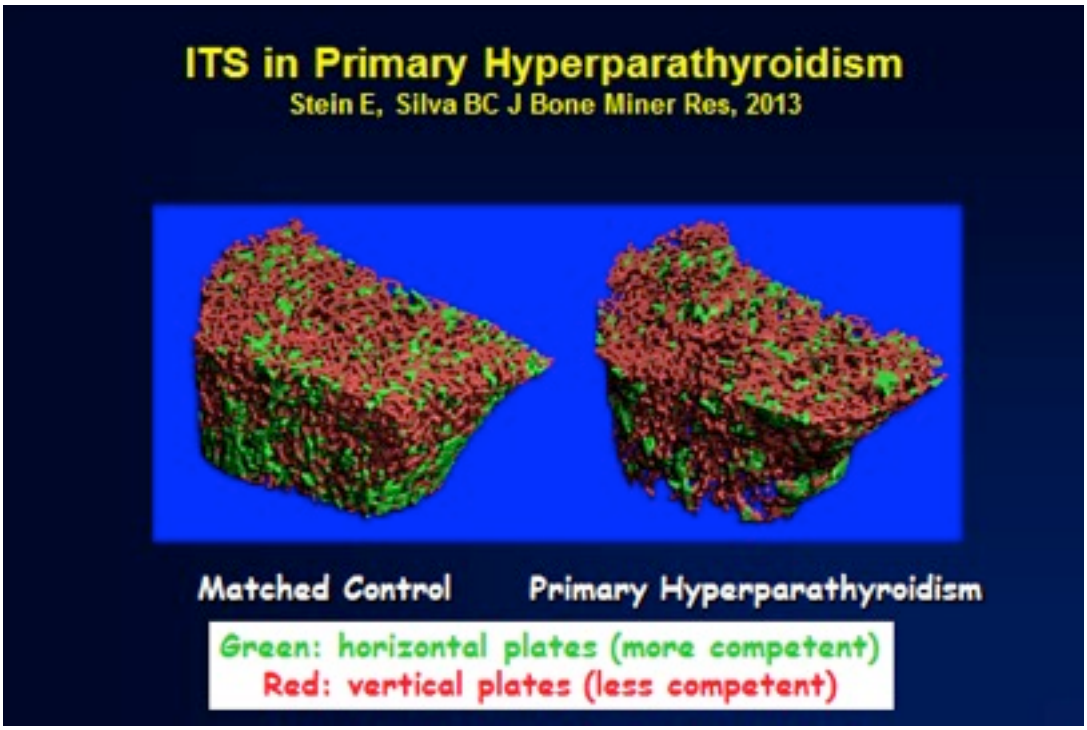


Figure 2. Microstructural abnormalities by HRpQCT in primary hyperparathyroidism. (adapted from reference 102)

While HRpQCT is a most valuable research tool, it is not going to gain widespread use clinically because of the expense of the instrument and the paucity of sites that house this technology. Alternatively, the Trabecular Bone Score (TBS) is a way to discern some aspects of bone quality from the lumbar spine DXA image and, thus, is available to anyone who has access to the TBS software for the DXA instrument (104-105). The concept of the TBS is a comparative one, namely the extent to which the textural patterns of the lumbar spine fit more comfortably as a homogenous or heterogenous array. The more discontinuous, heterogeneity of the textual analysis suggests worse skeletal microstructure. The analysis by TBS has been shown to be correlated with measures of connectivity density, trabecular number and trabecular separation by uCT. Morever, it provides an independent index of fracture risk (106). Silva et al. showed that lower mean TBS scores was seen in a much greater percentage of the hyperparathyroid population than showed reductions in BMD by DXA (107). Similar data were reported by Romagnoli et al. (108).

With these newer data, it now clear that in primary hyperparathyroidism, abnormalities in both cortical and trabecular bone can be identified, observations that are now concordant with epidemiology studies that showed increased fracture risk at all sites in this disease.

Renal Involvement

Also noteworthy with regard to the changing clinical profile of the disease is the reduction in the incidence of stone disease from approximately 60% in the preautoanalyzer era to current series in which the incidence is less than 20% (76). Still, stone disease is the most common complication of primary hyperparathyroidism. What disposes some individuals to have stone disease is not known but work by Schillitani et al. suggests that specific polymorphisms of the calcium receptor gene might be an important pathogenetic factor (109). Other pathophysiological aspects of renal disease in primary hyperparathyroidism are well summarized by Peacock (110). Other renal manifestations of primary hyperparathyroidism include hypercalciuria, which is seen in approximately 40 percent of patients, and nephrocalcinosis, the frequency of which is unknown. Recent studies, however, have shown that when imaging studies are conducted among patients who do not have any history or manifestations of renal

stone disease, nephrolithiasis and/or nephrocalcinoisis is much more common that might be expected (111). In study recent report of Cipriani et al, 55% of patients with primary hyperparathyroidism were shown to have unsuspected kidney stones by abdominal ultrasound (112). These observations have led to the widespread recommendation that renal imaging, with ultrasonography, CT or other modality, should be performed in primary hyperparathyroidism. In addition, urinary calcium should be measured. While the urinary calcium excretion, alone, may not be a highly predictive risk factor for kidney stones in primary hyperparathyroidism (113), hypercalciuria along with other urinary risk factors are helpful predictive indices (1,110).

An unexplained reduction in the creatinine clearance has also been regarded to be a potential renal manifestation of primary hyperparathyroidism. The value set by the Hyperparathyroidism Workshop Panel is a GFR of 60 ml/min/1.73 m^2 below which it is thought that PTH levels begin to rise in individuals with chronic kidney disease in the absence of PHPT. However, recent work by Walker et al. has indicated that PTH levels are not higher among individuals whose creatinine clearance is 30-60 cc/min when compared to those with clearances greater than 60 cc/min (114). However, in those with reduced renal function, <60 cc/min, histomorphometric parameters of more active parathyroid disease were evident (115).

Gastrointestinal Manifestations

Glucose Tolerance:

Attempts to link carbohydrate intolerance and frank diabetes mellitus to primary hyperparathyroidism have been made (116-118), but the association is even more tenuous than other associations that have been proposed (see below). Whether there is a true increase in the prevalence of Type 2 diabetes mellitus among subjects with asymptomatic primary hyperparathyroidism is not established (119-120).

Peptic ulcer disease.

Most studies place the incidence of peptic ulcer disease in primary hyperparathyroidism to be 10%, about the same percentage as in the general population. On the other hand, in genetic syndromes such as MEN1, in which 40% of patients may have clinically apparent gastrinomas, one does see more peptic ulcer disease (121). In these patients, improvement in the gastrointestinal symptomatology after parathyroidectomy has been reported (122).

Pancreatitis.

Although hypercalcemia can underlie pancreatitis, most large series have not reported an increased incidence of pancreatitis in primary hyperparathyroidism (123-125). The Mayo Clinic experience reported only 1.5% of those with primary hyperparathyroidism had coexistent pancreatitis (126). Most studies no longer support a clear association between primary hyperparathyroidism and pancreatitis (126-127).

Neuromuscular.

The classical neuromuscular dysfunction that used to be associated with primary hyperparathyroidism (128) is virtually never seen anymore. In a detailed neurologic study of 42 patients with a mean serum calcium concentration of 11.1 $\pm$ 0.1 mg/dl, Turken et al. (129) found no consistent pattern of abnormalities either on physical examination or on electromyography. Diniz et al. have reported peripheral neural alterations as demonstrated by reductions in reduced sural nerve conduction velocity but these abnormalities were not associated with any overt neurological symptoms or signs (130).

Vitamin D deficiency.

An important association has been made between the presence of overt vitamin D deficiency and clinical manifestations of primary hyperparathyroidism (131-132). Years ago, Lumb and Stanbury suggested that primary hyperparathyroidism is worse in the presence of vitamin D deficiency (133). This hypothesis has been extended even to mild asymptomatic primary hyperparathyroidism in which low 25-hydroxyvitamin D levels are associated with increased indices of disease activity (134). Many studies have documented the widespread prevalence of vitamin D deficiency in primary hyperparathyroidism (135-136), although recent studies suggest that with the more common use of vitamin D supplements, the incidence has

fallen (137). The idea is that even in primary hyperparathyroidism, where usual controls of parathyroid hormone secretion are deficient, vitamin D deficiency further fuels the hyperparathyroid state. To this point, Stein et al. has shown that when vitamin D levels, as measured by circulating 25-hydroxyvitamin D, are lower, PTH levels are higher (138). Target organs that might be expected to be adversely affected by vitamin D deficiency, such as the skeleton have been documented histomorphometrically. The picture is more mixed when microstructural and densitometric indices are assessed in patients with primary hyperparathyroidism who are or are not vitamin D deficient (139-141).

The logic follows that vitamin D replacement should be associated with better control of the hyperparathyroid state. Grey et al. (142) administered vitamin D3 (cholecalciferol) to 21 patients with mild primary hyperparathyroidism whose 25-hydroxyvitamin D levels averaged 20 ng/mL. Repletion consisted of a 50,000 International Unit (IU) capsule weekly for the first month and then 50,000 IU monthly for the next 12 months. Mean 25-hydroxyvitamin D levels after 12 months of vitamin D repletion rose to 31 ng/ml. Serum PTH levels fell by an average of 25% but the serum calcium did not change. Although urinary calcium excretion did not change significantly in most individuals, three subjects did develop marked hypercalciuria (.>400 mg/day). There was a tendency for bone turnover markers to fall but only the total alkaline phosphatase activity fell significantly. This report provides evidence for the hypothesis that vitamin D deficiency makes the biochemical features of primary hyperparathyroidism worse but does not give clear guidelines as to how vitamin D should be replaced in these subjects. In the only randomized control trial of reasonable levels of vitamin D supplementation (e.g., 2800 IU/day for 6 months), mean PTH levels fell by 17% without any change in the serum calcium concentration. In addition, the resorptive bone turnover marker, CTX, fell by 22% and BMD of the lumbar spine rose, surprisingly for such a short study, by 3.5%. (143). Amstrup et al. have reported a relationship between vitamin D deficiency and muscle strength in primary hyperparathyroidism (144), but more recent work by Rolighed et al. in a short 6-month study, did not find any beneficial effect of vitamin D supplementation on muscle function (145).

Non-Classical Manifestations of Primary Hyperparathyroidism

Neurobehavioral and Neurocognitive Features.

Neuropsychiatric and cognitive complaints are common but any specific relationship to the hyperparathyroid state continues to be controversial (146). One of the issues related to complaints of weakness, easy fatigability, depression, anxiety and related symptomatology is that they are non-specific and are found in many chronic disorders. Furthermore, it is very hard to quantitate these features on a verifiable scale that can be tested both before and after parathyroid surgery. Some, but by no means all, studies that have attempted to associate neuropsychiatric elements with primary hyperparathyroidism (147-151), suggest that there are psychological features of the disease that improve with surgery. Review of this literature underscores confounders among them such as variability in their observational design, small sample sizes, inclusion of subjects with symptomatic PHPT, lack of appropriate control groups, and short testing intervals following parathyroidectomy. Nevertheless, ongoing studies have added to our knowledge in this area.

Using newer instruments to test quality of life measures, a significant improvement in some aspects of well being and energy, as well as in the perception of health status have beenreported (152-154). Several observational studies of cognitive function (149-150, 154) have been inconsistent with some reports suggesting improvement after parathyroidectomy, and others not showing any changes (155-157).

The 2013 Workshop on the Management of Asymptomatic Primary Hyperparathyroidism reviewed relevant randomized studies of neurocognition and quality of life measures before and after parathyroid surgery in subjects with mild hypercalcemia. Rao et al. found no difference in baseline SF-36 scores between hyperparathyroid patients and normal subjects (158). They did show significant improvements after surgery in social functioning and emotional role function, but no differences were reported in other measures such as depression, somatization, aggression, obsessive-compulsive, interpersonal sensitivity, paranoid ideation and psychoticism. No significant differences between groups were noted in the 3

composite scores (Global Severity Index, Positive Symptom Distress Index, Positive Symptom Total), or in any or the 9 individual or 3 composite scores in the observational group alone over time.
Bolleslev et al. reported that the parathyroid patient population scored lower in all psychological domains and the mental component summary of the SF-36 (159). PHPT was associated with more psychiatric symptoms than controls. Two years after parathyroidectomy, there were no improvements in SF-36-assessed physical function, psychological domains of functioning or in psychiatric symptoms. In some of these domains, however, the control group was shown to have deteriorated.

Ambrogini et al. studied 50 patients with asymptomatic PHPT (160) and showed minimal but significant baseline differences between hyperparathyroid and normal subjects in emotional role function score that improved following surgery. Between-group analysis demonstrated a benefit of parathyroidectomy in bodily pain, general health, vitality and mental health. No differences were noted in any of the other SF-36 or SCL-90 domains between the two groups, and no worsening in the non-operated group was noted.
Walker et al. (161-162) have published their experience and commented on the neurocognitive domains after successful parathyroid surgery. In some, but not in all domains, improvement was seen, with the control population being individuals without primary hyperparathyroidism who had the same test 6 months apart and did not change.
In the study of Roman et al (163), successful parathyroidectomy was associated with improvements in depressive and anxiety symptoms as well as visuospatial and verbal memory. Pasieka et al reported a 10-year longitudinal study with a post-thyroidectomy control group showing that, at baseline, quality of life was worse in the patients with primary hyperparathyroidism and improved in a sustained manner in comparison to the control group in which there was no change (164). Using functional magnetic resononance imaging, Perrier et al. in a very small but controlled study did not demonstrate any lasting effecs of parathyroidectomy (165).

The difficulty in applying currently available metrics to neurocognitive and quality of life measures in primary hyperparathyroidism continues to prevent any definitive conclusions to be drawn in terms of any specific association with primary hyperparathyroidism and whether the association, if it exists, is reversibile after successful parathyroid surgery. The call for the 3rd international workshop on the management of asymptomatic primary hyperparathyroidism (166) for more studies in this area has been reiterated by the 4th International Conference (1). At this time, the published findings in patients on this matter are still not regarded to be sufficient alone for a recommendation for parathyroid surgery

Cardiovascular manifestations
Hypertension has long been regarded to be associated with primary hyperparathyroidism when the disease was typically symptomatic. In the more common clinical presentation of mild disease, hypertension is not clearly seen as a feature that can be specifically attributed to primary hyperparathyroidism (167). Although older studies showed a reduction in blood pressure immediately after parathyroidectomy (168-169), the much more common outcome as documented in most studies is that hypertension is not reversible with surgical cure (170-171). For these reasons, hypertension is not included among the guidelines for parathyroid surgery.
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Coronary artery disease in primary hyperparathyroidism was reported as a common feature by Roberts et al, but again that experience invokes a time when primary hyperparathyroidism was typically characterized by much higher serum calcium levels than we typically see today (172). Many of those subjects also demonstrated traditional cardiovascular risk factors. Using the coronary artery calcification score as measure of coronary artery calcification, several studies have not shown an association with primary hyperparathyroidism, beyond what one would expect on the basis of accepted cardiovascular risk factors (173-174). Similarly, myocardial and valvular calcifications, while clearly demonstrated in PHPT patients with marked hypercalcemia, are less likely to be seen in those with only mildly elevated serum calcium (175-176).
Left ventricular mass index (LVMI) has been associated with primary hyperparathyroidism in some , but not all (177-178), studies across a wide range of calcium levels. Some data suggest that LVMI is independent of hypertension, and is instead, associated with the PTH level (176-180). When studies

have been adjusted for cardiovascular risk factors, no increase in LVMI could be demonstrated (181-182). Interestingly, in the study of Walker et al., higher LVMI was associated with lower 25-hydroxyvitamin D levels. Whether or not LVMI, when abnormal, is reversible in primary hyperparathyroidism is key to determining the management implications of these findings. LVMI has been found to regress following parathyroidectomy in some, but not all, studies (177-180, 183-185). Other cardiovascular features which have been monitored such as the metabolic syndrome are not clearly improved after successful parathyroid surgery (186).

Population-based evidence supports an association between serum calcium concentration and carotid plaque thickness (187). In the study of Walker et al. (188), carotid intimal thickness was increased after adjustment for cardiovascular risk factors. After parathyroidectomy, there was no improvement (189). These studies have been limited by small sample sizes and by technical difficulties (190-192). Vascular dysfunction in patients with severe primary hyperparathyroidism has occasionally been shown (191-192), an observation that has also been made, at times, even in those with calcium levels as minimally elevated as 10.7-10.9 mg/dL (2.68-2.73 mmol/l)] (193). In mild PHPT, 2 studies have reported increased vascular stiffness (194-195).
The data summarized with regard to the cardiovascular system suggest that abnormalties in a number of categories, previously easily demonstrable when the disease was overly symptomatic, are now very difficult to establish even with modern and sophisticated instruments. More problematical are the conflicting data on the reversibility of these end points after successful parathyroid surgery. While the studies have been limited in size, the data, in the aggregate, do not make a compelling case for using any cardiovascular features, alone or together, as indications for surgery in primary hyperparathyroidism.

Malignancy
There are several reports of more cancers in patients with primary hyperparathyroidism (196-197). Many of these reports, however, are subject to selection bias. In patients with hypercalcemia detected unexpectedly on a biochemical profile, the most important cause to exclude is hypercalcemia associated with malignancy. Thus, the association between primary hyperparathyroidism and malignancy may be due simply to a more diligent search for cancer in patients with hypercalcemia. Another possible mechanism for a chance association between primary hyperparathyroidism and cancer results from the frequency with which clinically silent thyroid malignancies are found during neck exploration for parathyroid disease (198). Wermers et al. have reported, on the other hand, that following the diagnosis of primary hyperparathyroidism, the relative risk of death due to cancer is reduced with a relative risk ratio of 0.58 (199).

Mortality
Mortality does not seem to be increased in primary hyperparathyroidism, according to the epidemiology data from the Mayo Clinic experience (199). On the other hand, the Scandinavian and German literature does report increased mortality (200-201). The reason for this difference in mortality figures may again be explained by how advanced the disease presents. Mortality figures from the Scandinavian experience did correlate with the extent of hypercalcemia and the weight of the parathyroid adenoma (202). Also consistent with this idea is the Mayo Clinic experience in which those whose serum calcium was in the highest quartile did have an increased mortality (199). Another epidemiologica study reported increased mortality and morbidity in “mild hyperparathyroidism” (196). On the whole, these observations suggest that mild, asymptomatic primary hyperparathyroidism is not associated with increased mortality rates. On the other hand, when the disease presents in more symptomatic forms, mortality may be increased.

ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM
Although the discussion above covers a host of potential classical and non-classical target organs that can lead to symptomatology, most patients with primary hyperparathyroidism are asymptomatic. They have neither symptoms nor complications that are clearly and commonly associated with hypercalcemia or excessive parathyroid hormone. The preponderance of asymptomatic individuals raises important questions as to how to manage such individuals once the diagnosis is made. There is no controversy about the appropriate decision in individuals who are symptomatic. Surgery is clearly the right choice,

unless extenuating medical conditions preclude the surgery. Whether all patients, including those who are asymptomatic and whose hyperparathyroidism was discovered by accident, should have parathyroid surgery is a much more difficult question to address.

Indications for surgery in asymptomatic primary hyperparathyroidism

Primary hyperparathyroidism is cured when abnormal parathyroid tissue is removed. Since this is the only definitive approach to primary hyperparathyroidism, surgery is an acceptable approach to this disease even if patients are completely asymptomatic. However, the decision to recommend surgery is tempered by the fact that most patients with primary hyperparathyroidism are asymptomatic. In patients who are asymptomatic, a recommendation for an invasive procedure like surgery is not always met with ready acceptance on the part of the patient or the physician. On the other hand, the alternative, namely to recommend a conservative, non-surgical course, is tempered by the realization that there are few indices that predict who among the asymptomatic are at risk for experiencing complications of this disease (203) .

The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism has led to a revision of the guidelines for surgery (1-5, 204) since the previous Workshop that was held in 2008 (166). Among those with asymptomatic primary hyperparathyroidism, the following guidelines for surgery are shown in Table 2 and listed here:

1. Serum calcium concentration greater than 1 mg/dL above the upper limit of normal;
2. a. BMD by DXA T-score <-2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius;
   b. vertebral fracture by X-ray, CT, MRI, or Vertebral Fracture Assessment (VFA)
3. a. estimated GFR (eGFR) < 60 cc/min;
4. b. 24-hour urine for calcium > 400 mg/day (> 10 mmol/day) and increased stone risk by biochemical stone risk analysis; c. presence ofnephrolithiasis or nephrocalcinoisis by X-ray, ultrasound, or CT;
5. Age < 50.

Table 2. Guidelines for parathyroid surgery in asymptomatic primary hyperparathyroidism. Modified from Reference #1

2014 Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism (Bilezikian et al. JCEM, 2014)

Recommended Index	3rd Int'l Workshop (Bilezikian et al. JCEM 2009)	4th Int'l Workshop (Bilezikian et al., 2014)
Serum calcium (above normal)	>1.0 mg/dL	> 1 mg/dL
Skeletal	DXA: T-Score <-2.5 at any site; any fragility fracture	DXA: T-Score < -2.5 at any site; Vert Fx by X-ray or VFA
Renal	Clcr < 60 cc/min 24 hr urine: Not recommended	Clcr < 60 cc/min Stone by X-ray, CT, or ultrasound Urinary calcium: >400 mg/d plus other urinary biochemical indices of increased stone risk
Age	<50	< 50

[1] Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.
[2] If any one of these criteria are met, the patient is considered to be a candidate for parathyroid surgery.

If any one of these guidelines are met, the patient is a candidate for parathyroid surgery. It should be emphasized that these are guidelines, not rules. They are subject to modification by the physician and the patient. Some physicians will recommend surgery for all patients with asymptomatic primary hyperparathyroidism; other physicians will not recommend surgery unless clear-cut complications of primary hyperparathyroidism are present. Still others will use other criteria. The patient enters into this therapeutic dialogue as well. Some patients cannot tolerate the idea of living with a curable disease and will seek surgery in the absence of any of the aforementioned criteria. Other patients with coexisting medical problems may not wish to face the risks of surgery even though surgical indications are present.

It is important to recognize that the patient who presents with asymptomatic primary hyperparathyroidism and does not meet criteria for surgery may develop them over time (205). Particularly noteworthy is the 15-year natural history study of Rubin, Bilezikian et al. (206). In this study, years 10-15 were associated with reductions in cortical bone density and slight increases in the serum calcium concentration. Approximately 40% of patients met one or more guidelines for surgery over this period of time. Thus, monitoring is essential if patients are not to have parathyroidectomy. If a patient with asymptomatic primary hyperparathyroidism cannot be followed for any reason, therefore, surgery would seem to be the preferred option.

MONITORING PATIENTS WITH PRIMARY HYPERPARARATHYROIDISM WHO DO NOT UNDERGO PARATHYROID SURGERY.

Currently guidelines for monitoring are shown in Table 3 and summarized here.
1.. The serum calcium should be measured, annually.
2, On a regular basis- either yearly or every other year- 3-site DXA (lumbar spine, hip regions, and distal 13 radius) should be performed. If clinically indicated, X-ray or VFA of the spine should be performed (i.e., height loss, back pain).

3. eGFR annually. If renal stones are suspected in the interim, a 24-hour urinar for biochemical stone profile along with renal imaging by X-ray, ultrasound, or CT are advised.

Table 3: Management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroid surgery, Modified from #1

2014 Guidelines for Monitoring in Asymptomatic Primary Hyperparathyroidism
(Bilezikian et al. JCEM, 2014)

Index	3rd Int'l Workshop (Bilezikian et al. JCEM, 2009)	4th Int'l Workshop (Bilezikian et al, JCEM, 2014)
Serum Calcium	Annually	Annually
Skeletal	DXA: Every 1 or 2 years	DXA: Every 1 or 2 years; CT or VFA if clinically indicated
Renal	Clcr-Annually	Clcr-Annually; stone risk profile if clinically indicated Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated

SURGERY FOR PRIMARY HYPERPARATHYROIDISM.
In some respects the basic principles upon which surgery for primary hyperparathyroidism are based have not changed very much over the years. For example, it is as important now as it was in the past for parathyroidectomy to be performed by surgeons who are highly experienced and skilled in the operation (4). What has changed over the past decade is the operation itself. The standard operation for parathyroidectomy used to be a full exploration of the neck with identification of all 4 parathyroid glands. The rationale for identifying all four glands is that in 15-20% of patients with sporadic primary hyperparathyroidism, enlargement of more than one gland with four-gland hyperplasia will be present. Recent advances in preoperative imaging modalities by which the most likely cause of primary hyperparathyroidism, namely the single parathyroid adenoma, can be identified as well as the intraoperative use of the rapid immunoassay for PTH has changed the way most parathyroid surgeons perform the operation. The minimally invasive parathyroidectomy (MIP) under local anesthesia with intraoperative monitoring of PTH before and after removal is the preferred approach of most experts, (207). The MIP procedure has similar success rates and overall reduces operative time, does not require an inpatient setting, and is associated with fewer complications: all comparative benefits of the approach (208-209). MIP is dependent upon successful preoperative identification of the parathyroid adenoma. The operation consists of identification and removal, under local anesthesia and conscious sedation, of the abnormal tissue without visualization of other glands by the surgeon. Before and after the adenoma is removed, an intraoperative PTH level is obtained to ascertain that the gland removed is the only source of excess PTH (210-211). Such intraoperative PTH assays can be done literally within minutes, in the operating room, and thereby do not extend significantly the duration of the operation. If, within 2-10 minutes after removal of the adenoma, the intraoperative PTH level falls by greater than 50%, into the normal range, the adenoma removed can be safely assumed to be the only abnormal gland that was present and the operation is terminated. If the intraoperative PTH level does not fall by greater than

50% and/or remains above normal, the operation is extended and, if necessary, a full neck exploration is performed to seek other overactive glands (212). Success rates for parathyroid surgery with the MIP procedure are just as great as success rates with the classical 4-gland exploration, namely greater than 90% (207, 213). The advantages of the MIP procedure relate to the speed of the operation and the much more rapid recovery time in comparison to general anesthesia. In many centers, the patients is admitted to and discharged from the hospital on the same day.
In the case of parathyroid hyperplasia, options include subtotal parathyroidectomy with removal of 3.5 glands or total parathyroidectomy with immediate autotransplantation of parathyroid tissue into the forearm. If successful, the forearm site provides easy access to the transplanted tissue, should hyperparathyroidism recur. Cryopreservation facilities are necessary for autotransplantation in case the initial graft does not take. This approach is often used in cases of familial hyperparathyroidism in which 4-gland disease is generally the rule (214-215). The minimally invasive approach to surgical management of primary hyperparathyroidism has been extended to multigland disease as reported by Lebastchi et al. (216).

PARATHYROID GLAND IMAGING
Pre- operative imaging is of an important aspect of parathyroid surgery in order to identify the abnormal parathyroid tissue (217-219). It is important to note that the decision to proceed with parathyroid gland imaging presumes not only that the diagnosis of primary hyperparathyroidism has been made but also that surgery is planned. .

Sestamibi imaging is of value in localizing abnormal parathyroid tissue. The sensitivity and specificity varies among institutions and should be considered in evaluating the results of a study. In centers with experience, the technique can be highly sensitive (approaching 90%) and very accurate (97%). (220-221). The combination of sestamibi with single photon emission omputed tomography (SPECT) alone (222) or in combination with CT can improve localization (223). The sensitivity for small adenomas or double adenomas or hyperplasia is much lower. Sestamibi scans are helpful in identifying ectopic tissue, particularly in the mediastinum and can be a useful tool in guiding the surgical approach to parathyroidectomy.

Ultrasound is a non-invasive modality which is easily available at low cost. Co-existing thyroid pathology can be assessed and these results integrated with sestamibi imaging (224). Sensitivity can range from 42–82% with specificity of approximately 90% (225).

CT scanning of the neck and mediastinum is a valuable tool in assessing the parathyroid anatomy and can be particularly useful in identifying ectopic parathyroid glands in the mediastinum (226). Four dimensional CT Scans (4DCT) provide additional information of value, in guiding the surgical approach, and appears to be becoming a preferred localization approach in a number of centers (227-228). MRI with contrast can be of value for lesions in the mediastium and for those individuals who have persistent disease following parathyroidectomy (229).
Arteriography and selective venous sampling can be of value in those individuals with persistent or recurrent disease and in whom other imaging modalities have not been fruitful in indentifying the abnormal parathyroid tissue (230).

CLINICAL COURSE OF PRIMARY HYPERPARATHYROIDISM
The change in clinical presentation of primary hyperparathyroidism from a symptomatic to an asymptomatic disease has required longitudinal studies to assess the extent to which any features progress or complications appear over time. Attempts to document the natural history of primary hyperparathyroidism extend back to an earlier generation through the work of Sholtz and Purnell (231). With allowance for confounders that weakened conclusions that could be drawn from their longitudinal study, they did demonstrate that primary hyperparathyroidism is not necessarily a progressive disease. The first truly long-term prospective study of the natural history of primary hyperparathyroidism with or without surgery has been provided by Silverberg, Rubin, Bilezikian and their colleagues over a 10-15 period of surveillance (104,105, 206).

Natural History Without Surgery

About 50% of patients with asymptomatic primary hyperparathyroidism will not meet any guidelines for surgery. Although one could justify the recommendation for surgery, even without any guidelines being met, many of these subjects and their physicians are reluctant to recommend the surgical approach. Data are now available on these patients with mild, asymptomatic primary hyperparathyroidism who have been followed for up to 15 years without surgery or specific medical therapy (206, 232). Biochemical abnormalities associated with primary hyperparathyroidism are stable during long-term follow-up of mild, asymptomatic patients over the first 10 years. The serum calcium, however, does tend to increase slightly during the years 10-15. There is no evidence that mild primary hyperparathyroidism is associated with progressive renal impairment, at least as measured by the serum creatinine, blood urea nitrogen, or creatinine clearance. Over a 10-year period, yearly bone mass measurements did not reveal that the group as a whole showed any declines at the lumbar spine, hip, or distal radius. The individual data from the 10-follow up study however do indicate that about 25% of subjects show evidence of progressive disease. Four percent of patients developed substantial worsening of their hypercalcemia (serum calcium > 12 mg/dl) and 15% developed marked hypercalciuria (urinary calcium excretion > 400 mg/day). Approximately 12% of patients demonstrated declines in bone mineral density to the point where they met NIH guidelines for surgery. A total of 37% of subjects followed for up to 15 years met one or more indications for parathyroid surgery. There were no clinical, biochemical, or densitometric predictors of disease progression that could be identified, except for the observation that patients at risk were younger, on average, than those who did not progress over time (52 vs. 60 years old).

More recent data extending these results to 15 years indicate that bone mineral density at the hip and distal radius eventually does decline as a group (206). The lumbar spine bone density remains stable. These recent observations suggest that over time the proclivity of parathyroid hormone to be catabolic at cortical sites eventually surface in some patients. Alternatively, the need for such long term surveillance may highlight the slow but progressive nature of the bone disease in this disorder. The relative stability of BMD at the lumbar spine is supported by histomorphometric data from bone biopsies showing in primary hyperparathyroidism that age-related declines in indices of trabecular connectivity are not evident (233). Thus, despite advancing age, patients with primary hyperparathyroidism maintain microarchitecture of cancellous elements.

In all patients who met surgical guidelines, such as nephrolithiasis, and chose not to undergo parathyroid surgery, the disease clearly continued to progress as demonstrated by recurrent nephrolithiasis or other complication of primary hyperparathyroidism. Although only few patients in this category were followed without surgery, the fact that all of them showed evidence for progression argues that these patients are best advised to under parathyoidectomy.

Natural History With Surgery

Following parathyroid surgery, there is a prompt return to normal of serum and urinary calcium levels along with the PTH level per se. Studies of bone markers are limited but indicate a reduction of bone turnover following successful surgery. Although the choice of markers in individual studies varied, our group (234), Guo et al. (235) and Tanaka et al. (236) all report declining levels of bone markers following surgery. Data are also available concerning the kinetics of change in bone resorption versus bone formation following parathyroidectomy. Markers of bone resorption decline rapidly following successful parathyroid surgery, but indices of bone formation decline more gradually (234). Urinary pyridinoline and deoxypyridinoline fell as early as two weeks post-operatively, preceding reductions in alkaline phosphatase. Similar data were reported by Tanaka et al. (236), who demonstrated a difference beween changes in osteocalcin and urinary N-telopeptide following parathyroid surgery; and Minisola et al. who reported a decrease in bone resorption markers without any significant change in alkaline phosphatase or in osteocalcin (237). The persistence of elevated bone formation markers coupled with rapid declines in bone resorption markers indicates a shift in the coupling between bone formation and bone resorption toward an anabolic accrual of bone mineral after surgery.

After successful parathyroid surgery, increases in BMD are seen at the lumbar spine, hip regions, and, after some delay, at the distal third radius site as well (figure 3; 159-160, 206, 232, 238-241). In one study (206), this global increase in BMD after parathyroidectomy was sustained for as long as 15 years. Sankaran et al confirmed these individual reports in their meta-analysis of post-operative increases in BMD from a number of different studies (242). The effects of surgery on fracture risk was evaluated and compared to controls in a 10-year cohort study (243). Fracture-free survival was significantly improved with surgery in comparison to no surgery.

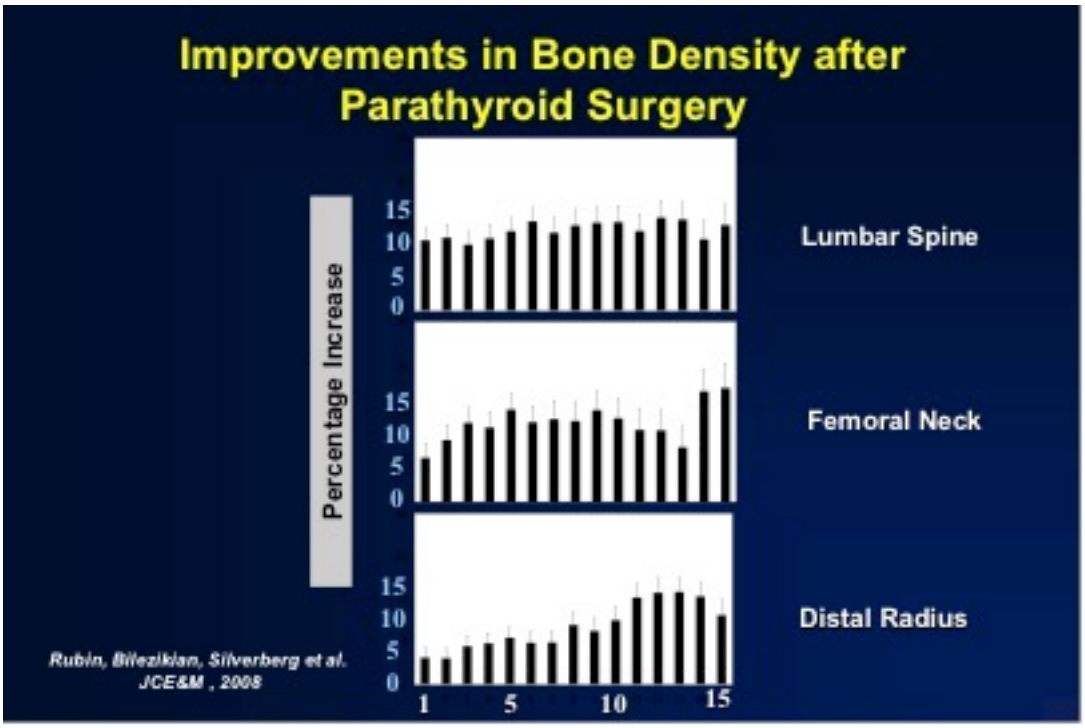

Figure 3. Conservative vs Surgical Management of Primary Hyperparathyroidism: changes in bone mineral density. Data shown are the cumulative percentage changes from baseline over 15 years of follow-up in patients who did not undergo parathyroidectomy and in those who underwent parathyroidectomy. (Reprinted with permission from reference #206)

Lumbar spine and femoral neck bone density increase to the same extent in a subgroup of postmenopausal women with primary hyperparathyroidism who underwent parathyroid surgery. Part of increase in bone density at these sites is related to remineralization of the enlarged remodeling space. Other potential explanations for the postoperative increase in bone density include the possibilities that normal pulsatility and amplitude of the secretory patterns of parathyroid hormone are restored. In patients who have vertebral osteopenia or frank osteoporosis (15% of the population of our hyperparathyroid subjects), the postoperative increase in bone density is even greater than the group as a whole, reaching an average of 20% higher after surgery (85).
The capacity of the skeleton to restore itself is seen dramatically in young patients with severe primary hyperparathyroidism. Kulak et al. (243) reported 2 patients with osteitis fibros cystica who experienced increases in bone density that ranged from 260 to 430%, 3-4 years after successful surgery.

An important question yet to be resolved is whether the postoperative improvement in bone mineral density is associated with an increase in bone strength and a reduction in fracture incidence. The complex relationship between bone strength and bone density in primary hyperparathyroidism, as already noted, involves other skeletal properties besides BMD, such as microarchitecture and bone size. It is clear that PTH is affecting these properties of bone in the disease that may well tend to counteract the impression that fracture risk is increased in primary hyperparathyroidism. On the other hand, after

parathyroid surgery, it is not known to what extent these other properties of bone may also change and conceivably mitigate or augment the salutary effects on BMD. Moreover, since it is now clear that changes in BMD in the context of therapeutics for osteoporosis do not account for more than a small component of the reduction in fracture incidence, a similar loose relationship could exist in terms of BMD and fracture risk after successful parathyroidectomy. The post parathyroidectomy study of Lundstam K et al. addressed the issue of fractures but the numbers were too small and the follow up time too short to be able to draw any conclusions (245). In patients who underwent parathyroid surgery because of their renal stone disease, there were no recurrences of nephrolithiasis over a decade. These observations are consistent with other published reports in which a reduction in stone incidence of 90% is typically seen after successful surgery. The 5-10% of patients who continue to form stones after parathyroidectomy may well have a non-parathyroid cause for their stone disease, which persists despite cure of their primary hyperparathyroidism (246-247). Alternatively, previous stone disease could have damaged the kidney such that the local environment continues to be hospitable for recurrent stones even after successful surgery.

NON-SURGICAL APPROACHES TO PRIMARY HYPERPARATHYROIDISM

Many patients who not meet guidelines for surgery are followed conservatively. Patients should be encouraged to maintain a normal intake of calcium, despite the temptation to place constraints on dietary calcium. Calcium excretion is not different when individuals on high or low calcium intakes are compared (248). On the other hand, in those with elevated levels of 1,25-dihydroxyvitamin D3, high calcium diets can be associated with worsening hypercalciuria (249). This observation suggests that dietary calcium intake in primary hyperparathyroidism can be liberalized to 1000 mg/day if 1,25-dihydroxyvitamin D levels are not increased, but should be more tightly controlled if 1,25-dihydroxyvitamin D levels are elevated. Jorde et al.showed that modest supplementation of dietary calcium in those with subnormal intake had no deleterious effects on any biochemical parameters of the disease (250).

Phosphate

Oral phosphate can lower the serum calcium by up to 1 mg/dL (248). Problems with oral phosphate included limited GI tolerance, possible further increase in PTH levels, and the possibility of soft tissue calcifications, after long term use (248). This agent is no longer advisable as a chronic treatment for primary hyperparathyroidism.

Estrogen

Although the beneficial effects of estrogen therapy in primary hyperparathyroidism are well documented in the literature (251-253**),** risks associated with estrogen use have also been well publicized (254**).** In addition, the amount of estrogen required to reduce the serum calcium in primary hyperparathyroidism is higher than most tolerate, although some positive results have been observed with lower doses (255). Nevertheless, among postmenopausal women who are not candidates for parathyroid surgery or refuse this option, and will agree to take estrogen, it remains a reasonable alternative. Estrogen use is associated with a 0.5 to 1.0 mg/dL reduction in total serum calcium levels in postmenopausal women. PTH levels do not change. Estrogen-treated patients also show a salutary effect on BMD at the femoral neck and lumbar spine (253). This makes estrogen replacement therapy an attractive approach in the postmenopausal woman with very mild primary hyperparathyroidism, who does not have any contraindications to such therapy.

Selective Estrogen Receptor Modulator (SERM).

The SERM, raloxifene is a potential alternative to estrogen. Rubin et al. (256) studied 18 postmenopausal women with primary hyperparathyroidism. They were randomly allocated to an 8-week course of raloxifene (60 mg/day) or placebo. There was a 4-week follow up period off therapy. In the raloxifene group, the average serum calcium fell significantly by about 0.5 mg/dL. The placebo group did not show any change in serum calcium over this period of time. Along with the reduction in the serum calcium concentration, bone turnover markers, osteocalcin and N-telopeptide, significantly fell. During the 4-week wash out period when the subjects on raloxifene were withdrawn, serum calcium concentration and bone turnover markers returned to baseline values. Raloxifene administration was not associated

with any changes in serum parathyroid hormone or in urinary calcium excretion. In an open pilot study of only 3 patients, Zanchetta and Bogado (257) showed a similar reduction in serum calcium with raloxifene. They also were able to show increases in bone mineral density in their subjects. Clearly, these are promising data but more extensive, controlled studies are needed.

Vitamin D.

Vitamin levels in primary hyperparathyroidism should be sufficient to prevent further worsening of the hyperparathyroid state. Most experts suggest that the level should be greater than 30ng/mL (75 nmol/l). Administration of vitamin D in primary hyperparathyroidism has been covered earlier in this chapter.

Bisphosphonates.

The conceptual basis for expecting that bisphosphonates have potential as a medical approach to primary hyperparathyroidism is due to their antiresorptive properties. In primary hyperparathyroidism, even when completely asymptomatic, bone turnover is increased (258)**.** Although they do not affect PTH secretion directly, bisphosphonates could reduce serum and urinary calcium levels. An additional benefit would be to increase BMD. Early studies with the first generation bisphosphonates (etidronate aand clodronate) were disappointing (259-260). The aminosubstituted bisphosphonates have been studied more extensively. In a very short 7-day study of 19 patients with primary hyperparathyroidism, risedronate lowered the serum and urinary calcium as well as hydroxyproline excretion significantly while the parathyroid hormone concentration rose (261). More extensive studies have been conducted with alendronate. A randomized, controlled study of 26 patients with primary hyperparathyroidism (262) evaluated effects on BMD after a two-year study with 10 mg every other day (5mg/d) of alendronate. Alendronate was associated with a reduction in bone turnover and an increase in BMD over baseline by 8.6+/-3.0%, in the hip by 4.8+/-3.9% and in the total body by 1.2+/-1.4%. The control group that did not received alendronate lost about 1.5% BMD in the femoral neck. Hassani et al. investigated 45 patients with asymptomatic primary hyperparathyroidism with alendronate, 10 mg daily, in a study that was not randomized (263). Nevertheless, the results also showed that alendronate was associated with increases in BMD of the lumbar spine and femoral neck. Three well-controlled studies following up on these experiences with alendronate have been even more impressive (264-266). The study by Khan et al. (266) was a randomized, double-blinded study of daily alendronate versus placebo in 44 patients with mild, asymptomatic primary hyperparathyroidism. After 1 year, the placebo group was crossed over to alendronate treatment while the group initially assigned to alendronate continued on the bisphosphonate for another year. After 1 year of alendronate, there was a significant 5.3% increase in lumbar spine, increasing further to 6.85 % by year 2. Total hip BMD increased by 3.7% in year 1 and by 4.01 % in year 2. There was no significant change in distal radius BMD. When the placebo group, that did not show any change in BMD at any site after the first year, was crossed over to alendronate in year 2, the increase in BMD matched the increase after 1 year in the group that was initially assigned to drug (figure 4). The bone turnover markers, N-telopeptide and bone-specific alkaline phosphatase activity fell by over 50%. There were no changes in ionized calcium, phosphorus or PTH. The results from the subgroup of men treated with alendronate were similar (267-268). The experience of Chow et al. (265) in their 1-year randomized, placebo-controlled study is remarkably similar to the experience of Khan et al. except that there was a significant alendronate-associated reduction in the serum calcium concentration, by 0.34 mg/dL.

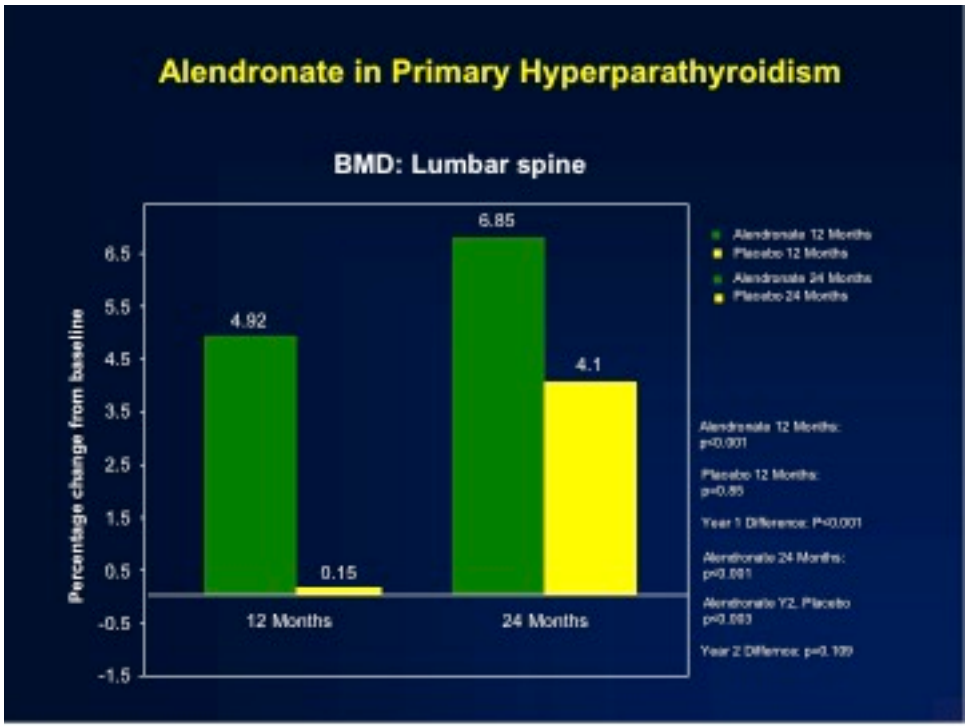

Figure 4. The effect of Alendronate on bone mineral density in primary hyperparathyroidism. With alendronate, bone mineral density increases significantly after 1 year, while the placebo group shows no change until it is crossed over to alendronate in year 2. (Modified from reference #266).

The cumulative investigative experience with alendronate in primary hyperparathyroidism suggests a use for this drug in subjects whose bone density is low, but not in the osteoporotic range. Such individuals might be at substantial risk for fracture because they have other risk factors. If these individuals do not meet any criteria for parathyroid surgery, it would seem reasonable to consider alendronate. This decision should be made with the full realization that no bisphosphonate has received yet an indication for use in primary hyperparathyroidism by the FDA. A recent report associated the use of alendronate with an increase in fracture risk after successful parathyroidectomy (269). It is hard to draw any conclusions from this study because of the likelihood of selection bias that would have targeted those at greatest risk for fracture for alendronate therapy.

Calcimimetics.

A more targeted approach to the medical therapy of primary hyperparathyroidism is to interfere specifically with the production of PTH. Agents that alter the function of the plasma membrane cellular calcium sensing receptor exemplify this concept. By binding to a site different from the calcium binding site per se, these agents increase the affinity of the receptor for extracellular calcium. These calcimimetics.would be expected to increase the signal generated by the calcium-calcium receptor complex and lead to an increase in intraceullar calcium. An increase in the intracellular calcium should inhibit the synthesis and secretion of PTH from the parathyroid cell.

The phenylalkylamine (R)-N-(3-methoxy-alpha-phenylethyl)-3-(2-chlorophenyl)-1- propylamine [R-568], was the first such calcimimetic compounds to be tested clinically (270). In a pilot study by Silverberg et al., it was shown to reduce serum calcium concentration and PTH in a dose-related fashion among postmenopausal women with primary hyperparathyroidism (271). A more potent calcimimetic, cinacalcet hydrochloride has been approved by the FDA in the management of the hypercalcemia associated with primary hyperparathyroidism (272-273). Shoback et al. (274) studied cinacalcet hydrochloride in 22 patients with primary hyperparathyroidism. In this dose-ranging study, patients were given placebo or drug in amounts of 30, 40, or 50 mg twice daily for 15 days. In all dose groups, except placebo, cinacalcet hydrochloride was associated with a normalization of the serum calcium after the second dose and remained normal values for the entire 2-week period. Maximal reductions in PTH, over 50%,

occurred 2-4 hours after dosing. There were no significant changes in urinary calcium excretion. Peacock et al. have followed this pilot study with a longer trial in which subjects were treated for 3 years (275). Most patients treated with cinacalcet hydrochloride achieved the primary endpoint, namely normocalcemia (figure 5). The serum calcium remained normal for the entire duration of the study. This experience was extended to 5 years, again with maintenance of normal calcium levels throughout (276). Cinacalcet has been shown to be effective in primary hyperparathyroidism across a spectrum of severity (277-278) as well as in intractable disease (279).

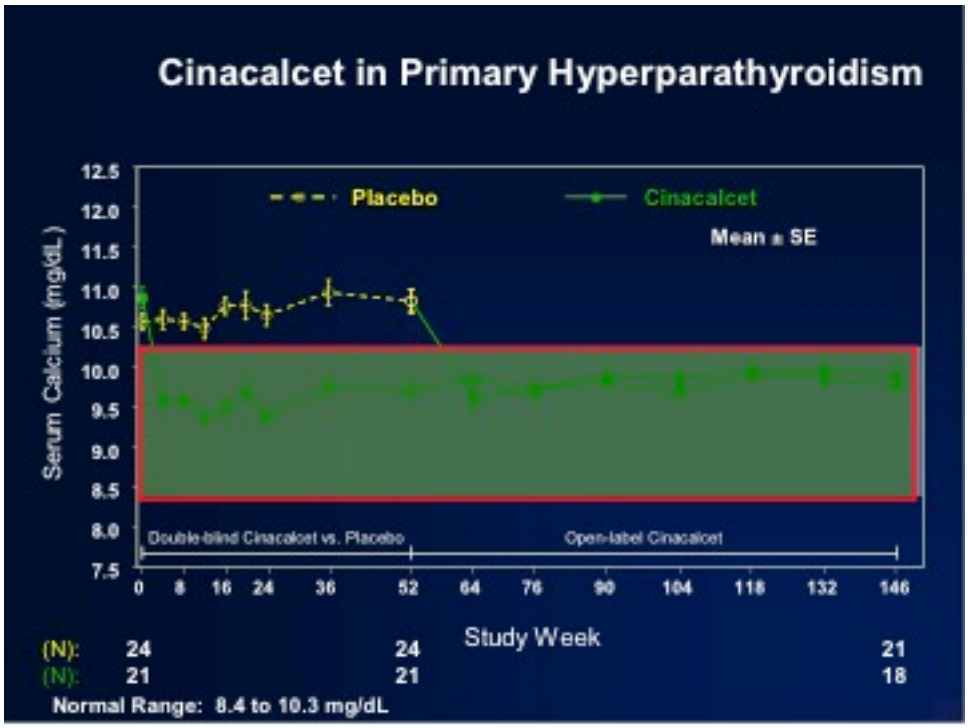

Figure 5. Cinacalcet in primary hyperparathyroidism. Cinacalcet is associated with a rapid and sustained normalization of the serum calcium concentration.(from reference #275 with permission).

The calcimimetics have also been studied in parathyroid cancer. The first experience with a patient with end-stage parathyroid cancer and intractable hypercalcemia was with the first generation calcimimetic, R568 (280). On R568, the patient's hypercalcemia remitted from 17 mg/dL to 11-12 mg/dL and was controlled at this level for 2 years. A much larger experience with cinacalcet hydrochloride has been gained in parathyroid cancer by Rubin et al. (281). In a study of 21 patients with parathyroid cancer, she showed that the serum calcium could be controlled in most patients although doses up to 90 mg four times daily were needed. The PTH did not uniformly fall; in some patients, there was even an increase in PTH, despite the reduction in the serum calcium. Additional studies have provided further evidence for the effectiveness of cinacalcet hydrochloride in parathyroid cancer and in severe primary hyperparathyroidism (282-284).

Acknowledgements:

The work in this chapter that refers specifically to the author's research was supported by NIH grant, DK32333 from NIDDK.

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