Medical Management of Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism

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Objective: Asymptomatic primary hyperparathyroidism (PHPT) is a common clinical problem. The only available definitive therapy is parathyroidectomy, which is appropriate to consider in all patients. The purpose of this report is to provide an update on calcium and vitamin D supplementation and medical management for those patients with PHPT who cannot or do not want to undergo surgery.

Methods: Questions were developed by the International Task Force on PHPT. A comprehensive literature search was undertaken, and relevant articles published between 2008 and 2013 were reviewed in detail. The questions were addressed by the panel of experts, and consensus was established at the time of the workshop.

Conclusions: The recommended calcium intake in patients with PHPT should follow guidelines established for all individuals. It is not recommended to limit calcium intake in patients with PHPT who do not undergo surgery. Patients with low serum 25-hydroxyvitamin D should be repleted with doses of vitamin D aiming to bring serum 25-hydroxyvitamin D levels to $\geq$ 50 nmol/L (20 ng/mL) at a minimum, but a goal of $\geq$75 nmol/L (30 ng/mL) also is reasonable. Pharmacological approaches are available and should be reserved for those patients in whom it is desirable to lower the serum calcium, increase BMD, or both. For the control of hypercalcemia, cinacalcet is the treatment of choice. Cinacalcet reduces serum calcium concentrations to normal in many cases, but has only a modest effect on serum PTH levels. However, bone mineral density (BMD) does not change. To improve BMD, bisphosphonate therapy is recommended. The best evidence is for the use of alendronate, which improves BMD at the lumbar spine without altering the serum calcium concentration. To reduce the serum calcium and improve BMD, combination therapy with both agents is reasonable, but strong evidence for the efficacy of that approach is lacking. **(*J Clin Endocrinol Metab* 99: 3607–3618, 2014)**

Medical management of asymptomatic patients with primary hyperparathyroidism (PHPT) may be considered in patients who meet criteria for surgery but whose physicians do not advise parathyroidectomy because of comorbidities, contraindications to surgery, or prior unsuccessful neck exploration. In addition, medical management may be considered in patients who refuse surgery.

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Abbreviations: BMD, bone mineral density; BSAP, bone alkaline phosphatase; DXA, dual-energy x-ray absorptiometry; MEN1, multiple endocrine neoplasia type 1; NTX, N-telopeptide; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D; PHPT, primary hyperparathyroidism.

Certain patients, because of age, gender, reduced bone mineral density (BMD), hypercalcemia, and/or other risk factors, are at increased fracture risk. They might benefit from therapy designed to improve BMD, to reduce the serum calcium concentration, or to accomplish both goals. Another medical approach, namely therapy with vitamin D, is advisable in patients with PHPT whose serum 25-hydroxyvitamin D (25OHD) levels are low.

This report focuses on approaches to the medical management of PHPT and is based on presentations at the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, which in turn were based upon an extensive review of the published literature on this topic. It has long been recommended that patients with PHPT not undergoing surgery be monitored for possible progression of the disease. Clear evidence for progression may occur in up to one-third of patients followed without surgery. This point is based on the experience of Rubin et al (1) in the Columbia University cohort of 116 patients. Among that cohort, there were a total of 57 patients in the medically followed subgroup. In that subgroup, declines in BMD at cortical sites (hip and one-third distal radius) were detected after 8–9 years of follow-up, which was followed in year 12 by a mild but statistically significant increase in serum calcium concentrations (1). Relatively few patients, however, remained in the subgroup of the cohort after 10 years of follow-up (n = 6–11). So overall conclusions should be tempered by that fact.

Advances in the medical management of PHPT over the past 5 years were the focus of the literature search, presentations at the workshop, and this summary. Evidence-based and outcomes-driven goals of medical therapy for PHPT have not been rigorously established or agreed upon by the research community. Therefore, the studies reviewed in this report should be viewed in that context. Future efforts should define biochemical and clinical benchmarks by which current and new therapies for this disorder can be evaluated.

The key questions addressed are:

1. Should the recommendation for calcium intake in patients with PHPT differ from that of the general population?
2. Do patients with PHPT who are insufficient or deficient in vitamin D benefit from supplementation? How should vitamin D deficiency/insufficiency be managed in patients with PHPT?
3. How effective is estrogen receptor-targeted therapy in postmenopausal women with PHPT?
4. What is the efficacy and safety of bisphosphonate therapy in men and women with PHPT?
5. Is therapy with cinacalcet effective and safe in patients with PHPT across the spectrum of serum calcium concentrations? Is it cost-effective?
6. Is therapy with cinacalcet effective in patients with familial PHPT?
7. Can cinacalcet and bisphosphonate be combined in patients with PHPT?

Literature Research Strategy

Electronic literature searches were undertaken, and relevant articles published between 2008 and 2013 were reviewed in detail. Key articles published before 2008 were also included in the data synthesis.

Calcium and Vitamin D Supplementation

Question 1: Should the recommendation for calcium intake in patients with PHPT differ from that of the general population?

The intake of calcium in the diet is known to influence serum PTH levels, with low intake stimulating PTH secretion and subsequently, via increasing 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] synthesis, enhancing intestinal calcium absorption (2). Animal studies have shown that chronically low calcium intake is associated with parathyroid gland hyperplasia (3, 4). A prolonged stimulus of low calcium intake could lead to enhanced parathyroid cell proliferation and perhaps altered expression of key growth regulatory genes. Such a pathophysiological scenario could enhance the development of PHPT. Support for this idea comes from The Nurses' Health Study, in which a cohort of over 58 000 nurses followed for 22 years was examined with regard to the relationship between dietary calcium intake and the development of PHPT (5). During follow-up, 277 incident cases of PHPT were noted. Increased risk of developing PHPT was shown in those whose intake of calcium was in the lower quintiles. Calcium supplementation was associated with reduced risk of PHPT (5). This epidemiological study does not establish causation for the effects of a chronically low calcium intake on the development of PHPT, and a number of variables were not independently accounted for. The highest quintile of calcium intake, for example, was also associated with the highest intake of vitamin D and protein (6).

Dietary management of patients with asymptomatic PHPT is a subject of controversy primarily because data are insufficient. Restriction of calcium intake in PHPT would be expected to lower urinary calcium excretion and decrease the risk of kidney stones. On the other hand, lowering calcium intake could further increase PTH levels,

exacerbating the tendency for bone demineralization in PHPT and presenting to the kidney an even greater filtered calcium load. Based on dietary records from patients enrolled in a longitudinal study of the natural history of PHPT, patients were characterized according to calcium intakes of <300 mg daily, between 300 and 800 mg daily, and >800 mg daily (7). No significant effects of differing dietary calcium intake could be demonstrated on biochemical markers of bone turnover or bone mass by dual-energy x-ray absorptiometry (DXA). A concern was expressed, however, that patients with elevated serum $1,25(OH)_2D$ and higher serum PTH levels might demonstrate increased urinary excretion of calcium (7).

In an unblinded 1-year study based on the Tromsø epidemiological study (1994–1995), the hypothesis that patients with asymptomatic PHPT with a low calcium intake would benefit from calcium supplements was tested (8). Patients with a daily intake of calcium <450 mg were given a calcium supplement (500 mg elemental calcium daily), whereas patients with an intake >450 mg were followed without intervention. A total of 31 patients were included in this study, of whom 17 were assigned to calcium supplements. Calcium supplements were associated with a significant decrease in PTH levels and an increase in femoral neck BMD. Study investigators concluded that patients with mild PHPT and a low calcium intake might benefit from a calcium supplement, but patients need to be monitored closely (8).

Summary and recommendations

It is prudent to adhere to the Institute of Medicine guidelines for calcium intake in the general population (9). There is no rationale for dietary calcium restriction in patients with asymptomatic PHPT.

Question 2: Do patients with PHPT who are insufficient or deficient in vitamin D benefit from supplementation? How should vitamin D deficiency/insufficiency be managed in patients with PHPT?

Vitamin D status is defined by the serum 25OHD level, with levels of ≥50 nM (20 ng/mL) defining vitamin D sufficiency for the general population (10). This cutoff value is not agreed upon by all experts in the field (11, 12). In fact, authors of The Endocrine Society Guideline on Vitamin D defined vitamin D sufficiency as a 25OHD value ≥75 nM (30 ng/mL) (13).

Serum levels of 25OHD are typically low in patients with PHPT (14, 15). However, there are important geographical variations in the extent to which serum 25OHD levels are reduced in PHPT (14). The substantial variability might be ascribed to differences in access to medical services, sun exposure, and nutritional status. Most patients with PHPT in the Western world have only moderately decreased serum levels of 25OHD. In contrast, in developing countries, cases of severe PHPT with marked vitamin D insufficiency are seen regularly and are typically accompanied by high serum levels of PTH and clinical symptoms (15, 16). A modest inverse association between serum intact PTH and 25OHD levels has been demonstrated in patients with asymptomatic PHPT (17). In general, serum 25OHD levels are inversely correlated with parathyroid gland weight (18). In asymptomatic PHPT, low serum levels of 25OHD have been associated with more end-organ involvement, including higher bone turnover, lower bone mass (19, 20), and greater cardiovascular risk factors in some (21, 22), but not all studies (23).

Low serum levels of 25OHD in asymptomatic PHPT may be explained in part by increased conversion of 25OHD to $1,25(OH)_2D$ due to increased 1α-hydroxylase activity stimulated by high serum PTH levels. However, there is an approximately 1000-fold difference in the serum 25OHD and $1,25(OH)_2D$ levels. Increased conversion does not satisfactorily explain the lowered serum 25OHD levels. A more plausible explanation is increased inactivation of 25OHD by the 24-hydroxylase enzyme (24). In subjects whose body mass index is high, low serum 25OHD concentrations are also more likely (25). As expected, therefore, after successful parathyroid surgery, serum 25OHD levels typically increase without specific intervention (26).

Three recent studies have investigated the effect of vitamin D administration on serum PTH levels, biochemical markers of bone turnover, and BMD in asymptomatic PHPT. First, in a 1-year, open-label study, 25 patients with asymptomatic PHPT (serum calcium levels <12 mg/dL and serum 25OHD levels <50 nM) were given 50 000 IU weekly of cholecalciferol for 4 weeks (without calcium supplementation), followed by monthly supplementation for the next 11 months (27). Serum 25OHD levels rose to above 50 nM in all 21 patients who completed the study. Serum calcium levels did not change significantly, and none of the patients experienced levels above 12 mg/dL. However, declines in serum PTH and alkaline phosphatase levels were demonstrated without significant effects on bone mass by DXA. Three patients developed urinary calcium excretion >400 mg/24 h, although the group statistics did not assign significance to the increase in urinary calcium excretion. Kidney stones were not observed (27). Nevertheless, there is concern about the number of patients who developed hypercalciuria (n = 3), given the small number of subjects in the study. The study was interpreted to demonstrate that vitamin D repletion is safe in asymptomatic PHPT and that it reduces PTH levels, as

shown previously with activated vitamin D (28). Caveats are that this study was small and of relatively short duration. The increase in calcium excretion in certain patients is a concern long term due to the potential risk of kidney stones.

In the second study, 56 patients with PHPT and moderately elevated serum calcium levels (of whom 14 patients met criteria for surgery) were repleted with vitamin D (29). At baseline, 51 patients had serum 25OHD levels <50 nM. Vitamin D in the form of weekly cholecalciferol (50 000 IU) for 8 weeks was followed by a titration protocol to keep individual serum 25OHD levels >75 nM for up to 34 weeks. Serum calcium and PTH levels did not change significantly, nor did biochemical markers of bone turnover. Urinary calcium levels did not increase, and patients did not report side effects. However, this short, uncontrolled study did not demonstrate any clinical benefits of vitamin D.

A third small, unblinded study of 27 patients with PHPT and mildly elevated serum calcium levels (<11.6 mg/dL) and vitamin D deficiency (serum 25OHD <50 nM) investigated the effects of 1-year repletion with calcifediol (480–960 IU daily), individually dosed to keep serum calcium levels <11.6 mg/dL and urinary calcium excretion <400 mg/24 h (30). The repletion protocol was stopped in almost half of the patients (12 of 27) due to increased serum calcium levels (three patients) and increased calcium excretion (nine patients). No significant changes in serum PTH levels were demonstrated, and no effects on bone turnover markers were found.

Apart from the studies reviewed above, another focus of interest regarding vitamin D in PHPT relates to the postoperative state. Most experts agree that replenishment of vitamin D stores in PHPT is important to prevent postoperative hypocalcemia due to the hungry bone syndrome (31).

Summary and recommendations

Although vitamin D depletion is clearly associated with evidence of biochemically more severe PHPT, vitamin D repletion studies are too small and uncontrolled to be definitive (27, 29, 30). With vitamin D repletion, modest reductions in serum PTH levels have been demonstrated, but the incidence of worsening hypercalcemia and increased urinary calcium excretion emphasize the need to be cautious when repleting vitamin D in PHPT. It is advisable to monitor serum and urinary calcium excretion when vitamin D is replete in PHPT. Supplemental doses (eg, 600–1000 IU cholecalciferol) appear the more prudent dosage regimen to follow than large doses. The goal of cautiously administered repletion regimens should be to increase the serum 25OHD levels to >50 and up to 75 nmol/L.

Medical Management

Medical management with pharmacological agents is an option for patients who have not been cured by surgery, have contraindications to surgery, or are unwilling to undergo parathyroidectomy.

Estrogen Receptor-Targeted Therapy

Both estrogen and selective estrogen receptor modulators decrease bone resorption. It was postulated that therapies targeting the estrogen receptor in postmenopausal women with PHPT might decrease PTH-mediated bone resorption and thereby lower serum calcium and ameliorate bone loss.

Question 3. How effective is estrogen receptor-targeted therapy in postmenopausal women with PHPT?

Estrogen

Early uncontrolled studies with estrogen demonstrated a lowering of serum calcium (32, 33). However, randomized controlled trial data published by Grey et al (34) did not confirm calcium-lowering effects. In a 2-year randomized controlled trial with conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (5 mg/d) compared with placebo, increases in BMD were observed with estrogen therapy. Total body BMD by DXA increased by 1.3 ± 0.4% compared with baseline ($P = .004$). Lumbar spine and femoral neck BMD rose by 5.2 ± 1.4% ($P = .002$) and by 3.4 ± 1.5% ($P = .05$) in comparison to baseline, respectively. In the hormone treatment group, serum alkaline phosphatase activity levels decreased by 22% ($P < .001$), but there were no changes in serum ionized calcium or PTH levels.

Raloxifene

There are only a few reports on the use of this selective estrogen receptor modulator in PHPT. Rubin et al (35) studied 18 postmenopausal women with asymptomatic PHPT who were randomized to 8 weeks of raloxifene (60

[1] The first randomized, placebo-controlled, double-blind study of vitamin D treatment in PHPT was published at the time of submission of this manuscript (71). The study showed beneficial effects of cholecalciferol (2800 IU daily) for 26 weeks before and 26 weeks after parathyroidectomy. These beneficial effects of vitamin D treatment included an increase in serum 25OHD and a reduction in serum PTH levels along with reduction in biochemical markers of bone turnover and improved spine BMD measurements. Treatment was well tolerated without increased serum or urinary calcium levels.

mg/d) or placebo followed by a 4-week washout phase. During the 8 weeks of treatment, serum total calcium decreased from 10.8 ± 0.2 to 10.4 ± 0.2 mg/dL ($P < .05$). Small reductions in serum osteocalcin (17%) and serum N-telopeptide (NTX) (18%) were observed. There were, however, no effects on serum PTH, $1,25(OH)_2D$, alkaline phosphatase, or urinary calcium. Zanchetta and Bogado (36) treated three patients with raloxifene. Bone loss was prevented at the spine and hip after 12 months.

Summary and recommendations

Limited data suggest that therapy with estrogen in patients with PHPT may reduce bone resorption. Improvements in BMD have been observed with estrogen therapy in postmenopausal women. No consistent effects have been observed on serum ionized calcium or PTH. There are no fracture data evaluating the effects of estrogen treatment in PHPT. This may be a useful option for those unable or unwilling to proceed with parathyroidectomy, especially in the presence of menopausal symptoms. The risk-benefit ratio must be evaluated in the individual patient with respect to known relative or absolute contraindications to the use of estrogen in postmenopausal women. The studies of raloxifene in patients with PHPT are too small and short to reach definitive conclusions or make recommendations.

Bisphosphonates

Question 4: What is the efficacy and safety of bisphosphonate therapy in men and women with PHPT?

Alendronate is the bisphosphonate that has been most extensively evaluated in PHPT. Most studies with alendronate have shown an increase in BMD and a reduction in bone turnover markers (37–40). For example, in a 48-week, randomized controlled trial of 40 postmenopausal women, BMD increased at the lumbar spine and femoral neck, and bone turnover markers fell with alendronate therapy (37). Serum calcium decreased significantly from 11.28 to 10.96 mg/dL ($P = .018$) with no significant changes in serum PTH. As another example, in a randomized, placebo-controlled trial, 44 patients were treated with alendronate (10 mg/d) compared with placebo for the first year. In the second year, the placebo group was crossed over to alendronate (38). In the alendronate arm of the study, BMD significantly increased at the lumbar spine (+6.8 ± 0.94%), compared with baseline ($P < .001$) (Figure 1). Urinary NTX fell by 66% at 3 months ($P < .001$), whereas bone alkaline phosphatase (BSAP) decreased by 49% at 6 months ($P < .001$). There were no significant changes in serum total and ionized calcium levels. Serum PTH levels and urine calcium excretion also did not change.

The experience with alendronate treatment in men with PHPT is similar to that of postmenopausal women (41).

Reports on the use of other bisphosphonates in PHPT are very limited. Pamidronate was shown, in a small study, to be associated with a transient decrease in serum calcium and increase in serum PTH (42). Risedronate, at 20 and 40 mg/d for 7 days, was associated with small decreases in serum calcium (43). There is no reported experience with ibandronate in the management of PHPT. Treatment with zoledronic acid in PHPT is limited to a single case report of a woman with hypercalcemia who was treated with zoledronic acid and cinacalcet (44). A decrease in serum calcium was observed.

Summary and recommendations

The randomized controlled trial data have shown a positive effect of alendronate on BMD at the lumbar spine and hip in PHPT. Bone turnover markers decrease with alendronate therapy. Serum calcium remains stable. In subjects whose BMD is low and who are not candidates for parathyroid surgery, alendronate provides skeletal protection and is a medical option. There are currently no fracture data with bisphosphonate therapy in PHPT.

Calcimimetics

Many studies have focused upon the use of cinacalcet, a calcimimetic, in the management of PHPT. We will concentrate on these reports and not discuss its use in the management of secondary hyperparathyroidism due to chronic kidney disease (45, 46) or of parathyroid cancer (47).

Question 5: Is therapy with cinacalcet effective and safe in patients with PHPT across the spectrum of serum calcium concentrations? Is it cost-effective?

Mild to moderate PHPT

Early experience with cinacalcet in PHPT at the time of the third International Workshop was reviewed (48). Since that review, additional data have become available. In a 52-week multicenter, randomized, double-blind, placebo-controlled study, the safety and efficacy of cinacalcet therapy in 78 patients with PHPT were evaluated (49). Normalization of serum calcium levels (<10.3 mg/dL) was achieved in 73% of study subjects. Although a modest 7.6% reduction in the serum PTH concentration was ob-

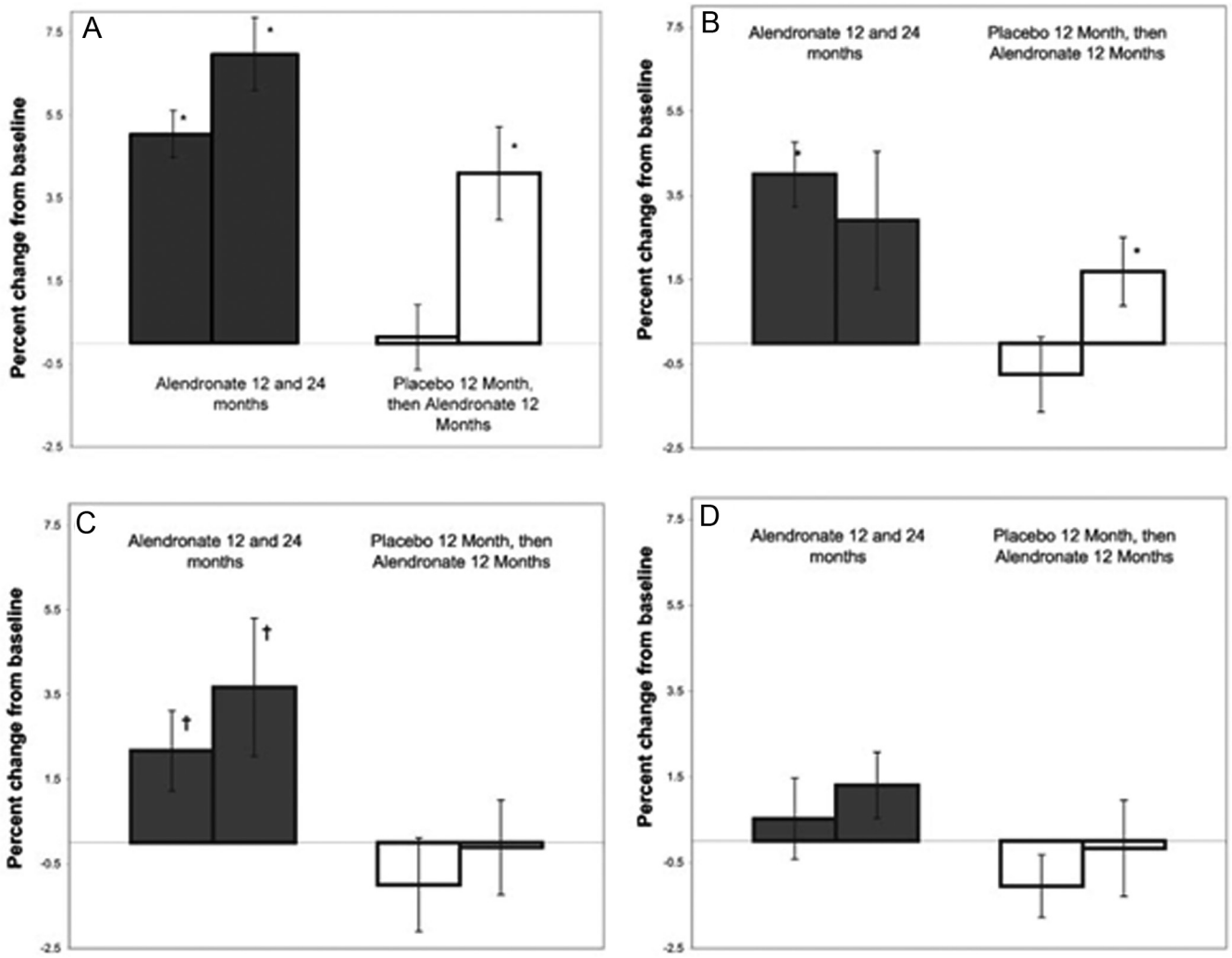

Figure 1. Effect of alendronate treatment for 24 months compared with placebo for 12 months (mo 0–12) followed by alendronate treatment for 12 months (mo 13–24). BMD is shown as percentage change from baseline for lumbar spine (A), total hip (B), femoral neck (C), and one-third distal radius (D) sites. Patients with PHPT treated with alendronate for 2 years are shown in the first two dark bars in each panel, and patients treated with placebo in the first year and alendronate in the second year are shown in the two open bars in each panel as labeled. *, $P < .001$ vs baseline; †, $P < .05$ vs baseline. [Reproduced from A. A. Khan et al: Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004;89:3319–3325 (38), with permission. © The Endocrine Society.]

served when measured before the morning cinacalcet dose, a more marked 37% decline was detected when serum PTH was measured 2 hours after cinacalcet was administered. At the 52-week end-point of the study, there was no significant change in lumbar spine BMD. Cinacalcet was generally well tolerated, with only nausea experienced in a greater number of subjects taking cinacalcet than placebo. Three subjects receiving cinacalcet experienced hypocalcemia at the lowest dose.

This investigation was extended to a 4.5-year, open-label period in which all patients were treated with cinacalcet (50). The single crossover design established two groups of subjects: those who received cinacalcet continuously and those who crossed over to cinacalcet after 1 year of placebo. At the end of the study, mean serum calcium was within the normal range. The group that had previously received placebo normalized their mean serum calcium levels, whereas those who had received cinacalcet from the outset remained normocalcemic on average throughout the open-label extension study (Figure 2). Eighty to 90% of patients normalized their mean serum calcium levels throughout the extension study. Serum PTH levels fell but were significantly lower only at years 4 and 5. BMD showed no statistically significant changes. Adverse events included arthralgias (38%), myalgias (27%), diarrhea (22%), upper respiratory complaints (20%), and nausea (20%). Five patients experienced at least one serum calcium value <8.0 mg/dL during the extension study. Four patients were able to restart cinacalcet at a lower dose. Of the 11 subjects who withdrew from the extension study, none withdrew due to treatment-related adverse events. Thus, the safety profile of patients in the

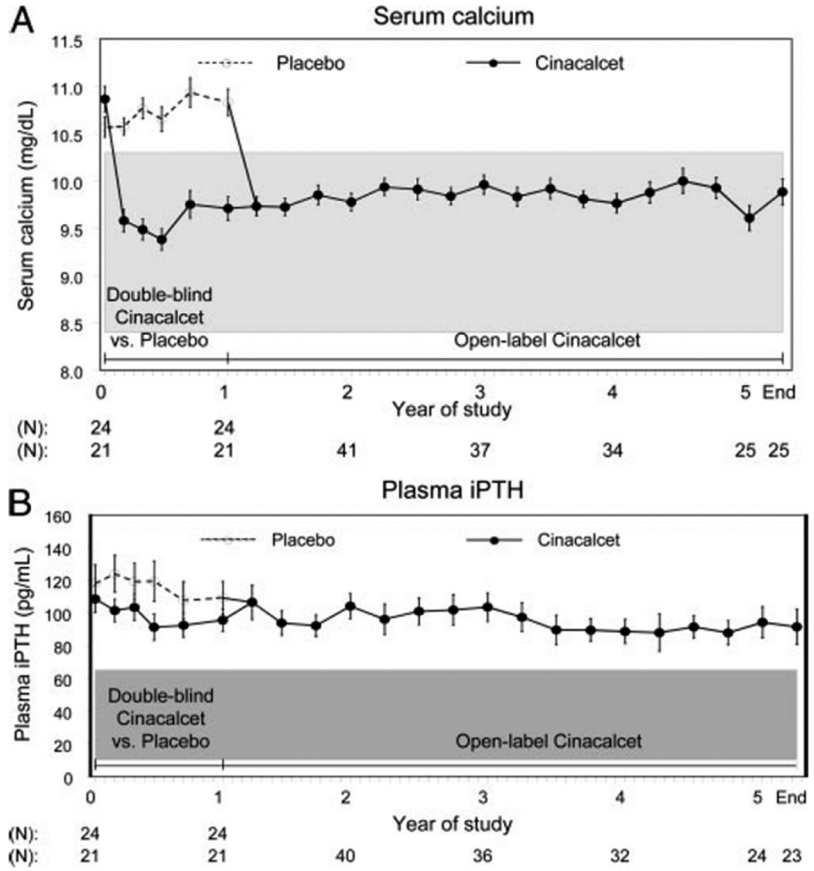

Figure 2. Responses (mean ± SE) in serum total calcium (A) and plasma intact PTH (iPTH) (B) levels obtained predose in patients with mild PHPT receiving placebo vs cinacalcet for year 1, followed by the responses in the 4.5-year open-label extension study described in the text. Predose blood sampling was done approximately 12 hours after the prior day's administration of cinacalcet or placebo. Shaded regions represent the normal ranges for both parameters (serum calcium, 8.4–10.3 mg/dL; plasma intact PTH, 10–65 pg/mL). The number of patients (N) remaining in the study at each time-point is shown. [Reproduced from M. Peacock et al: Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. *J Clin Endocrinol Metab*. 2009;94:4860–4867 (50), with permission. © The Endocrine Society.]

extension study of up to 5.5 years (50) was similar to that of the initial 1-year trial (49).

In the last 5 years, eight additional studies (five prospective, open label [51–55] and three retrospective data review papers [56–58]) have been published (Table 1). These studies included patients with previously failed parathyroidectomy or in whom parathyroidectomy was contraindicated, not indicated, or refused by the patient. Two studies included patients who were given cinacalcet to decrease serum calcium before parathyroidectomy (55, 58). The range of cinacalcet doses was 30 to 180 mg. A significant decline in mean serum calcium levels, compared with baseline values, was reported in all studies. Mean predose plasma PTH also declined in all studies, with a range between −5.1 and −29.8%. A trend for the serum phosphate to increase was observed in seven of eight studies and reached statistical significance in four (51, 53, 55, 56). Changes in bone turnover markers, when measured, were inconsistent. Lumbar spine and hip BMDs were unchanged (52, 56, 58). Adverse events considered to be drug-related occurred in about 15% of patients and required treatment withdrawal in approximately 6%.

A retrospective, multicenter study by Saponaro et al (58) is noteworthy. High surgical risk due to comorbidities, previous neck surgery, and/or age (34%); control of hypercalcemia before parathyroidectomy (24%); negative parathyroid imaging (19%); and a patient's refusal of parathyroidectomy (19%) accounted for 96% of the patients. The median follow-up was 9 months (range, 1–26). Using an upward titration protocol from 30 to 120 mg cinacalcet daily, as needed to control the serum calcium, mean serum calcium concentrations decreased from 11.6 ± 1.1 to 10.2 ± 0.9 mg/dL ($P < .001$). A normal serum calcium concentration was achieved in 65% of the patients. Mean predose serum PTH levels declined significantly from 164 to 127 pg/mL. Excluding those subjects who received combination therapy with a bisphosphonate, no changes were seen in BMD.

Intractable and symptomatic PHPT

An open-label, single-arm, multicenter study prospectively evaluated the efficacy and safety of cinacalcet in 17 patients with intractable PHPT (defined as PHPT unresolved after parathyroidectomy or with contraindications to parathyroidectomy) and serum calcium >12.5 mg/dL (59). Cinacalcet was titrated on the basis of the serum calcium levels, and doses ranged from 30 mg twice daily to 90 mg four times daily (50). At the end of the titration phase (2–16 wk), the median cinacalcet dose was 70 mg twice daily. The mean serum calcium level was 12.7 ± 0.8 mg/dL (range, 11.8–14.5) at baseline and fell with cinacalcet to 10.4 ± 0.3 mg/dL during the titration phase ($P < .0001$). Serum calcium normalized in nine patients. Baseline elevated mean serum PTH levels (243 ± 105 pg/mL) did not change. Serum NTX and BSAP also did not change. Using the SF-36 metric quantification scale for quality of life, this study showed improvement in seven of the eight testing domains with cinacalcet in about

Table 1. Cohort Studies Including Patients With Sporadic Mild to Moderate PHPT[a,b]

First Author (Ref.)	Study Design	No. of Patients	Duration of Treatment, mo (Range)	Final Daily Dose, mg (Range)	Serum Calcium, mg/dL				Plasma PTH, pg/mL			
					Basal	Final	*P*	% Change	Basal (IQR)	Final (IQR)	*P*	% Change
Sajid-Crockett (57)	Retrospective chart review	18	8 (1–19)	Median, 60 (30–90)	10.6 ± 0.5	9.5 ± 0.3	<.001	−10.8	141 ± 78	108 ± 64	.007	−22.9
Iglesias (54)	Prospective data collection	4	12	60	10.8 ± 0.6[c]	9.5 ± 0.2[c]	NA	−10.2	196 ± 83[c]	191 ± 95[c]	NA	−5.1
Arranz Martin (51)	Prospective open label	17	9.4 ± 6.4	30–60	11.5 ± 0.6	9.9 ± 0.9	<.001	−13.9	144 (99, 82)	119 (86, 167)	<.001	−17.4
Faggiano (56)	Retrospective data collection	13	12[d]	30–90	11 ± 0.2[c]	9.7 ± 0.1[c]	NA	−11.8	122 ± 14[c]	92 ± 12[c]	NA	−25.4
Cetani (52)	Prospective, open label	6	Median, 12 (3–21)	Median, 60 (30–120)	12.2 ± 1.2	9.7 ± 1.2	.0015	−20.4	249 ± 245	188 ± 131	.19	−24.5
Filopanti (53)	Prospective, open label	20	3[d]	Median, (30–60)	11.7 ± 0.5	9.5 ± 0.4	<.001	−11.8	181 ± 115	121 ± 39	.032	−29.8
Luque-Fernandez (55)	Prospective, open label	20	12[d]	Mean, 60 (30–180)	11.7 ± 0.8	10.2 ± 0.9	<.001	−12.8	182 ± 102	152 ± 70	.028	−16.0
Saponaro (58)	Retrospective data collection	100	Median, 9 (1–26)	15–120	11.6 ± 1.1	10.2 ± 0.9	<.0001	−12%	164 (109, 254)	127 (91, 200)	.038	−22.5

Abbreviations: IQR, interquartile range; NA, not available.

[a] These studies included patients with previously failed parathyroidectomy or patients in whom parathyroidectomy was contraindicated, inappropriate, or refused.

[b] Unless otherwise indicated, data are presented as mean, mean ± SD, and range.

[c] Mean ± SE.

[d] All patients were treated for the indicated times.

50% of patients. However, in the absence of a control group, one must be cautious in interpreting these data.

To address systematically the efficacy of cinacalcet across a broad spectrum of disease severity, Peacock et al (60) performed a pooled analysis of three prior multicenter clinical trials. Across a spectrum of disease severity, mean serum calcium declined into the normal range within the first 6 months of therapy and remained stable for up to 4 years. Normalization of serum calcium was achieved in more than 70% of patients. Mean plasma PTH significantly declined ($P = .001$) by 6 months in patients with an indication for parathyroidectomy. No changes in mean serum BSAP and NTX and in urinary NTX/creatinine and calcium/creatinine ratios were seen. Mean BMD at lumbar spine, total hip, and one-third distal radius remained stable in all three groups. Adverse events occurred in 47 patients (58%) and led to discontinuation of cinacalcet in 14 (17%). Most adverse events were less than 1 month in duration, and none were serious, life-threatening, or fatal.

Cost effectiveness

Zanocco et al (61) compared the cost-effectiveness of monitoring, parathyroidectomy, or cinacalcet therapy in a hypothetical 60-year-old woman with asymptomatic PHPT and no indication for surgery according to the 2002 criteria. The patient's life expectancy was estimated at 22 years. Outcomes were weighted by using quality-adjusted life years. The cost of cinacalcet intervention was based on a dose of 30 mg twice daily (total cost per year, about $7095). Parathyroidectomy was cost-effective. Monitoring was the least expensive, but also the least effective option. Cinacalcet therapy would become cost effective if the annual cost would be decreased to less than $221. Similar conclusions were reached in a subsequent study in which the same authors evaluated the impact of age at diagnosis on the cost-effectiveness analysis (62).

The European Medicines Agency (EMA) in 2008 and the US Food and Drug Administration (FDA) in 2011 approved the use of cinacalcet for specific indications in patients with PHPT. The approved use of cinacalcet by the EMA is for patients in whom parathyroidectomy is indicated, on the basis of serum calcium levels, but in whom surgery "is not clinically appropriate or is contraindicated" (63). The FDA-approved indication for cinacalcet in PHPT is for severe hypercalcemia in patients unable to undergo parathyroidectomy (64).

Summary and recommendations

Cinacalcet is effective in lowering, and often normalizing, serum calcium and increasing serum phosphate in patients with PHPT. Its effects on intact serum PTH concentrations are less pronounced, although marked declines can be observed in the first 2–4 hours after dose administration. Although activation of the calcium-sensing receptor in the renal tubule is expected to increase urinary calcium excretion, a significant reduction in urinary calcium excretion was often observed. This is likely due to the reduction of the filtered renal calcium load, which follows cinacalcet-induced reductions in serum calcium. In the few studies that have evaluated the effects of cinacalcet on bone turnover markers, the results have

been inconsistent. No consistent effects on BMD were observed.

In view of cinacalcet's clear effects to reduce the serum calcium in PHPT, it should be considered in those subjects who meet criteria as set forth by the EMA and the FDA.

Question 6: Is therapy with cinacalcet effective in patients with familial PHPT?

Ten to 15% of patients with PHPT have an inherited form of the disease (65, 66). In most cases, there is multiglandular involvement, but it may be asynchronous. Familial PHPT is usually treated surgically, but definitive cure is often difficult, not only because of multiglandular involvement, but also due to the presence of ectopic and supernumerary glands. Moreover, the risks of laryngeal nerve damage and permanent hypoparathyroidism are increased by repeated and more radical surgical approaches.

Falchetti et al (67) first showed that cinacalcet was effective in lowering serum calcium in a patient with multiple endocrine neoplasia type 1 (MEN1)-associated PHPT who refused parathyroidectomy.

Moyes et al (68) evaluated eight patients with MEN1-associated PHPT, aged 20–38 years. Two patients received cinacalcet as primary treatment, and six were treated for persistent PHPT after surgery. Median pretreatment serum calcium and PTH levels were 11.0 mg/dL (range, 10.5–11.6) and 144 pg/mL (range, 44–332). Patients were started on a dose of 30 mg twice daily, and follow-up ranged between 10 and 35 months. All patients achieved normocalcemia. The median serum calcium declined to 9.2 mg/dL (range, 8.5–10.2; $P = .012$ vs baseline); median serum PTH declined to 88 pg/mL (range, 22–267; $P = .012$ vs baseline). Serum phosphorus significantly increased ($P = .012$), whereas there was no change in 24-hour urinary calcium excretion. Two patients experienced gastrointestinal side effects that required treatment withdrawal in one case.

Filopanti et al (53) carried out a randomized, crossover, double-blind study in 15 patients with MEN1-associated PHPT. Patients were randomized to treatment with cinacalcet 30 mg daily or placebo. In the cinacalcet group, the dosage was increased until serum calcium concentrations normalized. Patients were re-evaluated after 3 months. After a washout period of 1 month, patients were switched to the other treatment and reassessed 3 months later. The outcome of cinacalcet therapy was compared with that observed in 20 consecutive patients with sporadic PHPT who were given the same cinacalcet treatment as patients with MEN1-associated PHPT. Serum calcium normalized in all MEN1-associated PHPT patients within 1–3 weeks and remained stable during the follow-up. Serum phosphorus significantly increased ($P < .001$); serum PTH significantly declined (median decrease, 26.3%; $P = .002$) and normalized in five patients. No significant changes were observed in 24-hour urinary calcium excretion or in gastrointestinal or neuromuscular symptoms. Similar biochemical changes were observed in patients with sporadic PHPT during cinacalcet therapy. The mean cinacalcet dose required to normalize serum calcium did not significantly differ between MEN1 and sporadic PHPT patients. Mild adverse events were experienced by a few patients, and none required treatment withdrawal.

The retrospective study by Saponaro et al (58) also included 35 patients with familial PHPT (32 MEN1, three familial isolated PHPT). Using a titration protocol, mean serum calcium concentrations decreased from 11.0 ± 0.7 mg/dL to 9.9 ± 0.6 mg/dL ($P < .0001$), and all patients became normocalcemic. Mean predose serum PTH levels did not significantly change compared with baseline. Mild upper gastrointestinal side effects occurred in eight patients (22%). Treatment withdrawal was necessary in one subject who developed symptomatic hypocalcemia while taking 30 mg cinacalcet daily.

Summary and recommendations

Cinacalcet is effective in lowering serum calcium in patients with familial PHPT and is a treatment option for patients who have persistent or recurrent hypercalcemia after parathyroidectomy. It is not recommended as initial therapy for these patients. Surgery remains the best initial approach for control of PHPT associated with familial syndromes. Whether cinacalcet is effective in the control of hypercalcemia over time, given the high proliferative rate of the parathyroid cells in this disease, remains to be determined. There is, furthermore, no evidence regarding the safety of chronic systemic calcium-sensing receptor activation by cinacalcet on the growth and function of the other nonparathyroid tumors in MEN1 and MEN2A and in the hyperparathyroidism-jaw tumor syndromes.

Question 7: Can cinacalcet and bisphosphonate be combined in patients with PHPT?

Cinacalcet is effective in the control of hypercalcemia in patients with PHPT but does not increase BMD significantly or consistently. Conversely, bisphosphonate therapy increases BMD in PHPT, but has little or no effect on serum calcium. Combination therapy with cinacalcet and bisphosphonate has considerable appeal, therefore, in PHPT patients for whom it is desirable to control hypercalcemia and improve BMD.

In a retrospective study, Faggiano et al (56) reported the results of 10 subjects who were given cinacalcet plus alendronate and 13 patients who received cinacalcet alone. In the cohort, osteopenia was present in 13 subjects and os-

teoporosis was present in five by DXA scan T scores. Vertebral fractures were noted on radiographs in three. After 3 months of treatment, serum calcium levels, which were not different in both groups at baseline, fell significantly ($P < .001$). Serum phosphorus levels rose ($P < .001$), and serum PTH levels declined significantly after 6 months of therapy ($P < .001$). Twenty-four-hour urinary calcium levels also fell ($P < .001$). None of these biochemical changes differed in magnitude when the two treatment groups were separately evaluated. On the other hand, significant densitometric differences were observed between patients treated with cinacalcet alone or combination treatment. Mean baseline T-scores did not differ at the lumbar spine (-2.02 ± 0.31 vs -2.15 ± 0.30) or the total hip (-2.10 ± 0.25 vs -2.25 ± 0.30) for the groups receiving cinacalcet vs cinacalcet plus alendronate, respectively. After 12 months, patients receiving combined therapy showed greater improvements in lumbar spine ($+9.6 \pm 1.4\%$) and in total hip ($+3.9 \pm 1.0\%$) BMD ($P < .01$ [spine] and $P < .05$ [hip]) compared with patients treated with cinacalcet monotherapy.

Cetani et al (52) evaluated the efficacy of cinacalcet in 14 patients with PHPT (12 sporadic and two MEN1-associated) in a prospective, open-label study. Eight patients had been treated with bisphosphonates when cinacalcet was started. Mean baseline serum calcium and PTH levels were 12.2 ± 1.0 mg/dL and 269 ± 179 pg/mL, respectively. Follow-up ranged from 3 to 21 months with a median of 12 months. By the last observational time-point, baseline serum calcium had fallen significantly by at least 1 mg/dL in all patients to a mean value of 9.9 ± 0.7 mg/dL ($P < .0001$). Mean serum PTH was 223 ± 42 pg/mL and did not significantly differ from baseline. The responses in serum calcium and PTH did not differ between patients who did or did not receive bisphosphonate. BMD in the former group (four patients) did not change.

In a retrospective evaluation of 475 patients with PHPT, Keutgen et al (69) identified 17 patients who had been treated with cinacalcet for at least 1 year. All but one were also given bisphosphonate treatment. Mean post-treatment serum calcium concentration (10.1 ± 0.7 mg/dL) was significantly lower ($P = .003$) compared with baseline, and normal values were observed in 12 of 17 (71%) patients. No significant changes were observed in serum PTH levels, although serum PTH normalized in six (35%) patients. The mean lumbar spine T-score significantly improved from -1.90 ± 1.2 to -1.45 ± 1.4 ($P = .045$), whereas no significant change was observed in the femur T-score.

Summary and recommendations

Although none of the studies of combination therapy with cinacalcet and bisphosphonate were prospective or rigorously controlled, combination therapy appears to achieve both calcium-lowering effects of cinacalcet and stabilization of BMD by bisphosphonate treatment. In subjects with low BMD and serum calcium levels in the range that is appropriate for cinacalcet use, combined therapy could be beneficial.

Overall Summary of Potential Indications for Nutritional and Pharmacological Therapy in PHPT

The recommended calcium intake in patients with PHPT should not differ from that of the general population. Patients with PHPT and vitamin D deficiency should be repleted with doses of vitamin D aiming for serum 25OHD levels consistent with country-specific guidelines (either >50 nM or >75 nM) with appropriate monitoring of serum and urinary calcium excretion.

Pharmacological management of PHPT should be targeted to patients who have failed surgery, have contraindications to surgery, or are unwilling to undergo parathyroidectomy. It should also be reserved for those individuals in whom it is desirable to lower the serum calcium, increase BMD, or both. The choice of a medical approach, when indicated, should therefore depend upon the desired goal. For control of hypercalcemia, cinacalcet is the treatment of choice. To improve BMD, bisphosphonate therapy is recommended. To reduce the serum calcium and improve BMD, combination therapy with both agents is reasonable, but it should be noted that strong evidence for efficacy is lacking. The workshop identified several areas of future research that are listed in the accompanying "Guidelines paper" (70).

Acknowledgments

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The authors constitute the subcommittee assigned to summarize the topic and discussions that occurred during the workshop and to address the questions posed by the Task Force.

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