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The Effect of Calcium Citrate on Bone Density in the Early and Mid-postmenopausal Period: A Randomized Placebo-Controlled Study

Lisa A. Ruml, Khashayar Sakhaee,* Roy Peterson, Beverley Adams-Huet, and Charles Y.C. Pak

This placebo-controlled randomized trial was conducted to ascertain the value of calcium citrate supplementation in averting bone loss in 63 postmenopausal women, 57 of whom were early postmenopausal (five years after menopause) and six of whom were mid-postmenopausal (five to ten years after menopause). Bone density data were available for 25 women who took 800 mg of calcium citrate daily and 31 women who received placebo for one to two years. The two groups were similar in baseline age, years postmenopause (3.3 in the calcium citrate group vs 2.7 in the placebo group), height, weight, calcium intake, and L2-L4 bone density. L2-L4 bone density did not change during calcium citrate treatment (+1.03% after two years), whereas it declined significantly by −2.38% after two years on placebo ($P < .001$). Femoral neck bone density did not change in either group. Radial shaft bone density did not change in the calcium citrate group (−0.02% after two years), but it declined significantly in the placebo group (−1.79% after one year and −3.03% after two years, $P < .01$). The difference in bone density of the L2-L4 vertebrae and radial shaft after two years of treatment was significant between the two groups. An analysis of covariance disclosed no significant effect of calcium citrate on L2-L4 bone density during the first three years after menopause, but a protective effect after three years.

Although serum PTH did not change, serum and urinary calcium increased and serum calcitriol and urinary phosphorus decreased in the calcium citrate group, indicative of parathyroid suppression. Serum bone-specific alkaline phosphatase and osteocalcin, and urinary hydroxyproline and N-telopeptide decreased during some calcium citrate treatment periods, indicative of a reduction in bone turnover. Thus, calcium citrate supplementation (400 mg of calcium twice daily) averted bone loss and stabilized bone density in the spine, femoral neck, and radial shaft in women relatively soon after menopause. This bone-sparing action was probably due to the inhibition of bone resorption from parathyroid suppression.

Keywords: calcium citrate, bone loss, osteoporosis, menopause.

INTRODUCTION

New treatment modalities have been introduced recently for the management of postmenopausal osteoporosis, including alendronate,[1] calcitonin, and raloxifene.[2] Although calcium supplementation has been widely employed, often in conjunction with the above agents, its exact role remains to be clarified. Available data on calcium's effect in inhibiting postmenopausal bone loss are conflicting.

An important reason for the variable response to calcium supplementation appears to be the length of time after menopause. In older postmenopausal women (older than 65 years of age), bone loss may be driven largely by parathyroid stimulation. McKane et al[3] reported that the relative increase in parathyroid function and bone resorption of the late postmeno-

University of Texas Southwestern Medical School, Center for Mineral Metabolism and Clinical Research, Dallas, TX, USA.
Supported by USPHS grants M01-RR00633 and R01AR-16061.
**Address for correspondence: University of Texas Southwestern Medical School, Center for Mineral Metabolism and Clinical Research, 5323 Harry Hines Boulevard, Dallas, TX 75235-8891, USA.*

pausal state could be brought down to the premenopausal state by supplementation with calcium citrate (1.5 g of calcium per day). In contrast, the rapid bone loss of early postmenopausal women (within five years of menopause) may also be mediated by other factors such as disturbed cytokine production occurring from estrogen deficiency.[4] The inhibition of PTH secretion by calcium supplementation may have a limited effect on bone resorption in that situation.

Thus, a stable or transient increase in bone density of the lumbar spine, radial shaft, and femoral neck has been reported in normal late postmenopausal women[5,6] or in patients with postmenopausal osteoporosis,[7] following treatment with calcium citrate-malate[5,6] or calcium citrate.[7,8] In early postmenopausal women, however, calcium supplementation has been shown to have a variable effect on forearm bone loss[6,9,10] and to produce a partial inhibition[11] or no effect on spinal bone loss.[5,9,10] Thus, calcium citrate-malate at the relatively low dosage of 500 mg of calcium per day did not inhibit spinal bone loss in early postmenopausal women,[5] whereas the same dosage of the drug produced a complete inhibition in late postmenopausal women.[6] However, a higher dose was not tested in early postmenopausal women.

This placebo-controlled randomized trial was undertaken to ascertain the effect on bone density of calcium citrate at a higher dosage of 800 mg of calcium per day in 50 early (less than five years after menopause) and six mid-postmenopausal (five to ten years after menopause) women. Moreover, the physiological mechanism for calcium's action was sought from the analysis of calcium-regulating factors throughout the two years of the trial.

MATERIALS AND METHODS

Clinical data

The study protocol was submitted to and approved by the Institutional Review Board of the University of Texas Southwestern Medical School at Dallas. The study closed in 1997 before accrual was complete because of the departure of a key investigator and the termination of funding. Prospective candidates were recruited by posted notice and newspaper advertisements. They were initially questioned by telephone to ensure that the eligibility criteria were met. They then underwent laboratory screening after informed consent was obtained.

Women were eligible for the study if they were no more than ten years after natural or surgical menopause and were not taking estrogen. Those who tried estrogen briefly but stopped it for at least six months prior to the study were permitted to participate. Menopausal state was assessed by history and confirmed by measurement of serum-luteinizing and follicle-stimulating hormones. Subjects were excluded if they had a history of kidney stones; renal, hepatic, or intestinal diseases; prior osteoporotic fractures or vertebral fractures on screening spine radiographs; if they were on any medications known to affect calcium metabolism (eg, bisphosphonates, thiazides, corticosteroids, fluoride, calcitonin, tamoxifen, or pharmacological doses of vitamin D preparations); or if the lumbar bone density was more than 1 standard deviation above average for the age-matched control value. Also, those smoking a half pack of cigarettes or more per day were excluded.

Sixty-three healthy postmenopausal women were enrolled in the study after meeting all of the above criteria. They were divided into two groups (calcium citrate and placebo) by a simple randomization scheme. Twenty-nine subjects were allocated to the calcium citrate group and 34 to the placebo group.

Twelve subjects in the calcium citrate group and six in the placebo group withdrew before completing two years of the study. In the calcium citrate group, four subjects withdrew after completing six months of the trial, two because of a desire to take estrogen and two because of lack of interest. Eight subjects withdrew after completing one year of the trial, four because of a desire to take estrogen, one because of a wish to take calcium, one because of the development of breast cancer, and two because of lack of interest. None of these causes for withdrawal was considered to be related to treatment.

In the placebo group, three subjects withdrew after completing six months of the trial, one because of constipation, one because of the development of inflammatory arthritis requiring steroids, and one because of departure from the city. Three subjects withdrew after one year of the trial, one because of a desire to take estrogen and two because of lack of interest.

Treatment scheme

Subjects in the calcium citrate group received calcium citrate at a dosage of 400 mg of elemental calcium twice daily (Citracal, Mission Pharmacal, San Antonio, TX). Those in the placebo group took tablets of identical appearance containing excipient only (prepared by Mission). Mission Pharmacal did not provide research support other than the provision of study medications and had no role in the design of the study, data retrieval or analysis, or the interpretation of data. None of the investigators had an equity in Mission Pharmacal or served as a consultant for the company.

Study outline and analytical methods

Subjects were evaluated before treatment and subsequently every six months during treatment for a total of two years. At each visit, a sample of venous blood was obtained for the measurement of calcium, phosphorus, parathyroid hormone (PTH), 1,25-$(OH)_2$vitamin D ($1,25(OH)_2D$), bone specific alkaline phosphatase (BAP), and osteocalcin. A 24-hour urine was collected for calcium, phosphorus, hydroxyproline, and N-telopeptide. A side-effect profile and interim fracture history was obtained at each visit. Before and after one and two years of treatment, bone density of the L2-L4 vertebrae, femoral neck, and radial shaft was obtained. Spine radiographs were also obtained for the assessment of fractures.

Serum calcium and phosphorus were obtained as a part of a multichannel blood screen (SmithKline Beecham, Philadelphia, PA). PTH was measured by an immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). $1,25(OH)_2D$ was assayed as previously described,[12] except that vitamin D receptor from bovine mammary gland was used instead of calf thymus.[13] The normal range is 18 pg/mL to 52 pg/mL. Serum osteocalcin was determined with a commercially available radioimmunoassay (INCStar, Stillwater, MN) using an antibody to bovine osteocalcin. The normal range in our laboratory is 1.8 ng/mL to 6.6 ng/mL. Serum BAP was measured with a commercial immunoassay using a monoclonal anti-BAP (Metra Biosystems, Inc., Mountain View, CA). Urinary hydroxyproline was determined by a colorimetric assay (Hypronosticon, Organon Teknika, Durham, NC). Urinary N-telopeptide of type I collagen was determined using a commercially available ELISA assay (Osteomark, Ostex, Seattle, WA).

The bone density of L2-L4 vertebrae and femoral neck was measured by Hologic quantitative digital radiography (Hologic QDR-2000, Waltham, MA) or Lunar dual energy x-ray absorptiometry (Lunar Corporation, Madison, WI). The bone density of the distal third of the radius was measured using Norland single photon absorptiometry. For the measurement of bone densities at all three sites, the same instrument was used throughout the trial in each subject. All measurements were performed and analyzed by the same technician. The coefficient of variation, obtained by repeat measurements in the same subjects, was 1% for L2-L4 bone density, 1% to 2% for femoral neck bone density, and 1% for radial shaft bone density.

Statistical methods

All available data were used for statistical analyses, regardless of whether the subject completed the study. Biochemical parameters were analyzed using data from all 63 subjects, and the analysis of bone density data was performed in the 56 subjects who had at least a twelve-month visit. Since bone density is the primary endpoint, baseline characteristics are presented for these 56 subjects.

In assessing the significance of percent change from baseline in bone densities, pairwise comparisons were made with paired *t*-tests within groups, and two-sample *t*-tests were used for between-group comparisons. Moreover, analysis of covariance models were used to assess the possible prognostic effects of variables such as age, years after menopause, body weight, body mass index, calcium intake, baseline serum PTH, $1,25(OH)_2D$, urinary calcium and N-telopeptide, and bone density. Where assumptions of equal slopes for the two groups were not met, the Potthoff extension of the Johnson-Neyman technique[14] was used to calculate simultaneous regions of significance for comparing groups while adjusting for covariates.

Repeated measures analysis of variance (ANOVA) models were used to assess the effect of treatment and time on biochemical parameters. The interaction between treatment and time (month of visit) is indicative of differences in treatment response. To identify transient changes, pairwise comparisons were also made with paired *t*-tests within groups and two-sample *t*-tests between groups. Because of skewness, N-telopeptide values were log transformed prior to analysis. No adjustment was made for multiplicity of testing. Instead, actual *P* values were presented where applicable. Data were expressed as mean ± standard deviation. SAS version 6.12 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Baseline presentation

Fifty-six women who completed at least one year of study were considered for bone density analysis; their baseline presentation is shown in Table 1. All but six of the women in the trial were five or fewer years postmenopausal (early postmenopause); of the six who were five+ to ten years postmenopausal (mid-postmenopause), four were in the calcium citrate group and two in the placebo group.

The average age in both groups was 52 years (Table 1). There was no significant difference in the time since menopause, height, weight, and estimated dietary calcium intake between the two groups. All 25 women in the calcium citrate group and 25 of the 31 women in the placebo group were Caucasian. Baseline density of L2-L4 vertebrae, femoral neck, and radial shaft did not

Table 1. Baseline characteristics of 56 study subjects who completed at least one year of trial.

	Calcium citrate group n = 25	Placebo group n = 31
Age (y)	52.1 ± 4.1	51.7 ± 3.8
Years postmenopausal	3.3 ± 2.3	2.7 ± 2.2
Height (cm)	161 ± 5	162 ± 7
Weight (kg)	66 ± 13	61 ± 9
Calcium intake (mg/d)	584 ± 164	637 ± 208
Race (C/H/A/AA)	25/0/0/0	25/2/3/1
Lumbar spine, L2-L4 (g/cm^2)	0.90 ± 0.12	0.90 ± 0.09
Femoral neck (g/cm^2)	0.73 ± 0.12	0.68 ± 0.09
Radius (g/cm^2)	0.63 ± 0.08	0.66 ± 0.06

Abbreviation: C/H/A/AA, Caucasian/Hispanic/Asian/African American.
Data are presented as mean ± standard deviation.

differ significantly between the two groups. The two groups had normal serum calcium, phosphorus, PTH, $1,25(OH)_2D$, BAP, osteocalcin, urinary calcium, phosphorus, hydroxyproline, and N-telopeptide at baseline (Table 2).

Bone density and spinal fractures

No vertebral fractures were noted during the trial. The changes in bone densities from baseline are depicted in Figure 1 and Table 3. L2-L4 bone density declined from baseline in the placebo group; the decline was significant at 24 months. It did not change significantly in the calcium citrate group. The change of −2.38% (95% CI: −3.55% to −1.20%) in the placebo group was significantly different from +1.03% (95% CI: −1.44% to 3.51%) in the calcium citrate group at 24 months ($P = .006$). In the placebo group, L2-L4 bone density declined in 20 subjects (65%) after one year and in 23 subjects (82%) after two years. In the calcium citrate group, L2-L4 bone density decreased in 13 subjects (52%) after one year and in seven subjects (41%) after two years. The difference between the two groups was significant after two years ($P = .008$).

Femoral neck bone density did not change significantly in either group. In the placebo group, bone density of the distal third of the radius showed a significant decline from baseline of −1.79% after one year and −3.03% after two years on the trial (Fig. 1, Table 3). No significant change from baseline occurred in the calcium citrate group. The difference between the two groups (−3.03% in the placebo group and +0.02% in the calcium citrate group) was significant at 24 months. In the placebo group, radial shaft bone density decreased in 20 subjects (69%) after one year and in 18 subjects (72%) after two years. In the calcium citrate group, radial shaft bone density declined in 13 subjects (52%) after one year and in nine subjects (53%) after two years. The difference between the two groups was not significant.

The analysis of covariance to adjust for possible confounding factors revealed a possible effect of years after menopause on the change in L2-L4 bone density at 24 months. Assumptions of equal slopes of the regression lines were not met in the analysis of covariance model for years after menopause; therefore, the Potthoff extension of the Johnson-Neyman technique was used to find the region of significance between the two groups. This method disclosed that the calcium citrate and placebo groups were statistically different when the subjects were more than three years postmenopausal, but were insignificant in the zero-to-three-years postmenopausal region. Femoral neck and radial shaft comparisons were not appreciably affected with covariate adjustment.

Biochemical changes

All 63 patients who completed at least six months of the trial were considered in this analysis.

By ANOVA, serum calcium concentration of the calcium citrate group rose significantly during treatment ($P < .001$), but remained within the normal range (Tables 2 and 4). Urinary calcium also increased significantly ($P < .001$). Serum and urinary phosphorus did not change significantly. Serum PTH remained within normal limits and did not change significantly from baseline. However, serum $1,25(OH)_2D$, BAP, and urinary hydroxyproline significantly decreased. In the placebo group, the only significant changes were in serum BAP and urinary N-telopeptide.

Comparisons of differences in biochemical parameters between the two groups were assessed using the treatment and time interaction from repeated measures ANOVA (Table 4). Significant interaction was found in serum and urinary calcium, urinary phosphorus, serum $1,25(OH)_2D$, and BAP; a marginal interaction was disclosed in N-telopeptide.

By *t*-tests, serum calcium concentration rose significantly during all time periods of treatment in the calcium citrate group, but remained within the normal range (Table 2). Urinary calcium increased, attaining significance at 24 months. Serum phosphorus did not change significantly, but urinary phosphorus declined, attaining significance at six months. Serum PTH remained within normal limits and did not change significantly from baseline. Serum $1,25(OH)_2D$ declined significantly at 12 and 24 months. Serum BAP, osteocalcin, urinary hydroxyproline, and N-telopeptide decreased significantly at six months.

Table 2. Serum and urine biochemistry in the calcium citrate and placebo groups.

	Calcium citrate group			
	Baseline (n = 29)	6 months (n = 29)	12 months (n = 25)	24 months (n = 17)
Serum				
Calcium (mg/dL)	9.3 ± 0.4	9.5 ± 0.4*	9.6 ± 0.4**	9.6 ± 0.3**
Phosphorus (mg/dL)	3.7 ± 0.6	3.7 ± 0.7	3.6 ± 0.5	3.8 ± 0.4
PTH (pg/mL)	36 ± 10	35 ± 16	35 ± 14	41 ± 18
$1,25(OH)_2D$ (pg/mL)	34 ± 12	33 ± 10	25 ± 8**	23 ± 8**
BAP (U/L)	17.6 ± 7.3	15.8 ± 4.4*	13.9 ± 2.8	15.5 ± 3.6
Osteocalcin (ng/mL)	4.1 ± 1.7	3.3 ± 1.1*	4.1 ± 2.2	3.8 ± 1.8
Urine				
Calcium (mg/day)	145 ± 76	169 ± 80	173 ± 84	184 ± 72**
Phosphorus (mg/day)	741 ± 249	591 ± 257*	665 ± 241	641 ± 266
OH-proline (mg/day)	18 ± 8	15 ± 7*	15 ± 6	15 ± 5
N-telopeptide, nM BCE/day	227 ± 141	160 ± 114**	216 ± 102	280 ± 159
median	207	124	204	250
	Placebo group			
	Baseline (n = 34)	6 months (n = 34)	12 months (n = 31)	24 months (n = 28)
Serum				
Calcium (mg/dL)	9.6 ± 0.5	9.5 ± 0.3*(**)	9.4 ± 0.3*(***)	9.7 ± 0.3(*)
Phosphorus (mg/dL)	3.9 ± 0.4	3.9 ± 0.4	3.8 ± 0.5	3.8 ± 0.5
PTH (pg/mL)	33 ± 14	38 ± 11*	38 ± 14	36 ± 13
$1,25(OH)_2D$ (pg/mL)	36 ± 9	35 ± 8	32 ± 10	33 ± 10
BAP (U/L)	13.8 ± 4.4	14.2 ± 3.3	13.9 ± 4.6(*)	16.0 ± 4.9*(*)
Osteocalcin (ng/mL)	4.3 ± 1.3	4.5 ± 1.5(**)	4.3 ± 1.7	4.3 ± 1.2
Urine				
Calcium (mg/day)	152 ± 57	168 ± 81	147 ± 69	157 ± 85(*)
Phosphorus (mg/day)	647 ± 171	687 ± 187(**)	659 ± 198	722 ± 240*(*)
OH-proline (mg/day)	17 ± 6	16 ± 7	15 ± 5	17 ± 7
N-telopeptide, nM BCE/day	254 ± 142	247 ± 137(*)	257 ± 154	329 ± 137*
median	202	216	215	302

Data are presented as mean ± standard deviation.
$^{(*)}P < .05$; $^{(**)}P < .01$; $^{(***)}P < .001$ for comparison of difference from baseline (of corresponding month) between study groups.
$^{*}P < .05$; $^{**}P < .01$ for changes within a study group compared with baseline.

In the placebo group, serum calcium declined slightly at six and twelve months from baseline (Table 2). There were significant increases in serum PTH at six months and serum BAP, urinary phosphorus and, N-telopeptide at 24 months. No other significant changes were present.

Changes in biochemical parameters from baseline were compared between the two groups; the statistical significance is shown within parentheses in Table 2. Compared with the placebo group, the calcium citrate group had significantly higher serum calcium during all treatment periods and significantly higher urinary calcium at 24 months. Moreover, the calcium citrate group had a significantly lower serum BAP (at 12 and 24 months), osteocalcin (at six months), urinary phosphorus (at six and 24 months), and N-telopeptide (at six months).

DISCUSSION

This randomized trial sought to assess the bone-sparing action of calcium citrate in normal, mostly early postmenopausal women, and to elucidate the biochemical–physiological background for that action. The results showed that calcium citrate was effective in averting the bone loss in the spine and radial shaft that occurred with placebo. These effects on bone mass produced by calcium citrate appear to have resulted from the PTH-dependent reduction in bone turnover.

The protection conferred by calcium citrate was less marked than that reported by estrogen[9] or alendronate.[1] The mean value for lumbar and femoral neck bone density remained unchanged with calcium ci-

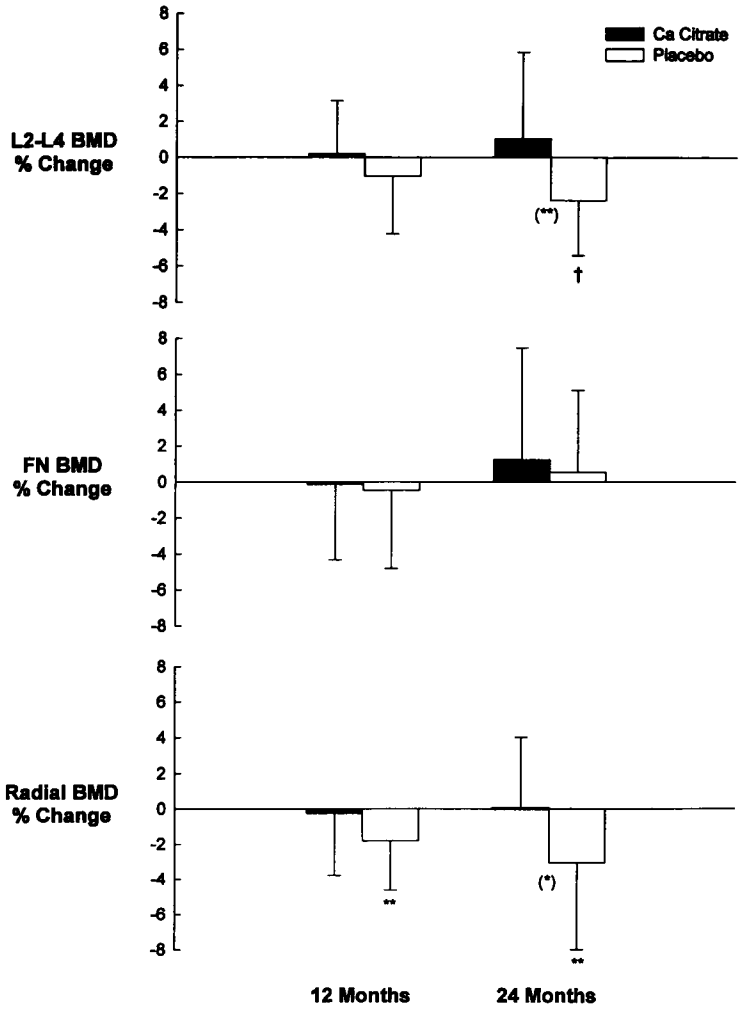

Fig. 1. The change in bone mineral density from baseline, following treatment with calcium citrate or placebo for 12 and 24 months. Abbreviations: BMD, bone mineral density; FN, femoral neck; **, $P < .01$ from baseline within a study group; †, $P < .001$ from baseline; (*), $P < .05$ between calcium citrate and placebo at corresponding time period; (**), $P < .01$ between groups. Upright and inverted T bars indicate the standard deviation.

trate, whereas it has been reported to increase transiently with other treatments.[1,9] Fifty-nine percent of the subjects taking calcium citrate in this trial showed an increase or no change in lumbar bone density, whereas it has been reported to increase in most patients taking alendronate. This finding may be explained by different modes of inhibiting bone resorption. Whereas calcium's action is mediated through

Table 3. Percent change in bone density in the calcium citrate and placebo groups.

	Calcium citrate group		Placebo group	
	12 months (n = 25)	24 months (n = 17)	12 months (n = 31)	24 months (n = 28)
BD, % change from baseline				
Lumbar spine, L2-L4	0.21 ± 2.93	1.03 ± 4.81(**)	−1.03 ± 3.21	−2.38 ± 3.04†
Femoral neck	−0.14 ± 4.19	1.24 ± 6.21	−0.48 ± 4.34	0.53 ± 4.56
Radius, distal shaft‡	−0.24 ± 3.54	0.02 ± 3.99(*)	−1.79 ± 2.81**	−3.03 ± 4.94**

Data are presented as mean ± standard deviation.
(*)$P < .05$; (**)$P < .01$ for comparison between study groups.
**$P < .01$; †$P < .001$ for changes within a study group compared with baseline.
‡For distal shaft radius in the placebo group the sample size is n = 29 for 12 months and n = 25 for 24 months.

Table 4. Analysis of variance results for serum and urine biochemistry in the calcium citrate and placebo groups.

	Calcium citrate (*P* value)	Placebo (*P* value)	Interaction* (*P* value)
Serum			
Calcium (mg/dL)	<.001	.93	<.001
Phosphorus (mg/dL)	.13	.71	.50
PTH (pg/mL)	.12	.49	.17
$1,25(OH)_2D$ (pg/mL)	<.001	.23	.03
BAP (U/L)	.007	.006	.01
Osteocalcin (ng/mL)	.85	.76	.12
Urine			
Calcium (mg/day)	<.001	.62	.03
Phosphorus (mg/day)	.17	.12	.03
OH-proline (mg/day)	.05	.80	.48
N-telopeptide, nM BCE/day median	.08	.04	.08

*Repeated measures analysis of variance *P* value for the interaction between treatment and time (month).

parathyroid suppression, other drugs probably also affect non-PTH-dependent bone resorption.

However, the inhibitory action against bone loss displayed by calcium citrate in this trial was more prominent than that shown in prior trials of calcium supplementation in early postmenopausal women. In studies using calcium carbonate,[9,10] calcium lactogluconate-carbonate,[11] or calcium citrate-malate,[5] variable changes in appendicular bone density have been reported, ranging from a prevention[5] or slowing[9,10] to a trend toward protection[11] of cortical bone loss. Available calcium trials have disclosed an incomplete or no inhibition of spinal bone loss in early postmenopausal women. Elders et al[11] showed a slowing of lumbar bone loss in the first year of supplementation with calcium carbonate-lactogluconate, but no change in the second year, compared with placebo. Other investigators[9,10,15] have shown a partial or no effect of calcium carbonate on spinal bone density in the early postmenopausal period. Dawson-Hughes et al[5] found that calcium citrate-malate at a dosage of 500 mg of calcium per day did not avert spinal bone loss. However, calcium citrate supplementation was found in this randomized trial to stabilize bone densities, not only in the radial shaft and femoral neck but also in the lumbar spine. The stability of spinal bone mass with calcium citrate was previously shown in a nonrandomized trial.[16]

The superior bone-sparing action of calcium citrate disclosed in this trial could be explained by differences in bioavailability and dosage of calcium supplements used. Calcium citrate given on an empty stomach has been reported to be better absorbed than calcium carbonate.[17–19] Calcium citrate has also been shown to suppress parathyroid function more effectively than calcium carbonate or calcium carbonate-lactogluconate.[20] Calcium citrate-malate has a bioavailability that is equivalent to that of calcium citrate.[21] However, calcium citrate was given at a higher dosage of 400 mg of calcium twice daily in this trial, whereas the calcium citrate-malate was offered at a lower dosage of 500 mg of calcium once daily.[5]

The exact physiological mechanism for calcium citrate's inhibition of bone loss in mostly early postmenopausal women in this study is not clear. During calcium citrate treatment, serum and urinary calcium rose, and serum $1,25(OH)_2D$ and urinary phosphorus decreased. These findings suggest that parathyroid function was suppressed by calcium citrate. While no change in serum PTH was disclosed in this study, this failure could reflect insensitivity of serum PTH obtained in the fasting state to detect relatively small changes induced by absorbed calcium. In an earlier study, fasting serum PTH did not detect the secondary hyperparathyroidism of a sodium load.[22]

Calcium citrate supplementation probably reduced bone turnover by suppressing PTH secretion. After six months of calcium citrate treatment, markers of bone formation (serum BAP and osteocalcin) significantly decreased, as did markers of bone resorption (urinary hydroxyproline and N-telopeptide). Although these markers did not show a significant change from baseline in later time periods, a significant difference in serum BAP was shown between the two groups after 12 and 24 months. The declining effect over time could be due to the compensatory decline in calcium absorption from suppression of calcitriol synthesis.[23]

The suppression of bone resorption disclosed in this study was less marked than that observed during calcium citrate treatment in older normal postmenopausal women and patients with postmenopausal osteoporosis.[3,8,24,25] The results suggest that the rapid bone loss of the younger postmenopausal women may be partially PTH-dependent, with interplay of other

factors such as the release of bone-resorbing cytokines.[4] This inhibition of PTH-dependent bone resorption was apparently still sufficient to inhibit bone loss in the majority of subjects, albeit less effectively than in older postmenopausal women.

It is noteworthy that the analysis of covariance disclosed an effect of duration after menopause on spinal bone density, with no significant effect of calcium citrate during the first three years of menopause, but a protective effect after three years. The overall positive effect of calcium citrate in protecting against spinal bone loss disclosed in this study could have been due to the fact that approximately one-half of the patients were from three to ten years postmenopausal when they began participation in the study.

The inhibition of bone loss obtained in this study was more prominent than that reported by Dawson-Hughes et al in early postmenopausal women,[5] possibly because of the higher dosage of calcium used in our study (800 mg of calcium as calcium citrate per day rather than 500 mg of calcium as calcium citrate-malate). Our results were more positive than those obtained with calcium carbonate,[9,10,15] possibly because of the superior bioavailability of calcium citrate.[17–19]

There were several drawbacks in this trial. First, the number of participating subjects was small, precluding detection of more clear-cut changes and limiting the clinical relevance of the study. Second, a proportionately larger number of subjects were in the placebo group because a number of calcium citrate group subjects left the trial for reasons unrelated to treatment. Finally, serum PTH did not show a decline in the calcium citrate group, even though other measures indirectly suggested that parathyroid function had been suppressed.

In summary, calcium citrate supplementation preserved bone mass in the spine, femoral neck, and radial shaft in a group comprised mostly of early postmenopausal women during two years of the trial. This bone-sparing action was probably due to parathyroid suppression and subsequent inhibition of bone resorption.

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