

Alendronate in Primary Hyperparathyroidism: A Double-Blind, Randomized, Placebo-Controlled Trial

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Primary hyperparathyroidism (PHPT) is often associated with reduced bone mineral density (BMD). A randomized, double-blind, placebo-controlled trial was conducted to determine whether alendronate (ALN), 10 mg daily, maintains or improves BMD in patients with PHPT. Eligible patients had asymptomatic PHPT and did not meet surgical guidelines or refused surgery. Forty-four patients randomized to placebo or active treatment arms were stratified for gender. At 12 months, patients taking placebo crossed over to active treatment. All patients were on active treatment in yr 2. The primary outcome index, BMD, at the lumbar spine (LS), femoral neck, total hip, and distal one third radius was measured every 6 months by dual-energy x-ray absorptiometry. Calcium, phosphorous, PTH, bone-specific alkaline phosphatase (BSAP) activity, urinary calcium, and urinary N-telopeptide (NTX) excretion were monitored every 3 months. Treatment with alendronate over 2 yr was associated with a significant (6.85%; $\mu_d = 0.052$; $\pm 0.94\%$ SE; $P < 0.001$) increase in LS BMD in comparison with baseline. Total hip BMD increased significantly at 12 months with alendronate by 4.01% ($\mu_d = 0.027$; $\pm 0.77\%$ SE; $P < 0.001$) from baseline and remained stable over the next 12 months of therapy. BMD at the one third radius site did not show any statistically significant change in the alendronate-treated group at 12 or 24 months of therapy. At 24 months, the alendronate-treated group showed a 3.67% ($\mu_d =$

0.022; $\pm 1.63\%$ SE; $P = 0.038$) gain in bone density at the femoral neck site in comparison with baseline. The placebo group, when crossed over to alendronate at 12 months, showed a significant change of 4.1% ($\mu_d = 0.034$; $\pm 1.12\%$ SE; $P = 0.003$) in the LS BMD and 1.7% ($\mu_d = 0.012$; $\pm 0.81\%$ SE; $P = 0.009$) at the total hip site in comparison with baseline. There was no statistically significant change seen in the placebo group at 12 months at any BMD site and no significant change at 24 months for the distal one third radius or femoral neck sites. Alendronate was associated with marked reductions in bone turnover markers with rapid decreases in urinary NTX excretion by 66% ($\mu_d = -60.27$; $\pm 13.5\%$ SE; $P < 0.001$) at 3 months and decreases in BSAP by 49% at 6 months ($\mu_d = -15.98$; $\pm 6.32\%$ SE; $P < 0.001$) and by 53% at 9 and 12 months ($\mu_d = -17.11$; $\pm 7.85\%$ SE; $P < 0.001$; $\mu_d = -17.36$; $\pm 6.96\%$ SE; $P < 0.001$, respectively) of therapy. In the placebo group, NTX and BSAP levels remained elevated. Serum calcium (total and ionized), PTH, and urine calcium did not change with alendronate therapy. In PHPT, alendronate significantly increases BMD at the LS at 12 and 24 months from baseline values. Significant reductions in bone turnover occur with stable serum calcium and PTH levels. Alendronate may be a useful alternative to parathyroidectomy in asymptomatic PHPT among those with low BMD. (*J Clin Endocrinol Metab* 89: 3319–3325, 2004)

WHEN PRIMARY HYPERPARATHYROIDISM (PHPT) used to present as a symptomatic disorder with bone and stone disease, surgery was the only clear therapeutic option (1). The widespread use of serum calcium measurements as part of biochemical screening, over the past 30 yr, is mainly responsible for the change in this clinical profile from a symptomatic disorder to an asymptomatic one. With many reports noting that as many as 80% of patients with PHPT are asymptomatic, it was no longer clear whether all patients should be advised to have parathyroidectomy. To address this clinical dilemma, the National Institutes of Health convened, in 1990, a Consensus Development

Panel on Asymptomatic Primary Hyperparathyroidism. That panel concluded that in some patients with mild asymptomatic disease, monitoring without parathyroid surgery was a safe and reasonable option. The panel, furthermore, established guidelines to assist physicians in determining who was best advised to undergo parathyroid gland removal and who could be safely observed without surgery (2). Since the time of that conference, major advances in our knowledge of PHPT with regard to its natural history and other aspects have occurred (3). As a result, these guidelines were revisited recently by a National Institutes of Health-sponsored Workshop on Asymptomatic Primary Hyperparathyroidism. The proceedings of that conference have been published (4). The summary statement by the Ad Hoc Panel that was convened after the workshop has recommended revised guidelines to be followed in establishing whether a patient is a surgical candidate or can be followed safely without surgery. National guidelines in Canada have since also been established (5). The panel upheld the prin-

Abbreviations: BMD, Bone mineral density; BSAP, bone-specific alkaline phosphatase; NTX, N-telopeptide; PHPT, primary hyperparathyroidism.

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ciple that some patients with asymptomatic PHPT can be monitored without surgery. The workshop summarized information about options for the medical management of PHPT. Although the data are still very limited, the published literature on the use of estrogens, raloxifene, calcimimetics, and bisphosphonates generated interest (6–16). In pilot, short-term studies, for example, raloxifene seems to reduce markers of bone turnover and the serum calcium concentration in individuals with PHPT (17–19). Calcimimetics are also showing promise (9).

Older bisphosphonates were first studied in PHPT by Shane *et al.* (10) and Hamdy *et al.* (11). More recently, the newer generation of bisphosphonates has been studied (12–16). Bisphosphonates are attractive because they increase bone density and reduce fracture risk in patients with osteoporosis. Patients with asymptomatic PHPT typically have reductions in bone mass when measured by dual-energy x-ray absorptiometry (3, 20). Because the bone loss seen in PHPT is different from that seen in postmenopausal osteoporosis, it is important to establish the usefulness of bisphosphonates to increase bone mass in this disease. Clinical trials with alendronate have shown promise in this regard, but they have not been conclusive due to a number of limitations in trial design such as nonrandomization, open-label, or short-term duration as well as a limited number of subjects (12–15). A 1 yr randomized, placebo-controlled trial of alendronate in PHPT demonstrated improvements in bone density with reductions in bone turnover with alendronate (16).

We report here the results of the first multicenter 2-yr randomized, placebo-controlled trial of alendronate in asymptomatic PHPT. The results strongly support the idea that this bisphosphonate may become a useful option in the medical management of patients with this disorder.

Patients and Methods

Patients with confirmed PHPT were invited to participate. This three-site study enrolled a total of 44 patients at McMaster University, Columbia University, and the University of Hong Kong. All subjects had to meet the following inclusion criteria: confirmed hypercalcemia and elevated levels of PTH by immunoradiometric assay on three separate occasions; reduced bone density, $T < -1.0$, at one or more skeletal sites (lumbar spine, hip, or radius). Patients with a T-score of less than -3.5 were advised to undergo parathyroid surgery and were included only if they declined that advice and still wished to participate. No patient was enrolled if any of the following criteria were met: any guideline for surgery (2); concomitant antiresorptive therapy; premenopausal women who still planned a future pregnancy and/or who were not using effective birth control; any other metabolic bone disease; use of hormone replacement therapy for less than 2 yr; impaired renal function as defined by a serum creatinine of more than $177 \mu\text{mol/liter}$ (2.00 mg/dl). Individuals with familial hypocalciuric hypercalcemia were excluded, as were those with a history of allergy or intolerance to bisphosphonates. Patients with active upper gastrointestinal symptoms were excluded. Patients with severe PHPT and a serum calcium of greater than 3.12 mmol/liter (12.2 mg/dl) were also excluded.

Patients were assigned to one of two treatment groups by random-numbered tables. The active treatment group received 10 mg alendronate daily for 1 yr. Control subjects received a placebo tablet, identical in appearance and in taste. After 1 yr, the placebo group was switched to active drug treatment, with continuation of active drug treatment for a second year in the alendronate-treated group. The allocation in the first year remained blinded until the end of the 2-yr trial period. Bone mineral density (BMD) data were not blinded. Moderate calcium intake was recommended along with adequate hydration and ambulation. Patients did not receive additional supplemental calcium or vitamin D. Stratification was by gender, ensuring an equal number of men and women with PHPT in the treatment and placebo arms (Table 1).

Both total and ionized serum calcium, phosphorus, PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and bone-specific alkaline phosphatase (BSAP) were measured every 3 months. The 24-h urine calcium and morning urine N-telopeptide (NTX) levels were also measured every 3 months. PTH, vitamin D, BSAP activity, and urinary NTX were evaluated at a central laboratory at Mt. Sinai Hospital (Toronto,

TABLE 1. Alendronate/alendronate vs. placebo/alendronate baseline characteristics

	Alendronate/alendronate	Placebo/alendronate	Normal range/value
No. of patients randomized	22	22	
No. of patients completed	18	19	
BMD			
Total hip (g/cm^2)	0.671 (0.141)	0.722 (0.138)	
Lumbar spine (g/cm^2)	0.759 (0.118)	0.83 (0.134)	
Distal 1/3 radius (g/cm^2)	0.521 (0.114)	0.551 (0.122)	
Femoral neck (g/cm^2)	0.594 (0.095)	0.621 (0.120)	
Total hip T score	-2.1 (1.19)	-1.8 (0.979)	
Femoral neck T score	-2.0 (1.04)	-1.8 (0.941)	
Lumbar spine T score	-2.8 (1.18)	-2.2 (1.146)	
Distal 1/3 radius T score	-1.8 (2.37)	-1.6 (2.011)	
Osteoporosis (at least 1 T-score < -2.5)	61.10%	68.40%	
On HRT therapy	5.60% (1 case)	0.00%	
Age	63.73 (9.36)	70.09 (10.36)	
Gender (male/female)	3/15	6/13	
Total calcium (mmol/liter)	2.68 (0.123)	2.64 (0.138)	2.2–2.6
Ionized calcium (mmol/liter)	1.35 (0.160)	1.31 (0.111)	1.17–1.33
24-h Urinary calcium (mmol/d)	4.97 (2.66)	5.77 (2.93)	1.2–6.2
Serum phosphate (mmol/liter)	1.16 (0.53)	1.23 (0.69)	0.90–1.45
BSAP ($\mu\text{g/liter}$)	32.61 (13.19)	31.79 (17.76)	Female >45 yr old postmenopausal: 14.2–42.7 Males >25 yr old: 15.0–41.3
NTX (nmol BCE/mmol Cr)	91.0 (45.25)	101.6 (95.61)	<85
PTH (pmol/liter)	17.23 (17.85)	15.56 (5.75)	1.3–7.6
Vitamin D-25 (nmol/liter)	45.5 (26.07)	46.47 (14.22)	<25 deficient, <40 insufficient, >250 toxic
Vitamin D-125 (pmol/liter)	119.5 (43.83)	129.33 (31.33)	40–140

Data are means \pm SD.

Canada). The normal ranges for these measurements are provided in Table 1. Dual-energy x-ray absorptiometry assessments using the Hologic QDR 4500 instrument were made at the L1–L4 lumbar spine (posteroanterior projection), total hip, femoral neck, and one third radial sites every 6 months. The precision or reproducibility error of the densitometers at the three investigative sites were virtually identical; lumbar spine, total hip, and one third radius were: 1.3, 1.5, and 1.7% (Canada); 0.7, 1.3, and 0.6% (United States); and 1.2, 1.8, and 1.6% (China). Patients were seen at 3-month intervals for 2 yr at all investigative sites. Primary end points were BMD, bone markers, and serum calcium. Patients were also monitored for adverse effects to study drug as well as for fractures. Any reported fracture was confirmed by x-rays. Screening radiographs for vertebral compression fractures were not done.

Statistical analysis

The treatment effect on BMD was tested by a two-tailed independent *t* test of the post-treatment minus pretreatment differences in the treated and control groups as per the original protocol. Paired *t* tests were used to detect differences in BMD within groups. Unpaired *t* tests were used to compare baseline characteristics between treatment and control groups. Independent *t* tests were used in a subgroup analysis to detect gender differences between treatment and control group 12- and 24-month differences. Because the subgroups were small, Levene's test for homogeneity was conducted first to test the assumption of equal variance. Repeated measures ANOVA was used to analyze serial biochemical data. Missing data were handled using the list-wise deletion method for each of the analyses.

Baseline characteristics

Baseline characteristics for treatment and control groups are shown in Table 1. The placebo and alendronate-treated groups were similar with respect to baseline characteristics and not statistically different for

any item including urine calcium. Ethnically, each group had similar proportions of Caucasians (alendronate, 55.6%; placebo, 42.1%), Chinese (alendronate, 38.9%; placebo, 47.4%); and African-Americans (alendronate, 5.5%; placebo, 10.5%) at baseline. There were no significant differences between BMD at baseline at the lumbar spine, hip, or the one third radial sites between the treatment and the placebo groups.

Informed consent was obtained, and the protocol was approved by each local Institutional Review Board.

Results

After 12 months, the alendronate-treated group showed a 4.92% ($\mu_d = 0.037$; $\pm 0.63\%$ SE; $P < 0.001$) increase in lumbar spine bone density in comparison with baseline (Fig. 1A). After 24 months, the alendronate group showed a 6.85% ($\mu_d = 0.052$; $\pm 0.94\%$ SE; $P < 0.001$) gain from baseline in lumbar spine bone density. The alendronate-treated group also showed statistically significant increases in comparison with placebo at 12 and 24 months.

After 12 months, the placebo group showed no significant change from baseline ($\mu_d = 0.001$; $P = 0.85$) in lumbar spine bone density. The placebo group was crossed over to alendronate therapy at the 12-month point of the protocol. Over the next 12 months, these subjects demonstrated a 4.1% ($\mu_d = 0.034$; $\pm 1.12\%$ SE; $P = 0.003$) increase in lumbar spine bone density in comparison with their baseline value.

The increase in bone density in the group treated with placebo in yr 1 and alendronate in yr 2 was not different from the alendronate group at the 2-yr time point. Similarly, there was no difference between the 12- and 24-month increases

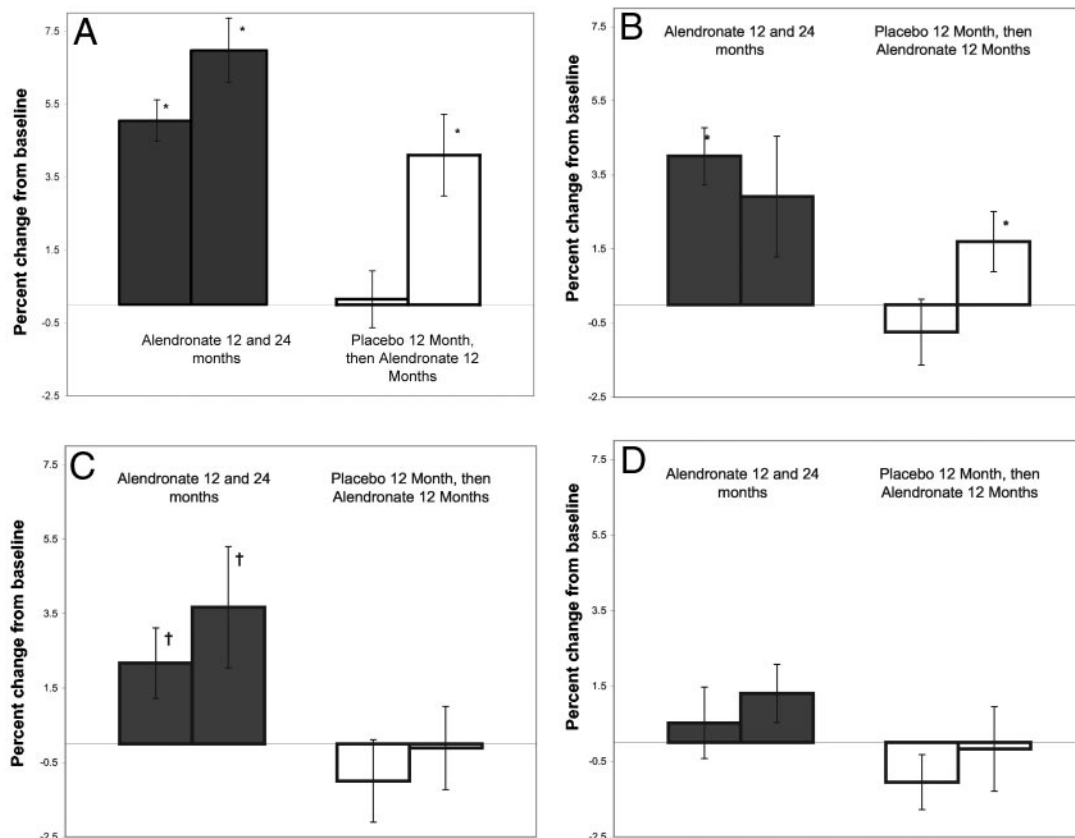


FIG. 1. Effect of alendronate on lumbar spine (A), total hip (B), femoral neck (C), and one third distal radius (D) BMD. *, Significantly higher than baseline ($P < 0.001$); †, significantly higher than baseline ($P < 0.05$).

among those who received alendronate for the entire 2-yr trial period.

Total hip BMD increased at 12 months in the group treated with alendronate by 4.01% ($\mu_d = 0.027$; $\pm 0.77\%$ SE; $P < 0.001$), with no further increases in the second year of therapy (Fig. 1B). The placebo group did not demonstrate any change in yr 1 ($\mu_d = -0.005$; $P = 0.41$). When the placebo group was crossed over to alendronate, there also was a significant increment of 1.7% ($\mu_d = 0.012$; $\pm 0.81\%$ SE; $P = 0.009$) in comparison with the baseline and 1-yr time point. The differences between the gains at yr 2 in comparison with those after yr 1 for alendronate were not different from each other.

BMD at the one third radius site did not show any statistically significant change in the alendronate-treated group at 12 months ($\mu_d = 0.003$; $\pm 0.95\%$ SE; $P = 0.59$) or 24 months of therapy (Fig. 1C). The group receiving placebo in yr 1 and alendronate in yr 2 also did not demonstrate any statistically significant change ($\mu_d = -0.001$; $\pm 0.74\%$ SE; $P = 0.83$) in BMD at the one third radius site.

After 12 months, the alendronate-treated group showed a 2.12% ($\mu_d = 0.013$; $\pm 0.94\%$ SE; $P = 0.035$) increase in femoral neck bone density (Fig. 1D). At 24 months, the alendronate-treated group showed a 3.67% ($\mu_d = 0.022$; $\pm 1.63\%$ SE; $P = 0.038$) gain in bone density in comparison with baseline. The group receiving placebo in yr 1 and alendronate in yr 2 did not demonstrate any statistically significant change in BMD at the femoral neck site ($\mu_d = -0.001$; $\pm 0.76\%$ SE; $P = 0.89$).

Alendronate had a major effect to reduce markers of bone turnover (Fig. 2). Urinary NTX excretion decreased rapidly by 66% ($P < 0.001$) at 3 months and remained suppressed in the alendronate-treated arm for the entire 2-yr treatment period (Fig. 2A). In the placebo arm, NTX remained elevated until patients were crossed over to alendronate at 12 months. Thereafter, NTX excretion promptly declined to levels indistinguishable from the group that had already received 1 yr of alendronate therapy.

Similarly, BSAP decreased in the alendronate group by 49% at 6 months ($\mu_d = -15.98$; $\pm 6.32\%$ SE; $P < 0.001$) and by 54% at 9 months ($\mu_d = -17.11$; $\pm 7.85\%$ SE; $P < 0.001$) and 12 months (Fig. 2B; $\mu_d = -17.36$; $\pm 6.96\%$ SE; $P < 0.001$). In the placebo group, BSAP levels did not decrease until subjects were crossed over to alendronate, at which point levels declined and became indistinguishable from the group that had already received alendronate therapy. Although BSAP and NTX were significantly reduced with alendronate, the rates of change were different. NTX fell much more quickly, reaching a nadir within 3 months of alendronate administration, whereas BSAP did not reach its nadir until 6–9 months after alendronate was started.

Neither total calcium nor ionized calcium changed in either group for the entire period of therapy (Fig. 3, A and B). Similarly, 24-h urinary calcium did not change (Fig. 3C). PTH levels remained stable in both groups (Fig. 3D). There were no changes in 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, or serum phosphate concentrations in either group (data not shown). A subgroup analysis compared the effects of alendronate between men and women. Both sexes responded equally well to alendronate in all ways.

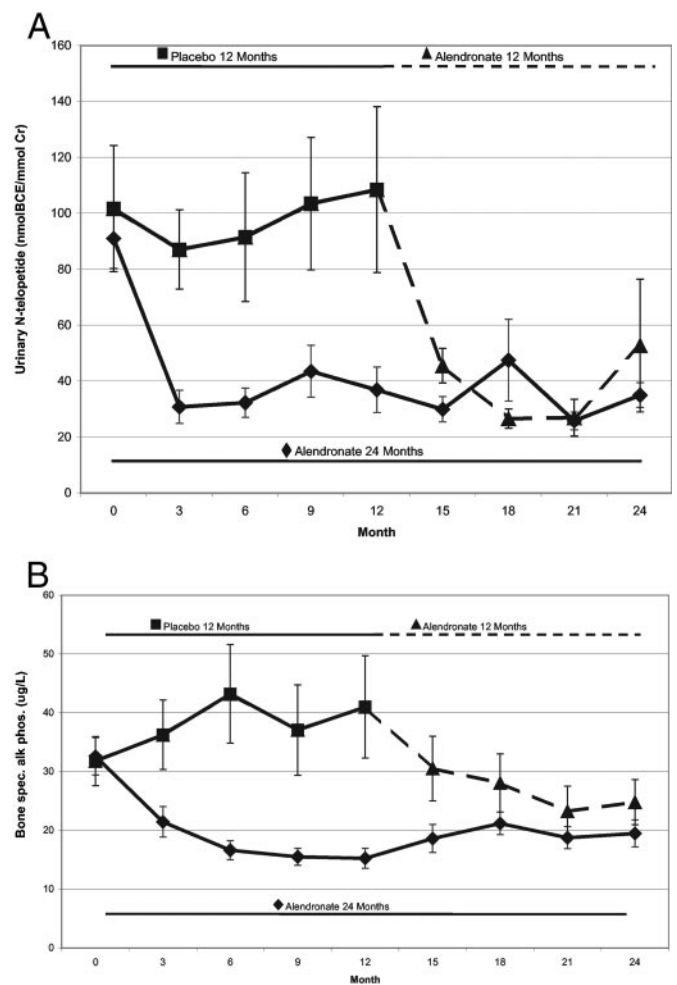


FIG. 2. Effect of alendronate on urinary NTX (A) and serum BSAP activity (B).

No fractures were observed or reported in the alendronate- or placebo-treated groups.

Safety and tolerability

No patient developed gastroesophageal symptoms requiring a change in therapy. There were no other adverse effects seen in the treatment or placebo groups.

Discussion

Using a prospective, blinded, randomized clinical trial design, the results of this study provide data that support the efficacy of alendronate in improving BMD of the lumbar spine and hip in patients with asymptomatic PHPT. Previous studies have shown similar results but have been limited in duration or in study population. It remained to be seen, therefore, whether those reports could be confirmed with a longer, placebo-controlled, double-blind trial conducted in both men and women. This report has achieved that goal.

The use of alendronate was associated with significant increases in BMD at the lumbar spine and the hip after only 1 yr. These gains were seen both in the group that was randomized to active drug in yr 1 as well as in the group that was crossed over to active drug in yr 2. Whereas the active

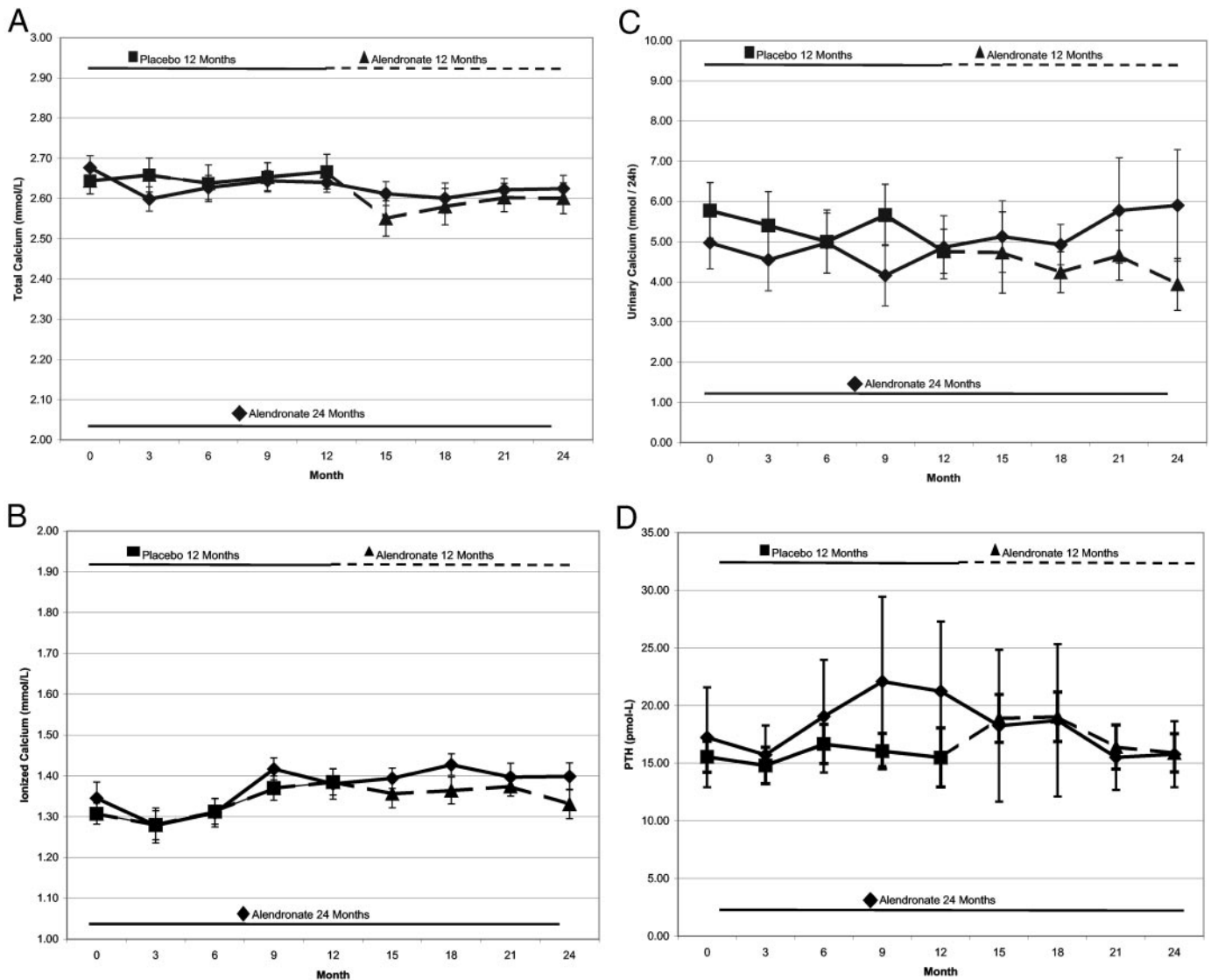


FIG. 3. Effect of alendronate on total calcium (A), ionized calcium (B), urinary calcium (C), and PTH (D).

treatment group continued to show gains in yr 2, these gains were not as dramatic as the changes in BMD in yr 1. In fact, the incremental gains in yr 2 in the group that had received placebo in yr 1 were so substantial that both treatment groups were not significantly different from each other at the end of the 2-yr study. This is to be expected, because the enlarged resorption space induced by excess PTH is probably reduced most dramatically during the first year of alendronate-induced suppression of bone turnover (21). Subgroup analysis confirmed that alendronate is effective in improving BMD in both men and women.

The distal radius (one third site) did not show changes in either treatment group. This is not surprising considering the fact that the rate of bone turnover at this site is relatively slow and classically changes little or none at all with antiresorptive therapy (3, 20).

One of the goals of management in patients with asymptomatic PHPT is maintenance of bone mass. Silverberg *et al.* (3) have shown that some patients who do not initially meet

surgical guidelines and are monitored conservatively do lose bone mass. This bone loss is reversed at the lumbar spine and hip after parathyroidectomy (22). It is this potential complication of PHPT that has caused concern and led to the recommendation by some that all patients with the disease should have parathyroid surgery (23). However, if there were an agent that could effectively prevent bone loss in PHPT, then the case for monitoring patients who are not surgical candidates becomes much stronger. In this regard, alendronate would seem to be an attractive alternative. No similar data are available yet for risedronate, the other oral bisphosphonate in common use.

The mechanism by which alendronate improves bone mass in PHPT would seem to be similar to its actions in postmenopausal women and men with osteoporosis. Alendronate demonstrated efficacy in improving BMD at the lumbar spine and hip. The radial site was not affected. The results of our study are consistent with previous observations using alendronate in PHPT (13–16). The first study, an

open-label, nonrandomized, observational study by Hassani *et al.* (13) of 45 patients, 19 of whom received alendronate, showed a 3.38% gain in lumbar spine and a 3.05% gain in femoral neck bone density. The difference between those who took alendronate and those who did not (there was no placebo control) was +4.8% in the lumbar spine and 3.9% at the femoral neck. There was no significant change in the distal radius bone density among the eight patients who were measured at this site. Subsequent studies have provided a more quantitative comparison of the effects of alendronate on BMD in PHPT. When alendronate was administered in doses of 10 mg given on alternate days over 2 yr, Rossini *et al.* (14) showed statistically significant increases, over baseline, in BMD at the lumbar spine ($+8.6 \pm 3\%$), total hip ($+4.8 \pm 3.9\%$), and total body ($+1.2 \pm 1.4\%$). Similarly, Parker *et al.* (15) reported gains in BMD after 2 yr among alendronate-treated patients (10 mg daily) of $7.3 \pm 3.1\%$. Nonsignificant trends toward improvement at the femoral neck ($+2.6 \pm 1.8\%$), total hip ($+2.1 \pm 1.8\%$), and mid-radius ($0.9 \pm 0.7\%$) were noted (15). A randomized controlled trial of alendronate (10 mg daily) *vs.* placebo over 48 weeks reported by Chow *et al.* (16) was also associated with statistically significant increases at the lumbar spine by $3.79 \pm 4.04\%$. The femoral neck BMD showed statistically significant increases with a $4.17 \pm 6.01\%$ gain. No significant change in BMD at the distal third radius was noted at 48 weeks between the treatment and placebo groups (16). Although the design of these studies differed, they are generally consistent and agree with our findings.

Bone turnover markers were promptly suppressed and maintained substantially below baseline values. The reduction of bone turnover is potentially of greater importance in this disease than in osteoporosis because patients with PHPT typically have more consistently high bone turnover. Such control of this dynamic parameter of bone metabolism has obvious advantages.

In fact, one might consider the possibility that increases in bone density and reductions in bone turnover might be associated with a reduction in fracture risk in patients with PHPT. If one can draw an analogy between the effects of alendronate on these parameters in osteoporosis, this expectation is reasonable. However, PHPT is a very different disorder, and such assumptions could be treacherous. What our study supports is another investigation sufficiently powered to address this hypothesis.

The effect of alendronate on bone mass and bone turnover did not occur in association with changes in serum total or ionized calcium or in PTH. Of note, alendronate did not increase PTH levels, an observation that has been made by some investigators as an early effect of alendronate in clinical trials for osteoporosis (21). Whether higher doses of alendronate would have been associated with reductions in the serum calcium, as parenteral bisphosphonates do in the context of hypercalcemia of malignancy (24), is not known. Variable effects on serum calcium with alendronate have been noted previously (13–16). Parker *et al.* (15) reported no significant change in serum calcium or PTH with 10 mg alendronate given over 2 yr. Rossini *et al.* (14) did note a transient decrease in serum calcium during the first 3–6 months when 10 mg alendronate was given on an alternate-day basis for 2

yr. After this transient decrease, serum calcium returned to baseline values. A transient increase in PTH was noted during the first year of treatment, which then also returned to baseline. Chow *et al.* (16) noted serum calcium to significantly decline after 1 yr of 10 mg alendronate daily. No significant change was noted in the placebo group. No significant changes were noted in serum phosphate or PTH. Hassani *et al.* (13) noted a significant increase in ionized calcium in seven patients treated with 10 mg alendronate daily for 6 months. There were no associated changes in serum PTH. Our study did not demonstrate significant increases in PTH. It does not seem, therefore, that alendronate is associated with additional increases in parathyroid gland activity in PHPT.

Ideally, an agent for PHPT should control biochemical parameters of disease as well as bone turnover and bone density. The calcimimetics have been shown to reduce the serum calcium and PTH level in PHPT, but in a trial with the calcimimetic cinacalcet, no changes in bone mass were noted (9). It thus remains to be seen whether any single agent will be able to control both biochemical and densitometric parameters at risk in this disease.

This study has helped to document that alendronate is an effective agent to increase bone mass in men and women with PHPT. It should be useful to those individuals with PHPT who are at risk for bone loss but who are not candidates for parathyroid surgery. Alendronate may also be useful in individuals who are candidates for surgery but either decline or for whom surgery is contraindicated.

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