Asymptomatic primary hyperparathyroidism: present management and future options

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Summary

Primary hyperparathyroidism is a common disorder of mineral metabolism characterized by incompletely regulated, excessive secretion of parathyroid hormone from one or more of the parathyroid glands. In adults with the disease, a single, benign adenoma is seen approximately 80 percent of the time, with multiple gland involvement making up for most of the remaining patients. Very rarely, a parathyroid cancer is responsible but malignant parathyroid disease is rare, being seen in less than 0.5 percent of patients with primary hyperparathyroidism. Primary hyperparathyroidism is the most common cause of hypercalcemia and should always be considered in any individual with hypercalcemia. In this article, we will review important clinical and diagnostic features of primary hyperparathyroidism. We will review current recommendations by which the clinician is guided as to the choice between surgery and medical management, and focus then directly on non-surgical options in the management of asymptomatic primary hyperparathyroidism.

KEY WORDS: Primary hyperparathyroidism, hypercalcemia.

Diagnosis

The diagnosis of primary hyperparathyroidism is generally very straightforward, even though there are many causes of hypercalcemia. Since in primary hyperparathyroidism, parathyroid hormone (PTH) is oversecreted, a PTH immunoassay that reliably detects this increased PTH production is a cornerstone of diagnosis. PTH levels by currently available immunoradiometric assay (IRMA) have the requisite sensitivity and specificity; they reveal PTH levels that are either frankly elevated or in the upper range of normal despite hypercalcemia. In malignancy, the other most common cause of hypercalcemia, the PTH level will be suppressed, even if the cause of the hypercalcemia in malignancy is parathyroid hormone related protein (PTHrP). The IRMA in general use in the United States for over 20 years, however, has recently been shown to detect not only the full-length (1-84) amino acid molecule, but also amino terminally truncated forms of PTH (1). Recent studies report a mixture of peptides similar in size to PTH (1-84) but with three to 14 amino acids deleted from the amino terminus (2); PTH (7-84) is the most prominent of these species (2). These forms constitute up to 50 percent of the circulating species of PTH in normal subjects (1, 2). In secondary hyperparathyroidism in renal failure and in primary hyperparathyroidism these forms constitute a higher percentage in the circulation than in normal subjects (1, 2). An IRMA for PTH that measures only the biologically active, full-length molecule [PTH(1-84)] has become available (3, 4). The newer IRMA does not detect the large PTH fragment. It remains to be seen whether this newer assay will be shown to have more diagnostic utility in primary hyperparathyroidism (2, 3, 5). Silverberg et al. (5) compared this newer assay with the older IRMA and a mid-molecule-specific radioimmunoassay (RIA) in 56 subjects with primary hyperparathyroidism. The newer assay was shown to be elevated in 96 percent of subjects as compared to 73 percent and 63 percent using the older IRMA and the RIA, respectively. However, in chronic renal failure and secondary hyperparathyroidism where the newer IRMA assays might be expected to more discriminant, results appear similar (5a). The presumptive diagnosis of primary hyperparathyroidism in subjects whose calcium and PTH levels are elevated has to take into account other situations in which the serum calcium and PTH levels can be elevated. Drug-induced hypercalcemia due to lithium or thiazide diuretics is readily apparent because of the history. In familial hypocalciuric hypercalcemia (FHH), the PTH can also be elevated, but it is distinguished from primary hyperparathyroidism by family history and exceedingly low urinary calcium excretion. If needed in the management of families suspected of FHH, detection of a specific gene abnormality in the calcium receptor can be sought (see other article in this series).

Although most patients with primary hyperparathyroidism have elevated serum calcium levels, a subgroup has been characterized with normal serum calcium levels. Patients with normocalcemic primary hyperparathyroidism are distinct from patients with primary hyperparathyroidism and abnormal PTH levels in whom the serum calcium level is intermittently elevated. The key consideration in this setting in which PTH levels are elevated when the serum calcium is normal, however, is not primary hyperparathyroidism but secondary hyperparathyroidism in which the parathyroid glands are appropriately responding to a hypocalcemic stimulus. It is particularly important to rule out vitamin D insufficiency because it is so common in the population. The initial descriptions of normocalcemic primary hyperparathyroidism included a requirement that 25-hydroxyvitamin D (25(OH)D) levels had to be greater than 20 ng/ml. Maruani et al. (6) and Silverberg and Bilezikian (7) have described patients in whom this situation exists. With a revision upwards in the definition of sufficient vitamin D levels (8), it is important to

be sure that these patients are truly vitamin D sufficient. Vitamin D repletion to levels of 25(OH)D that are greater than 30 ng/ml without an alteration in the elevated PTH levels is necessary to sustain the diagnosis. Patients with normocalcemic primary hyperparathyroidism may represent the earliest manifestations of primary hyperparathyroidism.

An explanation for why this entity is being recognized more commonly today may reside in the fact that many endocrinologists and other osteoporosis specialists evaluate the skeletal status of women at risk for osteoporosis not only with determination of bone density but also with calciotropic hormone measurements. When these patients are discovered, it is of interest that certain clinical manifestations of primary hyperpara-thyroidism are already present (9, 10). It would appear that the hyperparathyroid process is being established in this earliest phase of the disease when patients are not hypercalcemic. The natural history of this variant of primary hyperparathyroidism is not known. Discussions in this article and others generally do not address therapeutic and management recommendations for these individuals because we do not know their natural history. It is likely that some of these patients will develop more overt primary hyperparathyroidism with hypercalcemia but it is also possible that some of these patients will continue to show elevated levels of PTH without hypercalcemia for years, having achieved a new steady state that does not progress.

Evaluation

Skeletal manifestations

The demonstration of skeletal involvement in asymptomatic primary hyperparathyroidism depends upon dual energy X-ray absorptiometry (DXA). Classical radiographic features are rarely seen. DXA shows classic pathophysiological effects of PTH in terms of a reduction in bone density of the distal third of the radius, a site of cortical bone (11). The proclivity of PTH to be catabolic for cortical bone is in constrast to its protective effect on cancellous bone (Fig. 1). Thus, at a site enriched in cancellous bone, namely the lumbar spine, bone mineral density tends to be reasonably normal. At a site that contains a more even admixture of cortical and cancellous elements, namely the hip region, bone mineral density is intermediate between the cortical and cancellous sites. This pattern is seen not only in unselected cohorts of subjects with primary hyperparathyroidism but also in postmenopausal women (12), in whom one might expect to see selective reductions in lumbar spine bone density because of the estrogen deficiency. Although this classic densitometric profile is most commonly seen, a distinctive pattern characterized by vertebral osteopenia can also be detected at the time of diagnosis (13).

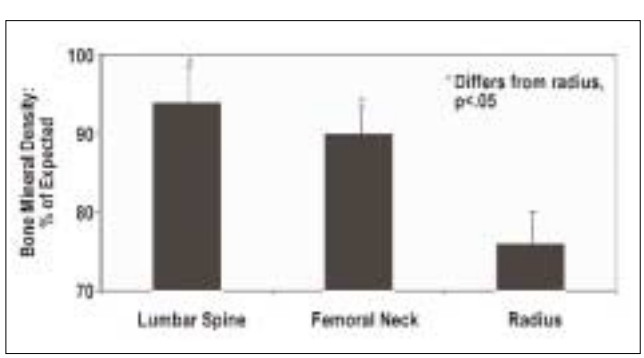

Figure 1 - The densitometric signature of primary hyperparathyroidism. Bone mineral density is shown at all three skeletal sites in a cohort of patients with primary hyperparathyroidism. Note preferential involvement of the distal radius, 1/3 site, with relative preservation of the lumbar spine (Adapted from reference #12).

Histomorphometric analysis of the bone biopsy in primary hyperparathyroidism shows cortical thinning, maintenance of cancellous bone volume, and accelerated bone remodeling (14, 15). Other features emphasize the point that the cortical bone compartment is at risk in primary hyperparathyroidism. The biopsy studies have also shown that indices of trabecular connectivity are actually greater than expected. Even the expected age-dependent loss of cancellous bone is not seen in primary hyperparathyroidism (14, 16-18). Based upon the densitometric data, it might be expected that the cortical skeleton would be at greater risk than the cancellous skeleton for fracture. The data are conflicting, however, with some studies showing an increase and other studies no increase in incidence of vertebral fractures (19-23).

The retrospective review of a 28-year Mayo Clinic experience concluded that overall fracture risk was increased at all sites except the hip (24). Expectations of fracture incidence in primary hyperparathyroidism have to take into account other skeletal effects of PTH besides a change in bone mineral density. If bone density were the only factor to consider, the distal forearm would be the site at greatest risk. It is now clear that bone density is only one of several important qualities of bone, all of which are influential in the overall assessment of fracture risk. Since PTH has important effects on some of these other qualities of bone, such as bone size and microarchitecture, reductions in bone mineral density may not directly relate to fracture risk. For example, cortical thinning through PTH-mediated endosteal resorption might be compensated in primary hyperparathyroidism by periosteal apposition, leading to bone that may be increased in cross sectional diameter (25), as demonstrated by Chen et al. (26) using pQCT technology. The increase in bone size would give greater biomechanical protection, even though bone density is reduced. Additionally, it is important to consider the generally well-preserved cancellous microarchitecture in primary hyperpara-thyroidism, another factor that might be protective. Thus, in primary hyperpara-thyroidism, certain skeletal features tend to compete with each other: cortical thinning favoring an increased fracture risk; increased bone size and preserved microarchitecture favoring a reduction in fracture risk. These considerations suggest the need for prospective studies of site-specific fracture incidence in primary hyperparathyroidism (27, 28).

Renal involvement

Although the incidence of nephrolithiasis is much less common than its incidence in the classic, older presentation of primary hyperparathyroidism, kidney stones remain the most common manifestation of primary hyperparathyroidism, with estimates placing the incidence of kidney stones now at 15 to 20 percent (29). 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.

Other organ involvement

Neurologic and cognitive signs or symptoms. Perhaps the most common nonspecific complaints of patients with primary hyperparathyroidism are those of weakness and easy fatigability (30). These complaints do not reflect the classic neuromuscular syndrome, in which type II muscle cell are dysfunctional

(31). In asymptomatic primary hyperparathyroidism, this specific neuromuscular disorder is rarely seen (32). Nevertheless, the nonspecific complaints of patients in this regard are noteworthy. They often report some degree of constitutional, behavioral and/or psychiatric symptomatology and, in some studies, such symptoms have been documented by psychometric testing (33). Reports exist in which there is apparent improvement after successful parathyroid surgery (34-36), while others have not been able to document changes postoperatively (36, 37). This issue remains unsettled.

Cardiovascular system. Interest in the effect of primary hyperparathyroidism on cardiovascular function is rooted in pathophysiologic observations of hypercalcemia in which hypertension, left ventricular hypertrophy and arrhythmias are common (38-41). The impression shared among investigators at the recent National Institutes of Health (NIH) Workshop on Asymptomatic Hyperparathyroidism and reviewed in the summary statement from that conference is that asymptomatic hyperparathyroidism is not associated with overt cardiovascular abnormalities (41, 53). It was noted that more severe forms of hyperparathyroidism detected in some European centers (38-40), especially when associated with hypertension, had left ventricular hypertrophy and valvular calcifications with evidence in some patients of regression after successful parathyroidectomy (38-41). In multiple endocrine neoplasia (MEN) syndromes, the presence of pheochromocytoma or hyperaldosteronism could, of course, lead to cardiovascular manifestations. In asymptomatic primary hyperparathyroidism, hypertension, when present, does not change after successful parathyroid surgery. Whether any cardiovascular abnormalities are demonstrable in mild asymptomatic primary hyperparathyroidism will require highly sensitive measurements of cardiovascular function (42-44).

Vitamin D in primary hyperparathyroidism

In countries where biochemical screening tests are not routinely employed, more classic presentations of primary hyperparathyroidism overtly involving the skeleton and the kidneys are described as common occurrences (45-47). Lack of routine screening tests helps, in part, to explain these findings but it is not an adequate explanation by itself. Vitamin D deficiency is also common, in countries where primary hyperparathyroidism is a symptomatic disorder, an observation that fits with the proposal made years ago by Lumb and Stanbury that primary hyperparathyroidism is worse in the presence of vitamin D deficiency (48). Even in mild, asymptomatic primary hyperparathyroidism, it has been shown that low 25(OH)D levels are associated with increased indices of disease activity (49). In these patients with primary hyperparathyroidism, it seems reasonable to consider restoring vitamin D to sufficient levels. The rationale is that to a certain extent, vitamin D deficiency may be fueling the pathophysiological processes associated with poorly controlled PTH secretion. By restoring vitamin D levels to normal, that component of the PTH secretory drive would be ameliorated. Despite the attractiveness of this approach, providing vitamin D to these individuals could raise their serum calcium further. To address this question, Grey et al. (50) recently reported on 21 patients with mild primary hyperparathyroidism whose 25(OH)D levels were < 20 ng/ml. Repletion was accomplished by the administration of vitamin D_3 (cholecalciferol), 50,000 IU weekly (1 tablet), for the first month and then 50,000 IU monthly for the next 12 months. The baseline serum calcium was 10.8 ± 0.5 mg/dl. PTH was 138 ± 70 pg/ml (nl: 10-65) and the 25(OH)D level was 11 ± 5 ng/ml (nl reference range, 11-55). Mean 25(OH)D levels after 6 and 12 months of vitamin D repletion were 30 ± 7 ng/ml and 31 ± 6 ng/ml, respectively. The serum PTH level declined by an average of 25 percent during vitamin D repletion, but the serum calcium did not change. There was a significant relationship between the increase in the 25(OH)D and the fall in serum PTH levels. Although urinary calcium excretion did not change significantly in most treated individuals, three of the 21 study subjects developed marked hypercalciuria (> 400 mg/day). There was a tendency for bone turnover markers to fall, but only the 12-month total alkaline phosphatase activity showed a significant decline. Although this report does give a rationale as to the safety for providing vitamin D to subjects with primary hyperparathyroidism, it remains clear that caution is needed and patients should be followed closely to detect worsening hypercalcemia or hypercalciuria.

Treatment options in asymptomatic primary hyperparathyroidism

This discussion is focused entirely upon the patient with asymptomatic primary hyperparathyroidism. Patients with symptoms or signs such as fractures, renal stones and the classic neuromuscular manifestations of primary hyperparathyroidism should have surgery. Since many patients, however, are not symptomatic, it is important to consider how best to treat these individuals. For example, it is quite reasonable to question the advisability of surgery in all patients with asymptomatic disease. Since many patients with primary hyperparathyroidism are known to have the disease only because an incidental serum calcium determination was obtained, it is possible the disease would have remained unrecognized without the serum calcium measurement. In fact, in their long-term natural history study of asymptomatic primary hyperparathyroidism, Silverberg and Bilezikian have shown that in some patients with asymptomatic primary hyperparathyroidism, the course is benign (51). Given the observation that some of these individuals do have an uneventful natural history, non-surgical approaches would appear to be a reasonable alternative. On the other hand, some patients, although asymptomatic, may have levels of serum and/or urinary calcium that are sufficiently above normal to give concern as to the wisdom of following them long term. In these asymptomatic individuals, bone mineral density measurements that are low could be a clue that they are at increased fracture risk, especially given the uncertainty about the effects of PTH excess on skeletal fragility.

These issues related to the management of asymptomatic primary hyperparathyroidism have been addressed at two NIH conferences, one held in 1990 (52) and more recently in 2002 (53, 54). The 2002 conference was held because the guidelines for surgery emanating from the meeting held 12 years before were felt to be in need of revision in light of new knowledge about key issues that had since become evident. Although the conference was not designed to discuss symptomatic disease, it was again emphasized that all symptomatic patients be advised to undergo parathyroidectomy.

The proposed quidelines (53) were revised modestly from those offered at the earlier conference (52) primarily to reflect greater conservatism about recommending medical management and monitoring as opposed to surgery. Principally, these changes involved lowering the acceptable upper levels of serum calcium elevations from 1.6 mg/dl above normal to 1.0 mg/dl above normal and tightening skeletal surveillance by recommending monitoring at three sites, using the T-score rather than Z-score cut-off to emphasize the importance of departure from optimum bone mass as an indication for surgery.

For asymptomatic patients, surgery is advised if any one of the following criteria is met: (1) serum calcium concentration greater than 1 mg/dl above the upper limits of normal; (2) marked hypercalciuria (> 400 mg/day) or reduction in creatinine clearance by more than 30 percent below age- and sex-matched reference values; (3) markedly reduced bone density (T-score <-.2.5 at any site); and (4) age less than 50 years. Table I summarizes these guidelines. Although these guidelines have been very useful for clinicians who are faced with the dilemma: to operate or not, it should be noted that surgery for asymptomatic patients who do not meet any of these guidelines is not necessarily ill-advised. Surgery for asymptomatic primary hyperparathyroidism is always a valid option as long as there are no medical contraindications.

Surgery

In the hands of an expert parathyroid surgeon, parathyroidectomy is a highly successful procedure with infrequent complications. Both the classic approach of neck exploration, usually with efforts to examine all four parathyroid glands and the increasingly popular minimimally invasive parathyroidectomy that uses local rather than general anesthesia are associated with cure in over 95 percent of cases (55).
The minimally invasive procedure requires successful preoperative localization of the abnormal parathyroid gland and capability to measure PTH rapidly in the operating room (56). Preoperative blood is obtained for comparison of the PTH concentration with an intraoperative sample obtained minutes after removal of the “abnormal” parathyroid gland. If the level falls by more than 50 percent immediately following resection, the gland that has been removed is considered to be the sole source of overactive parathyroid tissue and the operation is terminated. If the PTH level does not fall by more than 50 percent, the operation is extended to a more traditional one in a search for other overactive parathyroid tissue. There is a risk (albeit small) that the minimally invasive procedure may miss other overactive gland(s) that are less active in the presence of a dominant gland (57). With advances in imaging technology and growing experience with minimally invasive parathyroid surgery, it is likely that these newer approaches will become more widely used (58-61).

Results of surgery

Successful surgery cures primary hyperparathyroidism. Long-term follow up of these patients indicates a 10 to 12 percent improvement in bone density at the lumbar spine and femoral neck over 10 years (51, 62). Most of the gains are seen within the first three to four years after successful parathyroid surgery. Postmenopausal women show a similar pattern of increased cancellous bone density. In patients who have nephrolithiasis, surgery is of clear benefit in reducing the incidence of recurrent stones (63). Vague or constitutional symptoms may or may not improve after surgery, while hypertension and peptic ulcer disease, if present, are unlikely to remit. Recently, several cohorts have been observed with respect to changes in fracture incidence following successful parathyroid surgery. Two reports from Denmark (64, 65) suggest that fracture incidence might be reduced after parathyroid surgery. It is not clear how comparable such cohorts of operated patients are with subjects who were followed conservatively, without surgery (66). These discrepancies emphasize the need for controlled prospective studies.

Table I - Indications for surgery in asymptomatic primary hyperparathyroidism.

Serum calcium (above normal)	> 1.0 mg/dL
24-h urinary ca	> 400 mg/24 hours
Creatinine clearance	> 30% below expected
Bone density	T-score <-2.5 at any site
Age	< 50

From reference #53.

Conservative management of asymptomatic hyperparathyroidism

If the guidelines offered by the expert panel convened after the Workshop on Aymptomatic Primary Hyperparathyroidism are followed (53), about 40-50 percent of patients with primary hyperparathyroidism in the United States will fit into the non-surgical, conservative management category. The natural history of this cohort indicates that over a 10-year period, patients in general are remarkably stable (66, 67). The group data show that serum and urine biochemical parameters are stable. Similarly, in the majority of patients, bone mineral density is unchanged at lumbar spine, hip and distal radius after 10 years. When these data for the group as a whole are reviewed more closely, however, it is clear that some patients who are followed without surgery will show changes and thus meet criteria for surgery. In about 25 percent of these patients followed without surgery over 10 years, guidelines for surgery were met eventually by virtue of an increasing serum or urinary calcium or declining bone mineral density (66). The fact that an appreciable number of asymptomatic patients will progress to meet criteria for surgery emphasizes the need for all these patients to be monitored.

Monitoring asymptomatic patients who are not to undergo surgery

The Panel of the 2002 Workshop on Asymptomatic Primary Hyperparathyroidism recommended a plan for monitoring patients who are not to undergo parathyroid surgery (Table II). The serum calcium measurement should be made every six months, while it is not considered necessary to monitor the urinary calcium excretion on a regular basis. Renal function can

Table II - Monitoring asymptomatic primary hyperparathyroidism.

Measurement	Guidelines
Serum calcium	Semiannually
Urinary Ca	Not recommended*
Creatinine Clearance	Not recommended*
Serum Creatinine	Annually
Bone density	Annually (3-sites)
Abdominal X-ray ± ultrasound	Not recommended*

It is assumed that these tests were obtained as part of the initial evaluation.
From reference #53.

be monitored by the yearly serum creatinine concentration and the Cockcroft-Gault relationship (68). The panel emphasized the utility of measuring annually bone density at the lumbar spine, hip and distal 1/3 radius site.

Medical management

Hydration. It is important that patients maintain adequate hydration, particularly in summer and warm climates when fluid losses can be substantial. Thiazide diuretics are to be avoided because they can worsen hypercalcemia. Careful monitoring may be needed if patients must undergo prolonged immobilization as with major trauma. In such instances, the importance of hydration needs to be emphasized. Under these circumstances, the asymptomatic patient with primary hyperparathyroidism can rapidly develop marked hypercalcemia if hydration is not ensured.

Diet. Conventional wisdom suggests that patients should limit their dietary calcium intake because of the hypercalcemia. Many patients are given this advice by their own physicians. A counter argument, however, suggests that low calcium diets could lead to further increases in PTH levels as they do in normal individuals (69, 70). Given the fact that patients with primary hyperparathyroidism maintain some sensitivity to ambient calcium concentrations, even though the sensitivity is impaired, diets restricted in calcium could fuel processes associated with increased production of PTH. The logic of this argument could lead to diets that are enriched in calcium with the idea that such a challenge could suppress PTH levels in primary hyperparathyroidism, as shown by Insogna et al. (71). Levels of 1,25(OH)D have to be taken into account in this discussion, since patients with primary hyperparathyroidism typically have concentrations of this active metabolite that are at or above the upper limit of normal. The data of Locker et al. (72) are of interest in this regard. In subjects with elevated levels of $1,25(OH)_2D_3$, high calcium diets were associated with worsening hypercalciuria.
The prudent advice is that dietary calcium intake should be in the lower end of the range that is generally recommended for the non-hyperparathyroid population, namely approximately 1000 mg/day. If the $1,25(OH)_2D$ level is increased, calcium intake should be more limited. Similarly, calcium-enriched diets to levels greater than 1500 mg should also be avoided.

Pharmacological approaches. At the time of the 2002 Workshop, it was concluded that there were no specific medical or pharmacological therapies for which there was yet convincing evidence of efficacy and/or safety (53). Since that time, experience has accumulated with several of these therapies. These include the report from the Women's Health Initiative (73) that emphasizes increased risks for long-term estrogen alone or with progestin. Even without this evidence, there was little clear rationale for long-term estrogen use despite its documented ability at higher doses (1.25 mg or occasionally more) to lower calcium to normal without increasing PTH levels (74). Side-effect profile and the newer data about risk (73) would seem to limit its applicability. Experience has suggested, however, that selective estrogen receptor modulators, bisphosphonates and calcimimetics do have promise as specific pharmacological treatments.
In certain patients, such pharmacological approaches to the management of hyperparathyroidism are particularly desirable, such as those who meet guidelines for parathyroid surgery but refuse surgery or have medical contraindications. For those who do not meet surgical guidelines, approaches that safely lower serum calcium or increase bone density are attractive. These pharmacological approaches to control hypercalcemia are also useful in patients with parathyroid carcinoma when repeated attempts to resect malignant tissue have ultimately failed. In this section, we describe cumulative experience with pharmacological approaches.

Selective Estrogen Receptor Modulators (SERMS). The SERM, raloxifene, is a potential alternative to estrogen. Rubin et al. (75) studied 18 postmenopausal women with hyperparathyroidism. They were randomly allocated to an eight-week course of raloxifene (60 mg/day) or placebo. There was a four-week follow up period off therapy. In the raloxifene group, the average serum calcium fell significantly from 10.8 ± 0.2 mg/dl to 10.4 ± 0.2 mg/dl ($P < 0.05$). The placebo group did not show any change in the serum calcium over this period of time. Along with the reduction in serum calcium, markers of bone formation and bone resorption fell. The bone formation marker, osteocalcin, fell significantly from 11.1 ± 1.6 to 9.9 ± 1.6 nmol/l ($P < 0.05$). The bone resorption marker, serum N-telopeptide also fell significantly from 21.2 ± 3.4 to 17.3 ± 2.8 nmol bone collagen equivalents/l ($P < 0.05$). Again the placebo group did not show any change in either of these two bone turnover markers. After the four-week period off therapy, the group that had received raloxifene returned to baseline in terms of the serum calcium and bone turnover markers. Raloxifene administration was not associated with any changes in serum PTH, $1,25(OH)_2D$ or urinary calcium excretion (75). In a open pilot study of only three patients, but carried out for a year, Zanchetta and Bogado (76) showed a similar reduction in serum calcium with raloxifene and increases in bone mineral density of the lumbar spine and femoral neck. These promising data, which need to be followed up with more definitive observations, hold promise for a potential role that raloxifene might have in selected postmenopausal women with primary hyperparathyroidism.

Bisphosphonates. The conceptual basis for expecting that bisphosphonates have potential as a medical approach to primary hyperparathyroidism is evident. Primary hyperparathyroidism, even in patients who are asymptomatic, is frequently associated with increases in bone turnover (77). By reducing bone resorption, without affecting PTH secretion directly, bisphosphonates could reduce serum and urinary calcium levels. An additional potential benefit of bisphosphonates in primary hyperparathyroidism would be to increase bone mineral density. Early studies with the first-generation bisphosphonates, etidronate and clodronate, however, were disappointing (78). The fall in serum calcium was not sustained. Experience with alendronate has been

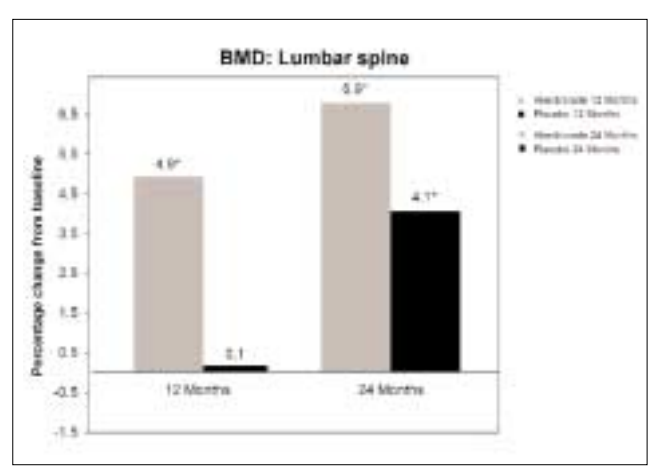

Figure 2 - Alendronate in primary hyperparathyroidism. Bone mineral density (BMD) of the lumbar spine in patients treated with alendronate. The group that was treated initially showed a significant increase after 1 year which was maintained in year 2. In the group that received placebo, there were significant gains only when they were crossed over to alendronate in year 2. Significance from baseline is noted by the asterisks. (Adapted from reference #82).

more encouraging. Two well-controlled doubled-blinded randomized clinical trials, following several open label studies (79, 80), have been conducted (81-83). The study of Khan et al. (82) was a randomized, placebo-controlled, study of 44 patients who were administered either alendronate 10 mg daily or placebo (Fig. 2). After 12 months, patients taking placebo were "crossed over" to take alendronate. Those who were taking alendronate in year one continued to take drug in year two. The primary outcome measure was the change in bone mineral density at all three sites. In comparison to baseline, treatment with alendronate was associated with a significant 6.85 ± .94 percent ($P < 0.001$) increase in bone mineral density of the lumbar spine after two years. Total hip bone mineral density also increased significantly in comparison to baseline by 4.01 ± .77 percent ($P < 0.001$). There was no significant change at the distal one-third radius site. When the placebo group, that did not show any change in year one, was crossed over to alendronate at 12 months, there was a significant 4.1 ± 1.12 percent increase in lumbar spine bone density ($P = 0.003$). The hip bone mineral density also increased at year two in the crossover group. As expected, alendronate was associated with substantial reductions in bone turnover markers. Urinary N-telopeptide fell by 66 percent and bone-specific alkaline phoshphase activity fell by 49 percent at 3 and 6 months respectively ($P < 0.001$). There were no changes in serum or urine calcium or serum PTH in either group. The experience of Chow et al. (81) in their one-year randomized, placebo-controlled trial of alendronate in primary hyperparathyroidism is remarkably similar to the study of Khan et al. (82). The only major difference was a significant alendronate-associated reduction in the serum calcium, by 0.34 mg/dl ($P < 0.02$). The only experience with risedronate was an acute, seven-day study of 19 patients with primary hyperparathyroidism in which the serum and urinary calcium fell significantly (83). These encouraging results suggest there may be a role for bisphosphonate therapy, specially in patients who are poor operative risks.

Calcimimetics. A more targeted approach to the medical therapy of primary hyperparathyroidism is to interfere specifically with the production of PTH. A new class of agents that alters the function of the extracellular calcium-sensing receptor offers an exciting new approach to primary hyperparathyroidism. By binding to an allosteric site, these agents increase the affinity of extracellular calcium for the calcium receptor, leading to reduction in PTH secretion. Such agents, therefore, could conceivably be utilized to reduce PTH and serum calcium levels in hyperparathyroid states. An early clinical experience with postmenopausal women who had mild primary hyperparathyroidism showed that, in principle, a calcimimetic can significantly reduce PTH and serum calcium levels in this disease (84). More recent experience has been gained with a newer calcimimetic, cinacalcet. This agent has been studied in the hyperparathyroidism associated with renal failure, in primary hyperparathyroidism and in parathyroid cancer (85). So far, cinacalcet has been approved by the FDA only for the management of patients in renal failure on dialysis with secondary hyperparathyroidism and in patients with parathyroid carcinoma. Even though the drug has not been approved yet for primary hyperparathyroidism, the early data are promising. Shoback et al. (86) studied 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 was associated with a normalization of the serum calcium after the second dose and remained within normal limits for the entire two-week period. Maximal reductions in PTH, over 50 percent, occurred two to four hours after dosing in all cinacalcet-treated groups. This reduction occurred when tested at both day one and day two of the study. There were no significant changes in urinary calcium excretion. Both serum calcium and PTH returned toward baseline by seven days after cinacalcet was stopped. Peacock et al. (87) have recently reported their experience in a longer study of cinacalcet. This multicenter, randomized, double-blind, placebo-controlled trial was designed to evaluated the longer term actions of cinacalcet in 78 patients with primary hyperparathyroidism. Cinacalcet was titrated from 30-50 mg twice daily during a 12-week period followed by a 12-week maintenance and 28-week follow-up period. Most patients treated with cinacalcet achieved the primary endpoint, namely normocalcemia (Fig. 3). Normal calcium concentrations were maintained for the entire duration of the study. Modest, but significant, reductions in the plasma PTH concentration were observed in the cinacalcet group. Similar to the study of Shoback, PTH levels fell quickly within hours after the administration of drug. This experience has been extended to three years over which time the majority patients with primary hyperparathyroidism who were treated with cinacalcet demonstrated excellent maintenance of a normal serum serum calcium concentration (88).

The calcimimetics have also been studied in parathyroid carcinoma. The first experience was a patient with end-stage parathyroid carcinoma and intractable hypercalcemia treated with R-568 (the first-generation calcimimetic) whose serum calcium fell from a pretreatment value over 17 mg/dl to 11-12 mg/dl (89). Over the course of the next two years, the serum calcium was controlled to within 1-1.5 mg/dl above the upper limits of normal. The PTH levels fell to approximately 30 percent below pretreatment values. With cinacalcet, promising results have been gained in 21 patients with parathyroid cancer (90, 91). These individuals were all highly symptomatic of diffuse, disseminated parathyroid cancer with marked hypercalcemia (average >14.5 mg/dl) and extremely high PTH levels. With titration up to a maximal dosage of 360 mg in four divided doses, serum calcium levels fell to an average of 12.4 mg/dl.

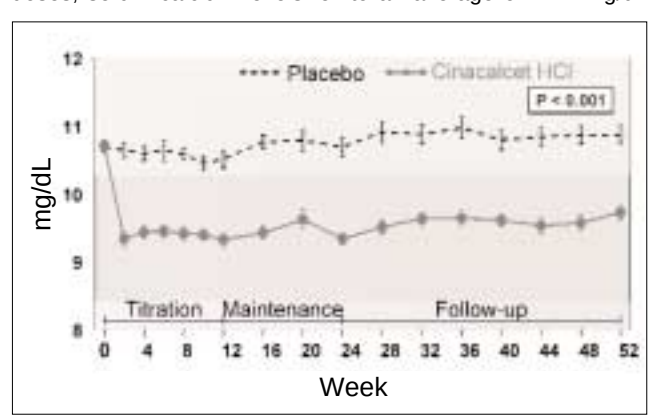

Figure 3 - Cinacalcet in primary hyperparathyroidism. Serum calcium of a group of subjects is shown after treatment with cinacalcet (30 mg twice daily) or placebo. The serum calcium quickly normalized and was maintained for the 52 week treatment period whereas subjects treated with placebo maintained mild hypercalcemia. The normal range is shaded (Adapted from reference #87).

Control of the serum calcium could be demonstrated in some patients for up to three years. The PTH level did not uniformly fall; in some patients there was an increase in PTH, despite the reduction in serum calcium. Nevertheless, after a given dose of cinacalcet in these patients, a rapid, but transient fall in PTH could be demonstrated.

Summary

As experience with asymptomatic primary hyperparathyroidism has grown over the past three decades, new approaches in diagnosis, evaluation, and treatment have emerged. Growth in knowledge about the natural history of this disorder suggests that certain patients can be safely followed without surgery. On the other hand, in all patients with the disease, if medical status permits, surgery is always an acceptable option, especially with improvements in minimally invasive parathyroidectomy and the knowledge that bone mineral density improves significantly as a result of surgical correction of the disease. Revised guidelines are offered that can serve to direct physicians and patients in their choice of treatment options while balancing risks and benefits of the decision made. Increasing experience with specific pharmacological treatments shows promise as yet another alternative to surgery or simple medical monitoring.

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