review article

Asymptomatic Primary Hyperparathyroidism

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ABSTRACT

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 comprising most of the remaining patients. Very rarely, a parathyroid cancer is responsible but it is seen in less than 0.5 percent of patients with primary hyperparathyroidism. In this article, we will review important clinical and diagnostic features of asymptomatic primary hyperparathyroidism as well as considerations for surgical or medical management of the disease. **(Arq Bras Endocrinol Metab 2006;50/4:647-656)**

Keywords: Primary hyperparathyroidism; Osteoporosis; Vitamin D; Bone markers

RESUMO

Hiperparatiroidismo Primário Assintomático.
O hiperparatiroidismo primário é uma distúrbio comum do metabolismo mineral, caracterizado por um excesso de secreção do hormônio das paratiróides, de uma ou mais glândulas paratiroidianas. Nos pacientes adultos portadores da doença, um adenoma único é responsável por aproximadamente 80% dos casos, e o envolvimento de múltiplas glândulas pelo restante dos casos. Muito raramente um câncer de paratiróide é a causa, sendo visto em menos de 0,5% dos pacientes com hiperparatiroidismo. Neste artigo, revisaremos as características clínicas e diagnósticas do hiperparatiroidismo primário assintomático, bem como o tratamento clínico e cirúrgico. **(Arq Bras Endocrinol Metab 2006;50/4:647-656)**

Descritores: Hiperparatiroidismo primário; Osteoporose; Vitamina D; Marcadores ósseos

DIAGNOSIS

SINCE IN PRIMARY HYPERPARATHYROIDISM, parathyroid hormone (PTH) is oversecreted, a reliable immunoassay for PTH is essential. The currently available immunoradiometric assay (IRMA) has the requisite sensitivity and specificity, revealing PTH levels that are either frankly elevated or in the upper range of normal. Even though the PTH is sometimes technically in the upper normal range, it is abnormal considering the presence of hypercalcemia. Moreover, in malignancy, the other most common cause of hypercalcemia, the PTH level is classically suppressed even when the cause of the malignancy-related hypercalcemia is parathyroid hormone related protein (PTHrP). Despite the reliability of the IRMA for PTH in general

use in the United States and throughout the world for over 20 years, it has recently been shown to detect not only the full-length (1-84) PTH molecule, but also forms of PTH foreshortened at the amino terminus (1). The most plentiful of these fragments, constituting up to 50% of the circulating species of PTH is PTH(7-84) (2). A newer IRMA for PTH that measures only the full length PTH molecule (1-84) has promise to be diagnostically more useful than the standard IRMA for PTH, but it remains to be seen whether this will be the case. (2-4). Vieira covers this topic completely in his article in this series. Although the differential diagnosis of hypercalcemia is long, the presumptive diagnosis of primary hyperparathyroidism in subjects whose calcium and PTH levels are elevated is generally accurate as long as the patient is not taking lithium or thiazide diuretics. 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.

Silverberg and Bilezikian, as well as others, have recently observed patients whose PTH is elevated but the serum calcium is normal (5,6). These patients with *normocalcemic primary hyperparathyroidism* are distinct from primary hyperparathyroidism that presents with overt hypercalcemia, the far more common clinical form, in which the serum calcium level can occasionally be normal. It is important to rule out all causes of secondary hyperparathyroidism, such as vitamin D deficiency and hypercalciuria, in which the parathyroid glands oversecrete PTH through physiologically normal compensatory mechanisms. It is particularly important to be sure that the level of 25-hydroxyvitamin D, the major storage form of vitamin D, is greater than 30 ng/ml the revised new low limit of normal (7, see article by Bandeira elsewhere in this supplement).

Discussions in this article and others that focus upon asymptomatic primary hyperparathyroidism generally do not consider patients with normocalcemic primary hyperparathyroidism because we know so little about them. Some of these patients will develop more overt primary hyperparathyroidism with hypercalcemia but it is also likely 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. This article will not address specific issues with regard to normocalcemic primary hyperparathyroidism.

EVALUATION

Skeletal manifestations

In parts of the world where multichannel screening is readily available, primary hyperparathyroidism presents primarily as an asymptomatic disease. The classical skeletal manifestations are uncommon. It this setting, the demonstration of skeletal involvement in asymptomatic primary hyperparathyroidism depends upon dual energy X-ray absorptiometry (DXA). As described by Bandeira in this series, however, there are still regions of the world in which symptomatic disease exists and radiologically manifestations are present. By DXA, the classic pathophysiological effects of PTH are seen, namely to reduce bone density at the distal third of the radius, a site of cortical bone (8). The proclivity of PTH to be catabolic for cortical bone is in contrast to its protective effect on cancellous bone. At the lumbar spine, for example, a site of cancellous bone, bone mineral density tends to be reasonably normal. The hip, which contains a more even admixture of cortical and cancellous elements, shows bone mineral density that is intermediate between the distal 1/3 radius and the lumbar spine (figure 1). Although this classic densitometric profile is most commonly seen, a distinctive pattern characterized by vertebral osteopenia can also

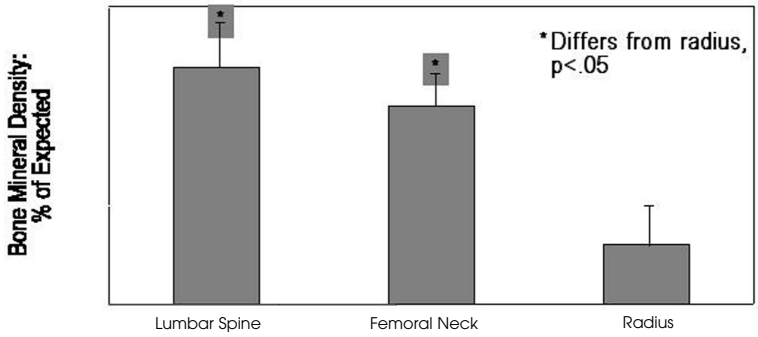

Figure 1. The densitometric signature or primary hyperparathyroidism. Bone mineral density is shown at all three skeletal sites in a cohort of patients with primary hyperparathyroidism. Note preferential involvement of the distal radius, 1/3 site, with relative preservation of the lumbar spine. (Adapted from reference #8)

be detected at the time of diagnosis (9). In more severe forms of primary hyperparathyroidism, generalized reductions in bone density at all sites can be seen.

Bone density is a very powerful predictor of fracture risk in osteoporosis. Whether it also predicts fracture risk in primary hyperparathyroidism remains to be seen because well-designed prospective studies are lacking. Surrogate data however raise interesting possibilities that argue for other considerations in primary hyperparathyroidism that may influence the predictive power of bone mineral density in this disease. Histomorphometric analysis of the bone biopsy in primary hyperparathyroidism shows cortical thinning, maintenance of cancellous bone volume, and accelerated bone remodeling (10). Bone 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 (10,11). Based upon both the densitometric and histomorphometric data, it might be expected that the cortical skeleton is at greater risk for fracture than the cancellous skeleton. The data are conflicting, however, with some studies showing an increase and other studies no increase in incidence of vertebral fractures (12,13). The retrospective review of a 28-year Mayo Clinic experience concluded that overall fracture risk was increased (14).

If bone density were the only factor to consider, the distal forearm would be the site at greatest risk and the lumbar spine would be the site at smallest risk. Since PTH has important effects on 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 as demonstrated by some (15) but not by others (16) using pQCT technology. In primary hyperparathyroidism, if there is an increase in cross sectional area of bone, it would be stronger, even though there is cortical thinning. Additionally, as described above, it is important to consider the generally well-preserved cancellous microarchitecture in primary hyperparathyroidism, another factor that might be protective. Thus, in primary hyperparathyroidism, 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 (17).

Renal involvement

Kidney stones remain the most common manifestation of primary hyperparathyroidism, but modern incidence figures of 15–20% are lower than they used to be. 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. An unexplained reduction in the creatinine clearance has also been regarded to be a potential renal manifestation of primary hyperparathyroidism.

Other organ involvement

Neurologic and cognitive signs or symptoms

Still vexing are the nonspecific complaints of patients with primary hyperparathyroidism such as weakness and easy fatigability (18). These complaints must be distinguished from the rare classic neuromuscular syndrome in which type II muscle cell dysfunctional is apparent (19). Nevertheless, nonspecific complaints of patients are noteworthy. They are often accompanied by some degree of constitutional, behavioral and/or psychiatric symptomatology. Prospective studies have reported apparent improvement after successful parathyroid surgery (20,21), while others have not been able to document changes postoperatively (21,22). 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 (23). When primary hyperparathyroidism is more severe, cardiovascular involvement has been noted, particularly in some European centers (24). This discussion excludes the multiple endocrine neoplasia (MEN) syndromes in which the presence of pheochromocytoma or hyperaldosteronism could, of course, lead to cardiovascular manifestations. Whether any cardiovascular abnormalities are demonstrable in mild asymptomatic primary hyperparathyroidism will require highly sensitive measurements of cardiovascular function that are currently ongoing (25,26).

Vitamin D in primary hyperparathyroidism

In the article by Bandeira, vitamin D is covered. The primary hyperparathyroid process appears to be fueled by vitamin D deficiency. 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 (27). 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 (28). Even in mild, asymptomatic primary hyperparathyroidism, it has been shown that low 25(OH)D levels are associated with increased indices of disease activity (29). In these patients with primary hyperparathyroidism, it seems reasonable to consider restoring vitamin D to sufficient levels. By restoring vitamin D levels to normal, that component of the increased 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. (30) recently reported on 21 patients with mild primary hyperparathyroidism whose 25(OH)D levels were < 20 ng/ml. After vitamin D repletion in which the mean 25-hydroxyvitamin D level rose from 11 ± 5 ng/ml to 31 ± 6 ng/ml after 12 months, the serum PTH level declined by 25 percent without any change in the serum calcium concentration. This report provides some support for the hypothesis that vitamin D deficiency worsens the hyperparathyroid state and vitamin D repletion improves some biochemical features of the disease. If subjects are to be given vitamin D, it should be done with care and at low doses.

TREATMENT OPTIONS IN ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

In the opinion of most experts, 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 was made. Silverberg and Bilezikian have shown, in fact, that some patients with asymptomatic primary hyperparathyroidism have a very uneventful course for many years (31). Given this observation, non-surgical approaches would appear to be a reasonable alternative in some patients. On the other hand, asymptomatic patients 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 addition, if bone mineral density measurements are low, they could be at increased fracture risk.

The management of asymptomatic primary hyperparathyroidism has been addressed at two NIH conferences, one held in 1990 (32) and another more recently in 2002 (33). At the more recent conference (33), the 1990 guidelines were revised modestly from those resulting from the earlier conference (32). The latest guidelines for surgery are noted here for asymptomatic patients: (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 1 summarizes these guidelines. The intent of the guidelines is to define a surgical candidate if 1 of these guidelines is met. The patient does not have to meet all or even more than 1. 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

An expert parathyroid surgeon will find all abnormal parathyroid tissue 95 percent of the time (34). Advances in surgery have popularized the minimally invasive procedure under local anesthesia. It requires successful preoperative localization of the abnormal parathyroid gland and capability to measure PTH rapidly in the operating room (35). A preoperative blood sample is obtained for comparison of the PTH concentration with an intraoperative sample obtained minutes after removal of the "abnormal" parathyroid gland. If the PTH level falls by more than 50 percent immediately following resection, the gland that has

Table 1. Indications for surgery in asymptomatic primary hyperparathyroidism (from reference #33).

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

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. 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 (36).

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 (31,37). In patients who have nephrolithiasis, surgery is of clear benefit in reducing the incidence of recurrent stones (38). 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. Vestergaard and Mosekilde report that fracture incidence might be reduced after parathyroid surgery (39). It is not clear how comparable such cohorts of operated patients are with subjects who were followed conservatively, without surgery (40).

CONSERVATIVE MANAGEMENT OF ASYMPTOMATIC HYPERPARATHYROIDISM

If the guidelines offered by the expert panel convened after the Workshop on Aymptomatic Primary hyperparathyroidism are followed (33), 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 stable (40). The group data show that serum and urine biochemical parameters do not change. 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 analyzed 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 (40). 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

A plan for monitoring was offered by the Panel of the 2002 Workshop on Asymptomatic Primary Hyperparathyroidism and is shown in table 2. A serum calcium measurement should be obtained every six months. Once the urinary calcium has been ascertained to be acceptable, the urinary calcium excretion is not measured on a regular basis. 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.

Diet

Many patients are advised by their physicians to limit their dietary calcium intake. A counter argument, how-

Table 2. Monitoring asymptomatic primary hyperparathyroidism (from reference #33).

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.

ever, suggests that low calcium diets could lead to further increases in PTH levels (41). 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. (42) 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. (43) 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

In certain patients, 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 also attractive. These pharmacological approaches to control hypercalcemia are additionally useful in patients with parathyroid carcinoma when repeated attempts to resect malignant tissue have ultimately failed.

Selective Estrogen Receptor Modulators (SERMS)

Rubin et al. (44) 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 from 10.8 ± 0.2 mg/dl to 10.4 ± 0.2 mg/dl ($P< 0.05$). Along with the reduction in serum calcium, markers of bone formation and bone resorption fell significantly. Raloxifene administration was not associated with any changes in serum PTH, $1,25(OH)_2D$ or urinary calcium excretion (44). The placebo group did not show any change in serum calcium or in bone turnover markers. In a open pilot study of only three patients, but carried out for a longer period of time, one year, Zanchetta and Bogado (45) showed a similar reduction in serum calcium with Raloxifene and increases in bone mineral density of the lumbar spine and femoral neck.

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 (46). 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. Two well-controlled double-blinded randomized clinical trials have been conducted (47,48). The study of Khan et al. (48) was a randomized, placebo-controlled, study of 44 patients who were administered either alendronate 10 mg daily or placebo. In comparison to baseline, treatment with alendronate was associated with a significant 7% increase ($P< 0.001$) 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% ($P< 0.001$). As expected, bone turnover markers fell significantly in the group that received alendronate. There were no changes in serum or urine calcium or serum PTH in either group (figure 2). The only major difference between this experience and that of Chow et al. (47) was a significant alendronate-associated reduction in the serum calcium, by 0.34 mg/dl ($P< 0.02$). These encouraging results suggest there may be a role for bisphosphonate therapy, especially in patients who are poor operative risks.

Calcimimetics

A new class of agents that alters the function of the extracellular calcium-sensing receptor offers a new approach to the medical management of primary hyperparathyroidism. By binding to an allosteric site on the calcium-sensing receptor, these agents increase the affinity of the receptor for extracellular calcium, leading to a reduction in PTH secretion. Such agents, therefore, could conceivably be utilized to reduce both PTH and serum calcium levels in hyperparathyroid states. Recent experience has been

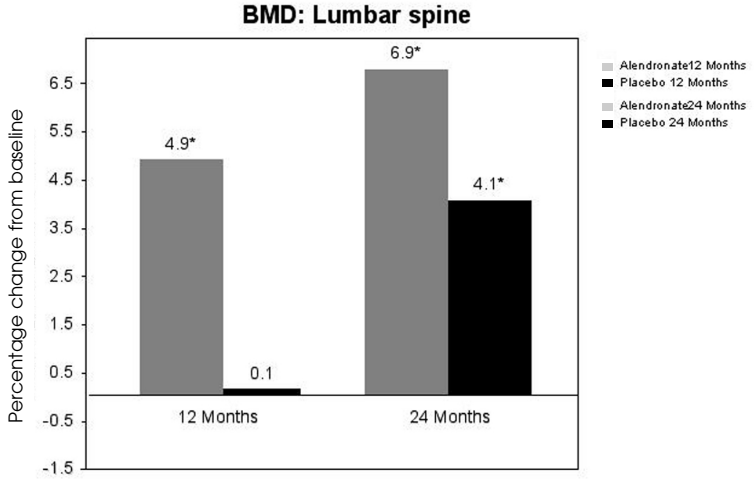

Figure 2. Alendronate in primary hyperparathyroidism. Bone mineral density (BMD) of the lumbar spine in patients treated with alendronate. The group that was treated initially showed a significant increase after 1 year, which was maintained in year 2. In the group that received placebo, there were significant gains only when they were crossed over to alendronate in year 2. Significance from baseline is noted by the asterisks. (Adapted from reference #48)

gained with the calcimimetic, cinacalcet. This agent has been studied in the secondary hyperparathyroidism of renal failure, in primary hyperparathyroidism and in parathyroid cancer (49). Shoback et al. (50) studied 22 patients with primary hyperparathyroidism in a dose-ranging study. In all dose groups, ranging from 30–50 mg twice daily, cinacalcet was associated with a normalization of the serum calcium after the second dose and remained within normal limits for the entire 2-week period. Reductions in PTH, over 50 percent, occurred 2 to 4 hours after dosing in all cinacalcet-treated groups. 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. (51) 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 normocalcemia, the primary endpoint (figure 3). Normal calcium concentrations were maintained for the entire duration of the study. Modest, but significant, reductions in the 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.

CONCLUSIONS

As experience with asymptomatic primary hyperparathyroidism has grown over the past three decades, new approaches in diagnosis, evaluation, and treatment have emerged. Greater 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 should help 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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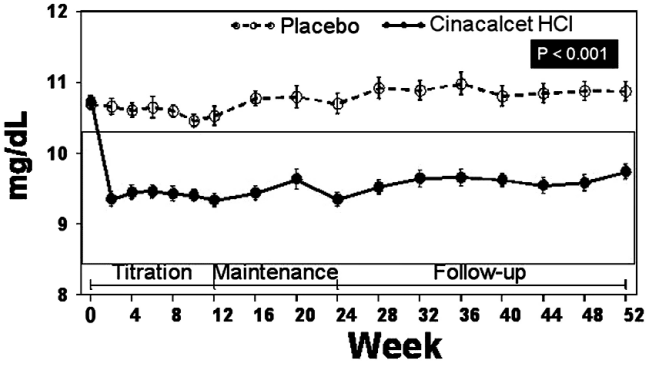

Figure 3. Cinacalcet in primary hyperparathyroidism. Serum calcium of a group of subjects is shown after treatment with cinacalcet (30 mg twice daily) or placebo. The serum calcium quickly normalized and was maintained for the 52-week treatment period whereas subjects treated with placebo maintained mild hypercalcemia. The normal range is shaded. (Adapted from reference 51)

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