Medical Management of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

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Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is frequently asymptomatic. The 2002 International Workshop on Asymptomatic PHPT addressed medical management of asymptomatic PHPT and summarized the data on nonsurgical approaches to this disease. At the Third International Workshop on Asymptomatic PHPT held in May 2008, this subject was reviewed again in light of data that have since become available. We present the results of a literature review of advances in the medical management of PHPT.

Methods: A series of questions was developed by the International Task Force on PHPT. A comprehensive literature search for relevant studies evaluating the management of PHPT with bisphosphonates, hormone replacement therapy, raloxifene, and calcimimetics was conducted. Existing guidelines and recent unpublished data were also reviewed. All selected relevant articles were reviewed, and the questions developed by the International Task Force were addressed by the Consensus Panel.

Results: Bisphosphonates and hormone replacement therapy are effective in decreasing bone turnover in patients with PHPT and improving bone mineral density (BMD). Fracture data are not available with either treatment. Raloxifene also lowers bone turnover in patients with PHPT. None of these agents, however, significantly lowers serum calcium or PTH levels. The calcimimetic cinacalcet reduces both serum calcium and PTH levels and raises serum phosphorus. Cinacalcet does not, however, reduce bone turnover or improve BMD.

Conclusions: Bisphosphonates and hormone replacement therapy provide skeletal protection in patients with PHPT. Limited data are available regarding skeletal protection in patients with PHPT treated with raloxifene. Calcimimetics favorably alter serum calcium and PTH in PHPT but do not significantly affect either bone turnover or BMD. Medical management of asymptomatic PHPT is a promising option for those who are not candidates for parathyroidectomy. (***J Clin Endocrinol Metab*** **94: 373–381, 2009)**

The Third International Workshop on Primary Hyperparathyroidism was convened by the co-chairs with the support of 10 international sponsoring societies to review advances made in the diagnosis and management of PHPT since the last workshop in 2002 (1). The PHPT Task Force, nominated by the sponsoring societies of the Workshop and divided into three teams, developed questions on the diagnosis, medical and surgical management, and preoperative imaging of patients with PHPT for the presenting authors and consensus panel to address. This manuscript reports on the literature review pertaining to advances in the medical management of PHPT (Table 1).

The key questions to be addressed were: 1) How effective are bisphosphonates in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium? 2) How effective is hormone replacement therapy (HRT) in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium? 3) How effective is raloxifene in preventing the skeletal complications of PHPT and in lowering PTH and serum

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Abbreviations: BMD, Bone mineral density; BSAP, bone-specific alkaline phosphatase; CaSR, calcium-sensing receptor; CEE, conjugated equine estrogen; DXA, dual-energy x-ray absorptiometry; HRT, hormone replacement therapy; NTX, N-telopeptide; PHPT, primary hyperparathyroidism; SERM, selective estrogen receptor modulator.

TABLE 1. Evidence for recommendations

Hierarchy of evidence	Refs.
Level Ia: Systematic review of randomized controlled trials	
Level Ib: Single randomized controlled trials	6–8, 18, 19, 21–23, 27, 28, 31, 32, 36–39, 43, 53–55
Level II: Systematic review of observational studies	
Level III: Single observational studies, low-quality randomized controlled trials	2–5, 9–17, 20, 24–26, 29–30, 33–35, 40–42, 44–52
Level IV: Case series, surveys	15, 17, 52
Level V: Consensus guidelines	1

calcium? 4) How effective is the calcimimetic cinacalcet in normalizing PTH and serum calcium and in providing skeletal protection?

Data presented at the Conference included studies pertinent to the diagnosis and clinical presentations of asymptomatic PHPT, and advances in the surgical and medical management of PHPT (2–8). Patients who do not meet surgical guidelines or are unable or unwilling to proceed with parathyroidectomy can be safely monitored. Medical management of these individuals is addressed in this section.

Recently, data from three small longitudinal studies of subjects with PHPT who did not undergo surgical therapy have been presented (2, 9, 10). Collectively, they suggest that biochemical indices (serum calcium, PTH, serum creatinine) remain stable over prolonged (10–18 yr) follow-up. There are discrepant results from analyses of BMD in these studies. In the study of Rubin *et al.* approximately 60% of asymptomatic subjects with PHPT followed for up to 15 yr lost more than 10% of their bone mass at lumbar spine, proximal femur or forearm (2). Interpretation of these results is hampered by the lack of a control group. In the study of Iksander and Rao, BMD Z scores did not change at any skeletal site (9), whereas in the study of Bolland *et al.* rates of bone loss in the PHPT subjects were not different from those observed in eucalcemic controls at total body or lumbar spine, but were accelerated at the femoral neck (10).

Despite uncertainty about whether long-term untreated PHPT is accompanied by accelerated bone loss, it is clear that many patients with PHPT, because of their age and gender, have low BMD and increased fracture risk. It is clear that surgical correction of PHPT is followed by reduction in bone turnover and significant improvements in BMD (6–8, 11). In patients with PHPT for whom low BMD and increased fracture risk are the reasons for intervention, it may be possible to provide skeletal protection with antiresorptive agents.

Study Identification and Selection

An electronic literature search was completed in MEDLINE and EMBASE using OVID on all published literature between 1996 and June, 2008 (Table 2). Keywords were combined to find the relevant articles. First, PHPT was combined with bisphosphonates, which generated 104 studies. PHPT was then combined with HRT, and 23 articles were identified. Calcimimetics and PHPT were combined, and 33 articles were identified. Lastly, the PHPT search was combined with the keyword raloxifene, which generated 31 articles, resulting in a total of 191 articles that were reviewed. The relevant articles of those identified by the search were reviewed. Key articles published before 1996, some of which were referenced in the 2002 Consensus Summary Statement (1), were also included in the data synthesis.

Articles were sorted according to their relevance to the key questions being addressed by the team. Studies were classified according to the study design (Table 2).

Question 1. How Effective are Bisphosphonates in Preventing the Skeletal Complications of PHPT and in Lowering PTH and Serum Calcium?

Background

Aminobisphosphonates, analogs of pyrophosphate and inhibitors of bone resorption, are significantly more potent than the non-nitrogen-containing bisphosphonates and have been evaluated in several studies of patients with PHPT. The pharmacology of the bisphosphonates as a class indicates that approximately 50% of the absorbed dose is cleared through the kidney, with the remaining 50% being deposited into bone, preferentially at active remodeling sites (12). The bisphosphonate buried under newly formed bone lies inert and has no skeletal effects until subsequent resorption occurs and the drug is released from the matrix and internalized by osteoclasts. In osteoclasts, bisphosphonates inhibit farnesyl diphosphate synthase, a key enzyme in the cholesterol synthesis pathway involved in

TABLE 2. Search strategy

Search word	Studies found
1. Primary hyperparathyroidism	2,085
2. Bisphosphonates	7,218
3. Hormone replacement therapy	17,187
4. Calcimimetics	191
5. Raloxifene	5,145
6. 1 + 2	104
7. 1 + 3	23
8. 1 + 4	33
9. 1+ 5	31

Search keywords: primary hyperparathyroidism, bisphosphonates, hormone replacement therapy, calcimimetics, raloxifene. Keywords were combined to find the relevant articles in MEDLINE and EMBASE using OVID. The search was conducted on all published literature between 1996 and June, 2008. First, PHPT was combined with bisphosphonates, which generated 104 studies. PHPT was then combined with HRT, and 23 articles were identified. Calcimimetics and PHPT were combined, and 33 articles were identified. Lastly, PHPT search was combined with the keyword raloxifene, which generated 31 articles resulting in a total of 191 articles; of these, the relevant articles were reviewed in detail.

posttranslational modification of important signaling molecules (Ras, Rac, Rho, and Rab). Inhibition of farnesyl diphosphate synthase disrupts several pathways involved in cytoskeletal organization, cell survival, and cell proliferation, leading to inhibition of osteoclast activity and apoptosis (13). This results in reduced bone turnover and enhanced bone mineralization because of the extended time available for mineral accumulation once the phase of resorption is truncated. Bisphosphonates are effective in the treatment of a variety of metabolic bone diseases, including osteoporosis in postmenopausal women and men, and glucocorticoid-induced osteoporosis (14). They are also effective agents in the management of skeletal complications of malignancy.

Clinical studies in PHPT

Clodronate (1200 mg/d for 12 wk) was first evaluated in patients with PHPT by Shane *et al.* (15). Serum calcium was lowered from 11.5 ± 0.1 to 10.8 ± 0.2 mg/dl (2.88 ± 0.025 to 2.7 ± 0.05 mmol/liter) ($P < 0.001$). Although PTH levels did not change, biochemical markers of bone resorption decreased. Similar results with clodronate were reported by Hamdy *et al.* (16) in nine patients with PHPT. A decrease in serum calcium was seen, with inhibition of bone resorption. The effects were not sustained, however, and treatment for longer than 3 months resulted in recurrence of hypercalcemia. Adami *et al.* (17) evaluated 27 patients with PHPT and noted increases in PTH with inconsistent effects on serum calcium. Licata and O'Hanlon (18) evaluated etidronate and found no change in serum calcium in patients with PHPT.

Schmidli *et al.* (19) evaluated pamidronate in patients with mild PHPT (20). Infusions (30 mg) were administered to 10 patients in a randomized crossover study and were effective in reducing serum calcium from 10.88 ± 0.24 to 9.96 ± 0.16 mg/dl (2.72 ± 0.06 to 2.49 ± 0.04 mmol/liter) after 1 wk. PTH levels, however, increased during this time period, and the effect on serum calcium was only transient (19). Reasner *et al.* (20) evaluated risedronate given in high doses (20 and 40 mg daily) for 7 d. This cycle was repeated after 3 wk in the 19 postmenopausal women and seven men in this study. Decreases in serum calcium from 11.04 ± 0.16 to 10.4 ± 0.16 mg/dl (2.76 ± 0.04 to 2.60 ± 0.04 mmol/liter) were noted after 1 wk. These decreases in serum calcium were accompanied by increases in PTH. There were no differences between the response to 20- *vs.* 40-mg doses of risedronate in terms of serum calcium or other biochemical parameters. Decreases in serum calcium were also accompanied by increases in renal calcium reabsorption. This would be expected in association with the rises in PTH. Thus, short-term treatment with risedronate was effective in lowering serum calcium in individuals with mild PHPT (20). No data are available from longer-term studies of risedronate in PHPT.

Alendronate is the bisphosphonate that has been most extensively evaluated in individuals with PHPT. Rossini *et al.* (21) evaluated 26 elderly women who were randomized to treatment with oral alendronate (10 mg every other day) or no treatment for 2 yr. Decreases in bone turnover markers were noted, with decreases in urinary deoxypyridinoline excretion within the first month of treatment. Alkaline phosphatase and osteocalcin fell more gradually, and their decreases became significant after 3 months of treatment. Bone turnover markers remained suppressed during the 2 yr of alendronate treatment. Increases in BMD at the lumbar spine, total hip, and total body were noted in comparison to baseline (8.6 ± 3, 4.8 ± 3.9, and 1.2 ± 1.4%). Of note, the increase in BMD in the alendronate-treated group was similar when compared with a nonrandomized group of postparathyroidectomy patients. Serum calcium and phosphate and urinary calcium excretion significantly decreased during the first 3–6 months but returned to baseline after treatment. Increases in PTH were statistically significant during the first year of treatment. Levels of vitamin D metabolites were not measured in this study (21).

Chow *et al.* (22) evaluated the effects of alendronate in 40 postmenopausal women randomized to receive alendronate (10 mg/d) or placebo for 48 wk, followed by treatment withdrawal for 24 wk. Mean changes in BMD were significantly higher with alendronate at 48 wk [+4.17 ± 6.01 *vs.* −0.25 ± 3.3% ($P = 0.011$) at the femoral neck, and +3.79 ± 4.04 *vs.* 0.19 ± 2.8% ($P = 0.016$) at the lumbar spine]. Serum calcium was reduced with alendronate but not with placebo [−0.09 *vs.* +0.01 mmol/liter ($P = 0.018$)]. Bone-specific alkaline phosphatase (BSAP) levels were lowered by alendronate treatment after 12 wk and increased 24 wk after treatment withdrawal. Levels of circulating osteocalcin decreased at 48 wk and increased 24 wk after alendronate withdrawal ($P = 0.019$). Alendronate was effective in reducing bone turnover markers in postmenopausal women with PHPT and produced increases in BMD. Urinary calcium did not change from baseline in the treated group or the placebo group (22).

Khan *et al.* (23) conducted a multicenter trial evaluating 44 patients with PHPT randomized to placebo or alendronate (10 mg/d) stratified for gender. After 12 months, the placebo group was crossed over to active treatment. All patients were on active treatment in the second year. The primary outcome was BMD at the lumbar spine, femoral neck, total hip, and distal 1/3 radial sites as measured every 6 months by dual-energy x-ray absorptiometry (DXA). Treatment with alendronate for 2 yr was associated with significant increases in lumbar spine BMD in comparison to baseline (6.8 ± 0.94%, $P < 0.001$) (Fig. 1). Total hip BMD increased at 12 months by 4.01 ± 0.77% ($P < 0.001$) and remained stable over the next 12 months of treatment. BMD at the 1/3 distal radius site did not show statistically significant changes in the alendronate-treated group at 12 or 24 months of therapy. Marked reductions in bone turnover markers were noted with alendronate therapy, with rapid decreases in urinary N-telopeptide (NTX) excretion by 66% ($P < 0.001$) at 3 months and decreases in BSAP by 49% at 6 months ($P < 0.001$). In the placebo-treated group, NTX and BSAP remained elevated. Serum calcium (both total and ionized), PTH, and urinary calcium did not change with alendronate therapy (Fig. 2).

In this study, 25-hydroxyvitamin D levels were 18.2 ng/ml (45.5 nmol/liter) at baseline in the group receiving alendronate for 24 months and 18.6 ng/ml (46.5 nmol/liter) in the group receiving placebo and then crossed over to alendronate (23).

Parker *et al.* (24) evaluated 32 patients with PHPT (27 women, five men). Fourteen individuals with femoral neck T

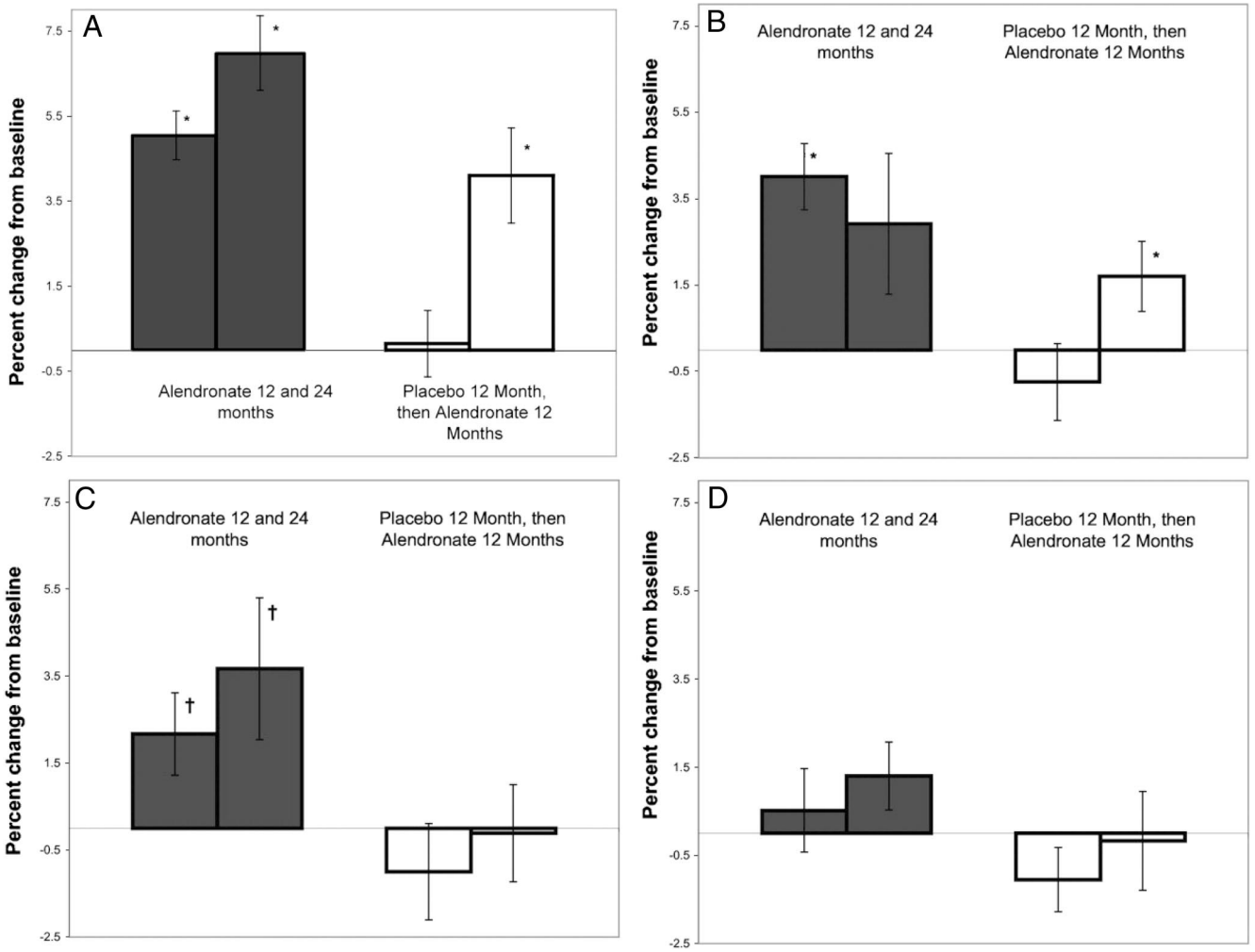

FIG. 1. Effects of alendronate on lumbar spine (A), total hip (B), femoral neck (C), and one third distal radius (D) BMD. *, Significantly higher than baseline ($P < 0.001$); †, Significantly higher than baseline ($P < .05$). [Reproduced with permission from Khan *et al.*: *J Clin Endocrinol Metab* 89:3319–3325, 2004 (23).]

scores of less than or equal to −2.5 or a femoral neck T score of less than −1 in the presence of a nonvertebral fracture were given open-label alendronate (10 mg/d) for 24 months. Those individuals with a femoral neck T score of greater than −2.5 (n = 18) were not treated. No significant differences were noted in serum calcium, creatinine, or PTH between the two groups. Alendronate treatment increased bone mass significantly at the lumbar spine. The mean increase in BMD at the lumbar spine after 2 yr was 7.3 ± 3.1% *vs.* baseline ($P = 0.04$). Untreated patients gained bone mass at the lumbar spine over 2 yr (4.0 ± 1.8%; $P = 0.03$), but their BMD declined at other sites. Serum calcium fell, but not significantly, in the alendronate-treated group between baseline [11.36 ± 0.12 mg/dl (2.84 ± 0.03 mmol/liter)] and 6 wk [11.08 ± 0.08 mg/dl (2.77 ± 0.02 mmol/liter)]. The change in PTH was not significant [baseline, 103.5 ± 14.6 pg/ml (103.5 ± 14.6 ng/liter); 6 wk, 116.7 ± 15.6 pg/ml (116.7 ± 15.6 ng/liter)]. At 3 months, the values had returned to baseline (24).

In summary, data from the randomized controlled trials have consistently demonstrated that alendronate decreases bone turnover and increases BMD at the lumbar spine and proximal femur in PHPT. The effect on serum calcium has been inconsistent and may have been affected by baseline 25-hydroxyvitamin D levels, which were not reported in all the studies conducted. With the introduction of a potent bisphosphonate, decreases in bone resorption may contribute to lowering of serum calcium, particularly in the presence of suboptimal vitamin D levels. This may result in further elevations in PTH. This requires further evaluation in a well-designed prospective format. Although these results suggest that bisphosphonate therapy in PHPT may lead to improvement in bone strength, there are no direct data to confirm this effect, and fracture outcomes have not been evaluated.

Question 2. How Effective is HRT in Preventing the Skeletal Complications of PHPT and in Lowering PTH and Serum Calcium?

Background

Estrogen is an effective antiresorptive treatment in the management of postmenopausal osteoporosis. In patients with PHPT, it was postulated that estrogen might decrease serum calcium in PHPT by inhibiting resorption-mediated efflux of calcium from skeletal stores and ameliorate bone loss associated with the disorder. PHPT is identified more commonly in post-

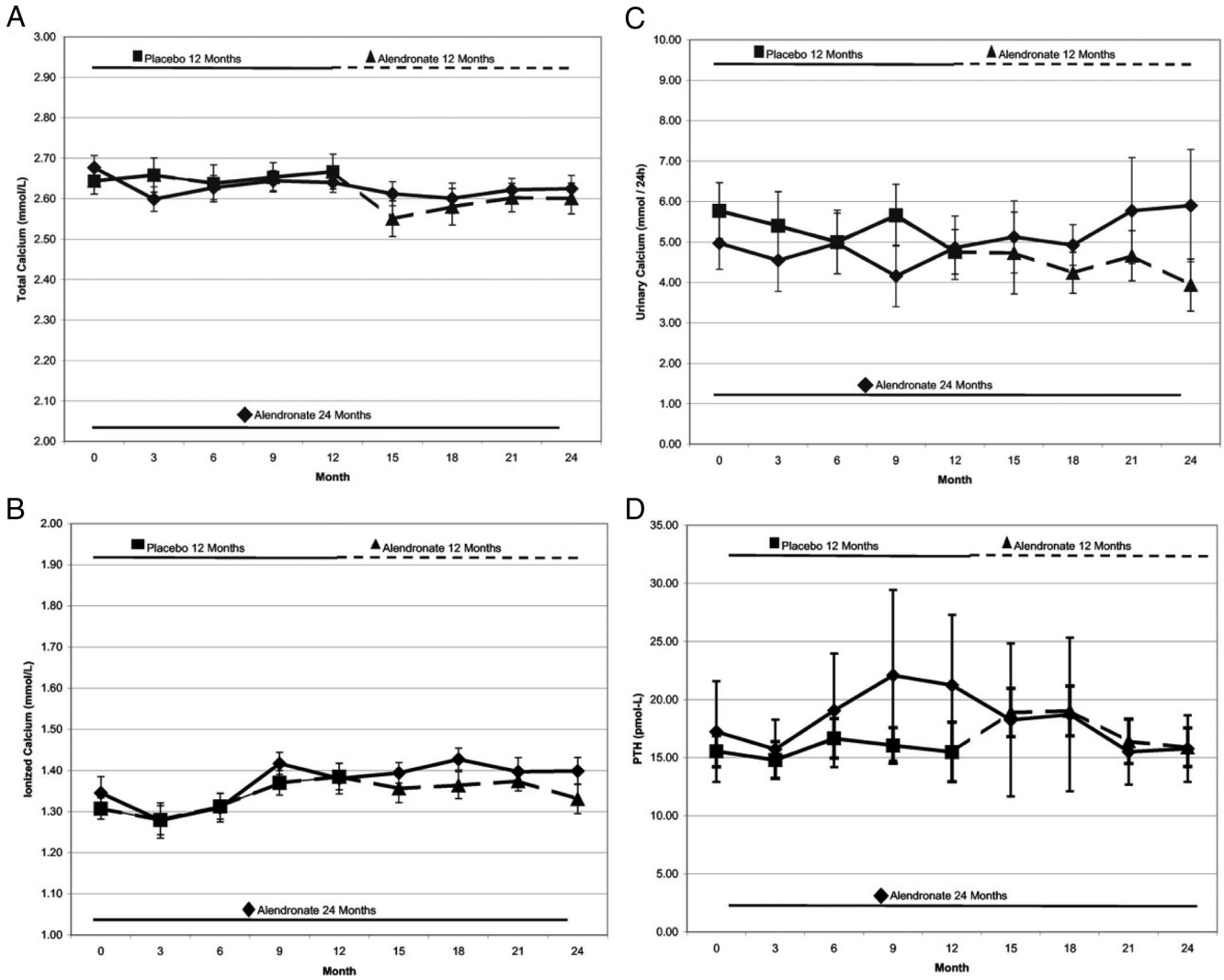

FIG. 2. Effects of alendronate on total calcium (A), ionized calcium (B), urinary calcium (C), and PTH (D). [Reproduced with permission from Khan *et al.*: *J Clin Endocrinol Metab* 89:3319–3325, 2004 (23).]

menopausal women, raising speculation regarding the effects of estrogen on parathyroid function and serum calcium.

Clinical studies in PHPT

Early, uncontrolled studies of conjugated equine estrogens (CEE), ethinyl estradiol, and norethisterone suggested that HRT may partially ameliorate hypercalcemia in PHPT (25, 26). Total serum calcium normalized in 10 of 14 postmenopausal women with PHPT treated with high doses (1.25 mg/d) of CEE (25). PTH levels were not altered by estrogen therapy in this study, and ionized calcium was not measured. Similarly, Selby and Peacock (26) reported improvement in total serum calcium without changes in PTH levels in small groups of women treated with high doses of ethinyl estradiol or norethisterone. Subsequently, a 2-yr randomized, placebo-controlled trial of HRT (CEE/medroxyprogesterone acetate) in postmenopausal women with PHPT reported a small decrease in total serum calcium in the group treated with HRT but no changes in either serum ionized calcium or intact PTH (27).

The findings that HRT does not change either ionized calcium or PTH levels in PHPT suggest that it decreases total serum calcium by affecting the fraction of protein- and/or anion-bound calcium. The effects of HRT to decrease serum bicarbonate levels (28) and induce hemodilution (29) in postmenopausal women may underlie the effects on total serum calcium. As seen in normocalcemic postmenopausal women, HRT reduces bone turnover in postmenopausal women with PHPT. Markers of bone resorption decrease by approximately 50% for the duration of therapy (27).

In normocalcemic postmenopausal women, HRT increases BMD and decreases fracture risk (30, 31). In postmenopausal women with PHPT, a 2-yr randomized, placebo-controlled trial demonstrated beneficial effects on BMD at multiple sites throughout the skeleton in the estrogen-treated women, with between-group differences at the end of the study (lumbar spine 6.6%, proximal femur 3.4%, forearm 5.4%, total body 3.6%) similar to those reported in eucalcemic women treated with HRT (27) (Fig. 3). These effects were maintained for at least 4 yr (32). The magnitude of the effects of estrogen on BMD in PHPT is comparable to that which occurs after surgical correction of PHPT. In each of two nonrandomized comparisons of the effects of HRT and surgery on BMD in PHPT, the interventions produced similar increases in axial bone mass (33, 34).

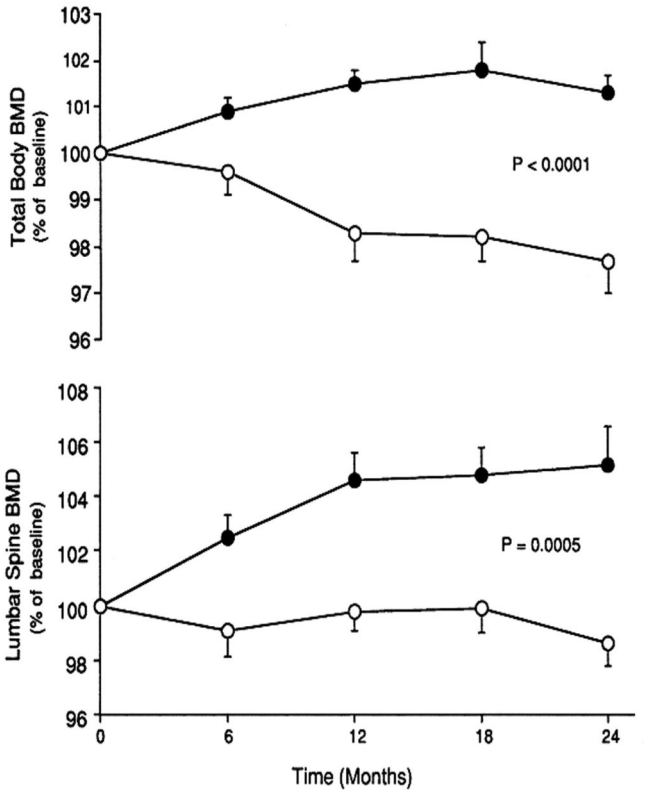

FIG. 3. The effects of HRT on total body (*upper panel*) and lumbar spine (*lower panel*) BMD in postmenopausal women with PHPT. Data are mean (SEM). [Reproduced from Grey *et al.*: *Ann Intern Med* 125:360–368, 1996 (27), with permission from the American College of Physicians.]

Question 3. How Effective is Raloxifene in Preventing the Skeletal Complications of PHPT and in Lowering PTH and Serum Calcium?

Background

Selective estrogen receptor modulators (SERMs) exhibit tissue-specific estrogen agonistic or antagonistic effects depending upon the specific SERM and the target organ. They therefore offer the potential to confer the beneficial effects of estrogen, for example, on the skeleton, without the adverse vascular and breast effects that are seen in response to HRT (35–38). However, the effects of the most-studied SERM, raloxifene, on bone resorption and BMD are inferior to those of CEE in normocalcemic postmenopausal women (36). Antifracture efficacy of SERMs has been demonstrated at the lumbar spine, but not at nonvertebral sites, in normocalcemic women (37, 38). Very limited data are available in regard to the biochemical and skeletal effects of SERMs in postmenopausal women with PHPT.

Clinical studies in PHPT

A small, placebo-controlled, randomized trial reported the effects of raloxifene (60 mg/d) on serum calcium and phosphorus over 2 months in postmenopausal women with PHPT (39). Total serum calcium declined in both raloxifene- and placebo-treated subjects, but the effects reached statistical significance by 2 months in the raloxifene-treated women. No changes were observed in levels of PTH; ionized calcium was not measured. Markers of bone turnover were also measured in this study, and although there was a significant decline in the levels of urinary NTX and serum osteocalcin in the raloxifene-treated women, the magnitude of these declines (18 and 17% from baseline, respectively) was substantially less than was observed in response to CEE in PHPT (27).

The only published data on the effects of SERMs on BMD in PHPT are from a case series in which pretreatment declines in BMD at both spine and hip sites in three subjects were arrested by the introduction of treatment with raloxifene (60 or 120 mg/d) (40).

Question 4. How Effective is the Calcimimetic Cinacalcet in Normalizing PTH and Serum Calcium and in Providing skeletal protection?

Background

The identification of the calcium-sensing receptor (CaSR) cDNA by Brown *et al.* (41) in 1993 was quickly followed by the development of molecules that target this receptor with the idea that they might be useful in PHPT and secondary hyperparathyroid states such as renal insufficiency (42–46). The key physiological ligand that controls PTH secretion is a change in extracellular ionized calcium. Activation of the CaSR increases phospholipase C and A activity, inhibits adenylate cyclase activity, and enhances MAPK signaling (44). These pathways bring about the inhibition of PTH secretion, PTH gene transcription, and parathyroid cell proliferation. Calcimimetics mimic the action of extracellular calcium on the CaSR, and thereby block PTH secretion and ultimately suppress cell growth and glandular hyperplasia in models of uremic secondary hyperparathyroidism (42, 44, 47, 48).

Strictly speaking, calcimimetics are not true ligands for the CaSR. Instead, they are allosteric modulators—sensitizing the CaSR to the ambient calcium level. This has been convincingly demonstrated *in vitro* with cinacalcet, an orally active phenylalkylamine calcimimetic (47). This agent has been further tested in a murine model of PHPT, generated by parathyroid-specific overexpression of the cell-cycle protein cyclin D1 (49). These studies showed that CaSR number in parathyroid tissue correlated with the ability of orally administered cinacalcet to reduce hypercalcemia in these animals (50).

Clinical studies in PHPT

A single-dose, range-finding study with a prototype compound NPS-R568 provided proof-of-concept that administration of a calcimimetic could suppress PTH in a time- and concentration-dependent manner in patients with PHPT (51). This same agent also substantially reduced hypercalcemia chronically in a patient with intractable hypercalcemia due to parathyroid cancer (52).

A similar compound, cinacalcet, was tested in a randomized, double-blind, placebo-controlled trial employing escalating doses (30, 40, or 50 mg twice daily) for 2 wk in patients with mild PHPT with serum calcium levels of 10.3 and 12.5 mg/dl (2.58 to 3.13 mmol/liter) [normal, 8.4–10.32 mg/dl (2.1–2.58 mmol/liter)] and intact PTH levels of at least 45 pg/ml (normal, 10–65 pg/ml) (53). Average serum calcium values were 10.4 mg/dl (2.6

mmol/liter) for the placebo group (n = 6), 10.52 mg/dl (2.63 mmol/liter) for the 30-mg group (n = 5), 10.6 mg/dl (2.65 mmol/liter) for the 40-mg group (n = 5), and 10.72 mg/dl (2.68 mmol/liter) for the 50-mg group (n = 5) in this study. Mean intact PTH values were 100 pg/ml (placebo group) and 102 pg/ml (all cinacalcet groups combined). Serum calcium levels fell in a dose-dependent manner over the period of active drug administration from baseline by 11, 18.7, and 18.5% on d 15 just before drug administration, whereas there was a 0.3% increase in serum calcium in the placebo group (54). When the serum calcium data from all the cinacalcet doses were combined and compared with responses in placebo-treated patients, there was a statistically significant 16% reduction in serum calcium due to cinacalcet ($P = 0.004$), which reflected a fall in the serum calcium to 8.92 ± 0.72 mg/dl (2.23 ± 0.18 mmol/liter) for the combined dose groups.

Pharmacodynamic assessments of serum calcium and PTH showed decreases in intact PTH of approximately 50% and approximately 35% 4 h after the first and second doses of cinacalcet, respectively, on d 15 of the study, compared with a 0.3% increase in PTH 4 h after placebo administration on d 15 (54). Intact PTH levels rose to baseline levels by 8 to 12 h after cinacalcet administration. There were no significant differences in 24-h urinary calcium levels in cinacalcet- *vs.* placebo-treated patients. Adverse events were mild to moderate and similar between cinacalcet- and placebo-treated patients. Most common were paresthesias occurring in three and two patients treated with cinacalcet and placebo, respectively. This study established proof-of-concept that orally administered calcimimetic could safely lower serum calcium into the normal range in patients with PHPT.

A double-blind, randomized, 52-wk, placebo-controlled multicenter trial examined the effectiveness of cinacalcet on biochemical and hormonal parameters as well as markers of bone turnover, and BMD by DXA, in patients with PHPT. This trial enrolled 78 patients (age range, 27 to 83 yr) with serum calcium concentrations of more than 10.32 mg/dl (2.58 mmol/liter) and less than 12.52 mg/dl (3.13 mmol/liter) and plasma PTH values of more than 45 pg/ml (54). Baseline serum calcium was 10.72 ± 0.4 and 10.72 ± 0.52 mg/dl (2.68 ± 0.1 and 2.68 ± 0.13 mmol/liter) in placebo- and cinacalcet-treated patients, respectively. Plasma PTH values were 120 ± 54 and 105 ± 36 pg/ml in placebo- and cinacalcet-treated patients, respectively. Twice-daily cinacalcet administration produced either a significant lowering [of 0.52 mg/dl (0.13 mmol/liter) or greater] or a normalization of serum calcium concentrations [defined as <10.32 mg/dl (2.58 mmol/liter)] in 73% of calcimimetic-treated patients during the study (Fig. 4). Patients in the placebo treatment arm did not show significant decreases in serum calcium. By wk 52, serum baseline PTH values pre-dose (*i.e.* approximately 12 h after the last drug administration) had fallen by approximately 13% in cinacalcet-treated patients *vs.* approximately 6% in placebo-treated patients, respectively. Serum phosphorus values rose significantly in cinacalcet- *vs.* placebo-treated patients from 2.7 ± 0.5 to 3.2 ± 0.5 mg/dl (0.87 ± 0.16 to 1.03 ± 0.16 mmol/liter) ($P < 0.001$). There were no statistically significant changes in the levels of

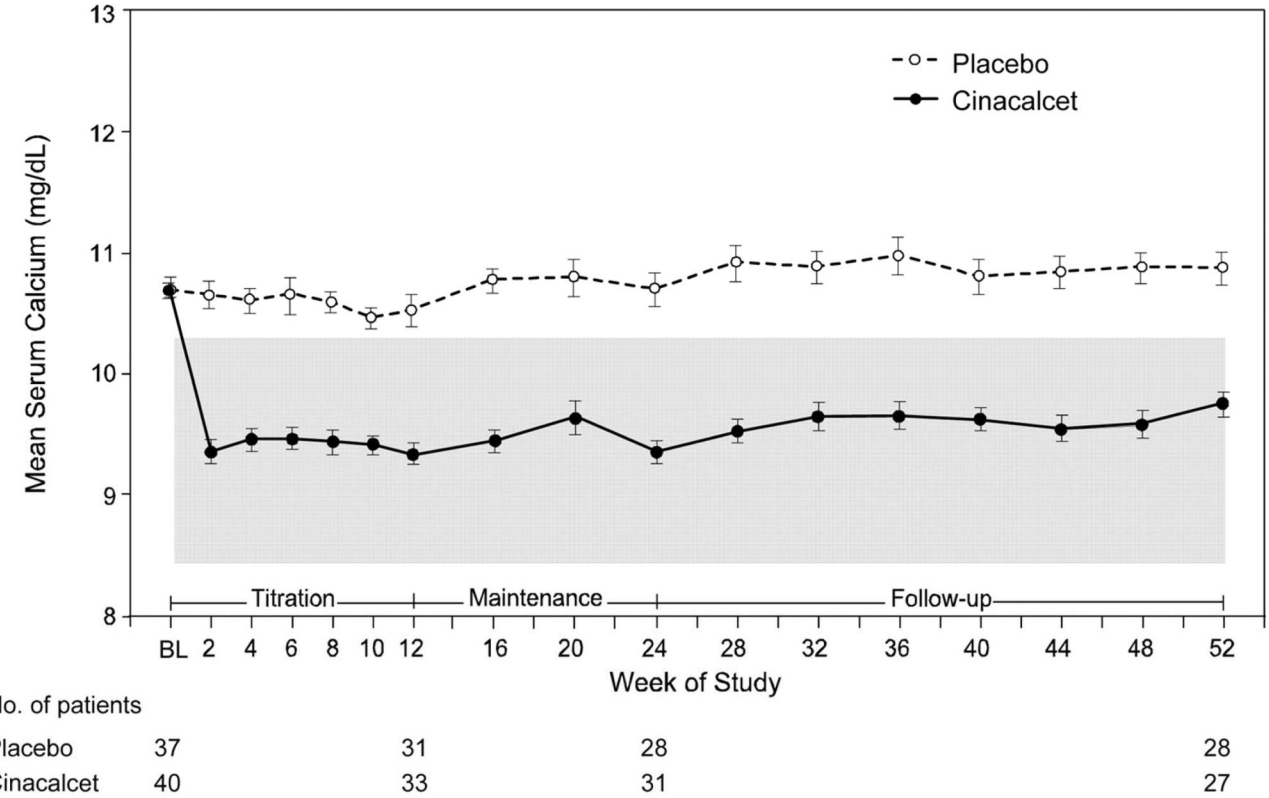

FIG. 4. Predose serum total calcium concentrations (mg/dl) in patients with PHPT treated with placebo or cinacalcet for 52 wk. Statistically significant reductions in serum total calcium were observed in response to cinacalcet administered twice daily. The *shaded area* depicts the normal range. [From Peacock *et al.*: *J Clin Endocrinol Metab* 90:135–141, 2005 (54).]

1,25-dihydroxyvitamin D, 24-h urinary calcium/creatinine, or biochemical markers of bone turnover (BSAP and serum and urine NTX) in patients treated with cinacalcet *vs.* placebo. Average DXA BMD Z scores (lumbar spine, total hip, and distal 1/3 radius) at baseline were between −0.10 and −0.33 (placebo-treated patients) and 0.15 to −0.46 (cinacalcet-treated patients), confirming overall that these subjects did not have significant bone loss. BMD Z scores did not change significantly in either group over the 52-wk course of the study (53). Adverse events were mild to moderate, and the agent was well-tolerated overall, with most common side effects being nausea (28% cinacalcet, 16% placebo) and headache (23% cinacalcet, 41% placebo). Hypocalcemia [serum calcium levels <8.0 mg/dl (2.0 mmol/liter)] occurred in three cinacalcet-treated patients, two of whom had symptomatic paresthesias. After 52 wk, this study was converted into an open-label extension for an additional 4 yr with 45 patients continuing into the extension. During this time, serum calcium was maintained in the normal range [8.4 to 10.32 mg/dl (2.1 to 2.58 mmol/liter)] in approximately 80% of patients. Thus, whereas increases in BMD due to treatment with cinacalcet were not evident in this trial, substantial biochemical efficacy, with lowering and normalizing of serum calcium, was clearly demonstrated. Adverse events during the extension study were similar to those observed during the first year of the placebo-controlled trial (54). There remains uncertainty as to which patients with PHPT might benefit from cinacalcet administration, given the convincing demonstration that surgical remediation of PHPT produces marked improvements in BMD in patients with biochemically mild disease (11, 55).

Potential Indications for Pharmacological Therapy in PHPT

PHPT is commonly diagnosed in asymptomatic patients. Nonetheless, occult skeletal complications, including decreased BMD and increased fracture risk, are present in many patients. Medical options for treating the skeletal complications of PHPT include antiresorptive treatments, such as bisphosphonates, HRT, and raloxifene. Evidence from randomized, placebo-controlled trials of bisphosphonates and HRT demonstrate that these agents effectively decrease bone turnover and increase BMD in PHPT to a degree comparable both to their effects in eucalcemic populations and to the response to surgical intervention in PHPT. Studies of their effects on fracture risk in PHPT are not available. Bisphosphonates and HRT are treatment options for those individuals with PHPT for whom skeletal protection is the primary reason for intervention. Of the two agents, bisphosphonates are clearly preferred, because of the adverse nonskeletal effects of long-term HRT. There are no clinical studies of the effects of raloxifene on BMD in PHPT. None of the antiresorptive therapies significantly alters serum calcium or PTH during long-term therapy. The calcimimetic cinacalcet effectively lowers serum calcium and PTH levels during long-term therapy in PHPT but does not alter bone turnover or increase BMD. At present, use of this agent in PHPT is limited to control of serum calcium in patients with symptomatic hypercalcemia who are unable to undergo corrective surgery. It may also be used as a therapeutic trial to determine the effect of lowering serum calcium and the potential benefits of parathyroidectomy in complex cases with significant comorbidity Further development of this class of drugs may yield agents that have a greater role in the medical management of PHPT.

Acknowledgments

This paper summarizes the results of a literature review addressing advances in the medical management of asymptomatic PHPT as well as the consensus statements from the Third International Workshop on Primary Hyperparathyroidism.

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