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A CONTROLLED TRIAL OF THE EFFECT OF CALCIUM SUPPLEMENTATION ON BONE DENSITY IN POSTMENOPAUSAL WOMEN

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Abstract *Background.* The effectiveness of calcium in retarding bone loss in older postmenopausal women is unclear. Earlier work suggested that the women who were most likely to benefit from calcium supplementation were those with low calcium intakes.

Methods. We undertook a double-blind, placebo-controlled, randomized trial to determine the effect of calcium on bone loss from the spine, femoral neck, and radius in 301 healthy postmenopausal women, half of whom had a calcium intake lower than 400 mg per day and half an intake of 400 to 650 mg per day. The women received placebo or either calcium carbonate or calcium citrate malate (500 mg of calcium per day) for two years.

Results. In women who had undergone menopause five or fewer years earlier, bone loss from the spine was rapid and was not affected by supplementation with calcium. Among the women who had been postmenopausal for six years or more and who were given placebo, bone loss was less rapid in the group with the higher dietary calcium intake. In those with the lower calcium intake, calcium citrate malate prevented bone loss during the two years of the study; its effect was significantly different from that of placebo ($P<0.05$) at the femoral neck (mean change in bone density [±SE], 0.87±1.01 percent vs. −2.11±0.93 percent), radius (1.05±0.75 percent vs. −2.33±0.72 percent), and spine (−0.38±0.82 percent vs. −2.85±0.77 percent). Calcium carbonate maintained bone density at the femoral neck (mean change in bone density, 0.08±0.98 percent) and radius (0.24±0.70 percent) but not the spine (−2.54±0.85 percent). Among the women who had been postmenopausal for six years or more and who had the higher calcium intake, those in all three treatment groups maintained bone density at the hip and radius and lost bone from the spine.

Conclusions. Healthy older postmenopausal women with a daily calcium intake of less than 400 mg can significantly reduce bone loss by increasing their calcium intake to 800 mg per day. At the dose we tested, supplementation with calcium citrate malate was more effective than supplementation with calcium carbonate. (N Engl J Med 1990; 323:878-83.)

THERE is little agreement about the effectiveness of supplemental calcium in retarding the rate of bone loss in postmenopausal women. Such supplements have been found to slow bone loss in some studies[1-5] but not in others,[6,7] and the effect of calcium may vary with the skeletal site examined.[8,9] Elucidating the role of calcium in retarding bone loss is difficult for several reasons: there are many determinants of bone loss, the rate of bone loss is slow and variable, there is wide variation in women's dietary calcium intake, and the effectiveness of supplementation may vary with age or with the stage of life. To our knowledge, no controlled intervention studies have indicated that calcium supplementation retards bone loss from the spine or hip.

In a pilot study conducted in preparation for this trial, we found that healthy postmenopausal women whose usual daily calcium intake was less than 400 mg lost mineral from the spine at a greater rate than women whose intake was higher.[10] It thus appeared that there is a threshold of calcium intake below which skeletal reserves may be used to meet daily calcium needs; therefore, the women most likely to benefit from calcium supplementation are those whose usual intake is low. To test this possibility, we compared the responses to calcium supplementation of women whose usual calcium intake was below 400 mg daily with the responses of women whose intake was just above 400 mg. A dose of 500 mg of supplemental calcium was selected because it would bring most of the women in the lower calcium-intake group up to the level of the current recommended dietary allowance (RDA) of 800 mg per day.[11] Two calcium sources were studied: calcium carbonate, because it is a widely used supplement, and calcium citrate malate, because of its demonstrated bioavailability.[12-14]

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METHODS

Subjects

The 361 women enrolled in this study were recruited with the help of local television stations and by direct mailings. The protocol was approved by the Human Investigation Review Committee of Tufts University, and written informed consent was obtained from each woman. The criteria for entry were white race, good general health, normal ambulation, age 40 through 70 years, at least six months since the last menses, and normal results on physical examination and screening laboratory tests. By design, half the women had a usual calcium intake of less than 400 mg daily, and half had an intake between 400 and 650 mg daily (seven women whose usual intakes ranged from 668 to 925 mg were also included). Women were excluded if they had a history of nontraumatic fracture of any bone; had renal, hepatic, or gastrointestinal disorders associated with abnormal calcium or bone metabolism; had used estrogen, glucocorticoids, or other medications known to affect calcium or bone metabolism within the past year; had evidence of a compression fracture on thoracic or lumbar-spine radiography; or had spinal bone-mineral–density values 2 SD or more below the age-matched reference mean.

Because the effectiveness of calcium supplementation might be different in women who were closest to menopause, particularly if they were undergoing accelerated bone loss, we examined the relation between bone loss from the spine and the number of years since menopause in the 229 women in this trial for whom complete spinal data were available and in whom the time of menopause could be

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estimated. The fitted curves revealed rapid bone loss in women during the first five years after menopause and a slower, fairly constant rate of loss thereafter. A two-phase regression analysis[15] gave similar results. Therefore, the clinical characteristics of the women who had undergone menopause five or fewer years earlier (early-postmenopausal women) and of those who had undergone menopause more than five years earlier (late-postmenopausal women) at the beginning of the study were analyzed separately (Table 1).

Study Design and Supplements

In this two-year double-blind, placebo-controlled trial, the half of the women whose usual dietary calcium intake was lower than 400 mg per day were randomly assigned to treatment with microcrystalline cellulose (placebo), 500 mg of elemental calcium in the form of calcium carbonate, or 500 mg of elemental calcium in the form of calcium citrate malate. With a separate randomization scheme, the half of the women whose daily intake was 400 to 650 mg were assigned to the same three treatment groups. The women in each of these six groups were instructed to take two tablets daily at bedtime and to maintain their usual diets. Each woman came to the center every six months for evaluation. During the first six-month visit, each underwent an assessment of physical activity. During the annual visits, each had a physical examination, urine and blood measurements, and bone-density measurements. During every visit, each woman's compliance with the study regimen and dietary calcium intake were assessed.

Calcium citrate malate was prepared as described previously[12] with a calcium:citrate:malate molar ratio of 6:2:3. This form of calcium is commercially available only to fortify citrus juices (Citrus Hill Plus Calcium, Procter and Gamble, Cincinnati). All placebo, calcium carbonate, and calcium citrate malate tablets were provided by Procter and Gamble.

Base-line measurements in subsets of these women have been reported previously,[16-21] and selected longitudinal data have been reported[22,23] or presented.[24]

Status of Subjects and Compliance

During the two-year study period, 46 of the 361 women (13 percent) dropped out of the study. Twenty dropped out for personal reasons (e.g., they lost interest or moved away), 11 because of serious illness, 9 to start estrogen or glucocorticoid therapy, and 4 because of side effects of treatment (in the calcium citrate malate group, 1 with constipation and 1 with epigastric distress; in the placebo group, 1 with bloating; in the calcium carbonate group, 1 with rash). Two were referred for treatment outside the study because their bone-mineral density fell to values at least 2 SD below the reference mean. In addition, 14 women were excluded from the analyses, 2 because they had primary hyperparathyroidism during the study and 12 because they were found to be taking excessive doses of thyroid hormone for hypothyroidism when their serum concentrations of thyroid-stimulating hormone were measured with a sensitive assay toward the end of the study. None had hypercalciuria. Compliance, as measured by the percentage of tablets taken, was 98 percent during the study.

Measurements

The women's dietary calcium and vitamin D intake was estimated every six months by means of a food-frequency questionnaire.[20] A separate questionnaire was used to record the use of vitamin and mineral supplements during the month before enrollment. Alcohol use and cigarette smoking were also assessed by questionnaire.

The bone-mineral density of the spine (L-2 to L-4) and femoral neck was measured with a model DP3 dual-photon scanner (Lunar Radiation, Madison, Wis.) with a coefficient of variation of 2.3 percent for the spine and 3.3 percent for the femoral neck. The scans were analyzed with software version 08B. The three gadolinium sources used during the study were obtained from Gulf Nuclear (Webster, Tex.). With the use of an external standard, each spinal value was corrected for any effects on bone-mineral density of the specific gadolinium source used, the strength of the source, and the truncal thickness of the subject.[25] Because they had radiographic abnormalities in the field of the scan,[22] 44 women were excluded from the analyses of spinal data. The bone-mineral density of the radius at the two thirds–distal site was determined with a model SP2 single-photon scanner (Lunar Radiation) with a coefficient of variation of 1 percent. The number of women with three scans at each site was 236 for the spine, 237 for the femoral neck, and 246 for the radius.

Physical activity was assessed with Caltrac accelerometers (Hemokinetics, Madison, Wis.) worn during waking hours for seven consecutive days. The monitors were suspended from the waist in close-fitting pouches that helped maintain the instrument in the horizontal position. The results are expressed as mean kilocalories per hour spent in physical activity during waking hours.

Serum ionized calcium was measured with a Nova 7 analyzer (Nova Biomedical, Waltham, Mass.), and serum alkaline phosphatase and serum and urinary creatinine by colorimetry with a Cobas Fera centrifugal analyzer (Roche Instruments, Belleville, N.J.). Intact immunoreactive parathyroid hormone in serum was measured with Allegro PTH kits obtained from Nichols Institute (Los Angeles), with intraassay and interassay coefficients of variation of 5.6 percent and 6.6 percent, respectively. Plasma levels of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) were measured by the competitive protein-binding method of Reinhardt et al.,[26] with an interassay coefficient of variation of 7.7 percent. Plasma levels of 25-hydroxyvitamin D were measured by the method of Preece et al.,[27] with an interassay coefficient of variation of 7.3 percent. Urinary calcium was measured by direct-current plasma emission spectroscopy with a Spectraspan 6 (Beckman Instruments, Palo Alto, Calif.). Creatinine clearance was corrected for body-surface area.[28] Serum gastrin concentrations were measured with radioimmunoassay kits obtained from Cambridge Medical Diagnostics (Billerica, Mass.), and serum pepsinogen I and II by the double-antibody radioimmunoassay method of Samloff.[29] In women who were receiving thyroid hormone therapy, levels of thyroid-stimulating hormone were measured with TSH-IRMA kits obtained from Celltech Diagnostics (Berkshire, United Kingdom).

Analyses were performed in batches as the samples were collected, except for serum levels of thyroid-stimulating hormone, which were measured only toward the end of the study.

Table 1. Clinical Characteristics at Enrollment of Women Who Had Measurements of Spinal Bone-Mineral Density before and after Treatment.*

Characteristic	Early Postmenopausal	Late Postmenopausal
No.	67	169
Age (yr)	54.5±3.4	59.9±5.4
Years since menopause†	3.2±1.4	13.0±5.6
Body-mass index‡	26.5±4.3	26.0±4.2
Physical activity (kcal/hr)§	22±11	22±11
Daily dietary intake		
Calcium		
<400 mg (n = 112)	274±80	283±89
400–650 mg (n = 124)¶	513±71	530±95
Vitamin D (IU)	171±185	194±307
Bone-mineral density (g/cm^2)‖		
Spine	1.13±0.02	1.06±0.01
Radius	0.65±0.01	0.60±0.01
Femoral neck	0.82±0.01	0.78±0.01

*Only the women for whom complete spinal data were available are included. Plus–minus values are means ±SD, unless otherwise specified.

†Seven women with partial hysterectomies were excluded from this category.

‡The weight in kilograms divided by the square of the height in meters.

§To convert kilocalories to kilojoules, multiply by 4.184.

¶Five women had initial intakes above 650 mg.

‖Values are means ±SE.

Statistical Analysis

The sample size for this study was estimated from a pilot study that was conducted to determine the variability of the rate of loss of

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bone-mineral density from the spine in this population.[10] For all analyses, the subjects remained in the calcium-intake category to which they were originally assigned. The LOWESS smoothing procedure for curve fitting[30] was used to examine the relation between the amount of bone loss and the number of years since menopause. Among the late-postmenopausal women in the lower calcium-intake category, the mean (±SD) body-mass index (the weight in kilograms divided by the square of the height in meters) was higher in the group that received calcium carbonate than in the group that received calcium citrate malate (28.1±5.1 vs. 24.9±3.3; P = 0.05), and the initial mean (±SE) bone-mineral density was higher in the calcium carbonate group than the calcium citrate malate group at the spine (1.11±0.03 vs. 0.99±0.03 g per square centimeter; P<0.05) and at the femoral neck (0.83±0.02 vs. 0.76±0.02 g per square centimeter; P<0.05). Before treatment effects were compared, the mean rates of bone loss for the groups were standardized for one-year periods and adjusted for differences in bone-mineral density and body-mass index at enrollment and in dietary calcium intake during the study by covariance analysis (with use of the SAS general-linear-models procedure[31]). Intergroup comparisons of bone loss were performed only when the overall analysis of covariance indicated that the difference was significant at the 0.10 level. To determine which treatment groups lost or gained bone-mineral density during the study, we compared annualized least-squares means of rates of change with zero. When adjustments were not necessary, comparisons among the treatment groups were made with analysis of variance and Tukey's honestly significant differences.[32] Unpaired t-tests were used to assess differences between the two calcium-intake groups and between laboratory values at base line and at two years. All P values are two-tailed.

Results

Early-Postmenopausal Women

The women who had undergone menopause five or fewer years earlier had lost bone from the spine after two years (Table 2). The decline in bone density was statistically significant in all three treatment groups and was not affected by calcium supplementation. The bone density of the femoral neck and the radius did not change significantly in any group. The sample size was not adequate to evaluate the results according to dietary calcium-intake category.

Table 2. Adjusted Mean Change in Bone-Mineral Density in Early-Postmenopausal Women after One and Two Years of Treatment with Calcium Citrate Malate (CCM), Calcium Carbonate (CC), or Placebo.*

Site and Treatment Group	No.†	After 1 Year		After 2 Years	
		P value	% change	P value	% change
Spine	—	0.649	—	0.915	—
CCM	25	—	−1.32±0.56‡	—	−3.11±0.77§
CC	28	—	−1.93±0.53§	—	−2.66±0.74§
Placebo	14	—	−1.21±0.75	—	−2.94±1.04§
Femoral neck	—	0.329	—	0.811	—
CCM	24	—	−0.48±0.78	—	−0.24±0.96
CC	23	—	0.32±0.79	—	−1.11±0.97
Placebo	11	—	−1.79±1.16	—	−0.89±1.42
Radius	—	0.823	—	0.456	—
CCM	22	—	−0.31±0.50	—	0.05±1.10
CC	21	—	−0.29±0.51	—	−0.42±1.13
Placebo	16	—	−0.73±0.58	—	−2.03±1.29

*Mean rates of bone loss were adjusted for differences in initial bone-mineral density, initial body-mass index, and dietary calcium intake during the study. Plus–minus values are means ±SE. P values were calculated by analysis of covariance.

†Women with complete data for each scan site are included.

‡P≤0.05 for the comparison with base-line values.

§P≤0.01 for the comparison with base-line values.

The women who took the calcium supplements had statistically significant (P<0.05) mean increases in serum levels of ionized calcium (from 1.28 to 1.29 mmol per liter; standard error of the difference [SED], 0.01) and 24-hour urinary calcium:creatinine ratio (from 432 to 528 mmol per mole; SED, 26) and decreases in serum levels of alkaline phosphatase (from 1.22 to 1.09 μkat per liter; SED, 0.03) and plasma levels of $1,25(OH)_2D$ (from 84 to 73 pmol per liter; SED, 3).

Late-Postmenopausal Women

Among the women who had undergone menopause six or more years earlier, those who received calcium citrate malate had no statistically significant loss of bone density at any site (Table 3). The bone density of the spine decreased significantly in the calcium carbonate and placebo groups, and the bone density of the femoral neck decreased significantly in the placebo group. The change in the bone-mineral density of the radius was significantly greater in the placebo group than in the calcium citrate malate group (P = 0.023).

The adjusted mean bone loss in the late-postmenopausal women, subdivided according to calcium intake, is shown in Figure 1. Among the women with the lower dietary calcium intake, the decrease in bone density after two years was significantly greater at the spine, femoral neck, and radius in the placebo group than in the calcium citrate malate group and greater at the radius in the placebo group than in the calcium carbonate group. The decrease in spinal bone density after two years tended to be greater in the calcium carbonate group than in the calcium citrate malate group, but the difference was not statistically significant (P = 0.081). In the women with the higher dietary calcium intake, there were no differences among the treatment groups at any site. The difference in the mean rates of change between two groups required to achieve significance at two years in these women was 1.6 percent for the spine, 2.4 percent for the hip (femoral neck), and 2.6 percent for the radius. All the late-postmenopausal women had significant bone loss from the spine except those with a lower calcium intake who received calcium citrate malate (Fig. 1). Significant bone loss from the femoral neck and radius occurred only in the women in the placebo group who had a lower calcium intake.

The effect of dietary calcium was examined by comparing the results for the women in the lower and higher dietary calcium-intake categories. Among the women treated with placebo, the mean change in bone density at the radius was greater in the lower-calcium-intake group than in the higher-calcium-intake group (−2.08±0.62 percent vs. 0.26±0.73 percent; P = 0.017). The trends were similar for the bone density of the spine (−3.04±0.77 vs. −1.61±0.60 percent) and the femoral neck (−2.04±1.11 vs. −0.61±0.81 percent). Since the two placebo groups did not differ in base-line bone-mineral density or body-mass

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Table 3. Adjusted Mean Change in Bone-Mineral Density in Late-Postmenopausal Women after One and Two Years of Treatment with Calcium Citrate Malate (CCM), Calcium Carbonate (CC), or Placebo.*

Site and Treatment Group	No.†	After 1 Year		After 2 Years	
		P value	% change	P value	% change
Spine	—	0.021	—	0.132	—
CCM	53	—	−0.26±0.39‡	—	−0.92±0.50
CC	52	—	−0.76±0.39§¶	—	−1.91±0.51‖
Placebo	64	—	−1.68±0.35‡§¶	—	−2.27±0.46‖
Femoral neck	—	0.168	—	0.140	—
CCM	54	—	0.60±0.56	—	0.41±0.69
CC	54	—	0.28±0.56	—	−0.07±0.69
Placebo	71	—	−0.72±0.49	—	−1.33±0.60§
Radius	—	0.332	—	0.069	—
CCM	53	—	0.33±0.43	—	1.01±0.59**
CC	57	—	0.15±0.42	—	−0.30±0.57
Placebo	77	—	−0.45±0.36	—	−0.73±0.49**

*Mean rates of bone loss were adjusted for differences in initial bone-mineral density, initial body-mass index, and dietary calcium intake during the study. Plus–minus values are means ±SE. P values were calculated by analysis of covariance.

†Women with complete data for each scan site are included.

‡When the P value (by analysis of covariance) is <0.1, adjusted means are compared. Like superscripts differ significantly from one another at the level of P = 0.007.

§P≤0.05 for the comparison with base-line values.

¶Like superscripts differ significantly at the level of P = 0.082.

‖P≤0.01 for the comparison with base-line values.

**Like superscripts differ significantly at the level of P = 0.023.

index, the rates of change were not adjusted for these measurements.

Calcium supplementation caused small but significant changes in several laboratory measures in the late-postmenopausal women (Table 4). The changes associated with the two supplements were similar, except that increases in urinary calcium excretion were limited to the women who received calcium citrate malate. Among the women who took calcium citrate malate, urinary calcium excretion was greater in the women with the lower dietary calcium intake ($P<0.05$).

There were no significant differences among the treatment groups at base line in alcohol use or cigarette smoking, creatinine clearance, or the length of time between study visits. The women's weight did not change significantly in any group during the study. The 11 women who had biochemical evidence of hypochlorhydria (i.e., an elevated serum gastrin level accompanied by a ratio of serum pepsinogen I to serum pepsinogen II that was less than 2.9) were evenly distributed among the treatment groups, and each had bone loss similar to that of her treatment group as a whole.

Discussion

The findings of this study support the hypothesis that the healthy postmenopausal women who are most likely to benefit from calcium supplements are those whose usual dietary calcium intake is low. The detection of significant effects with the low supplemental dose of calcium used in this study was probably related not only to the study subjects' low usual calcium intake and the separate analyses of early-postmenopausal and late-postmenopausal women but also to the relatively large sample and the careful standardization of the bone scanning. In addition, potentially confounding physical factors, including body size, truncal thickness, and calcification of the aorta, were accounted for, and the treatment groups were balanced for many demographic, dietary, and lifestyle factors known to affect the rate of bone loss. Although many of the women had vitamin D insufficiency in the winter,[20] the plasma 25-hydroxyvitamin D lev-

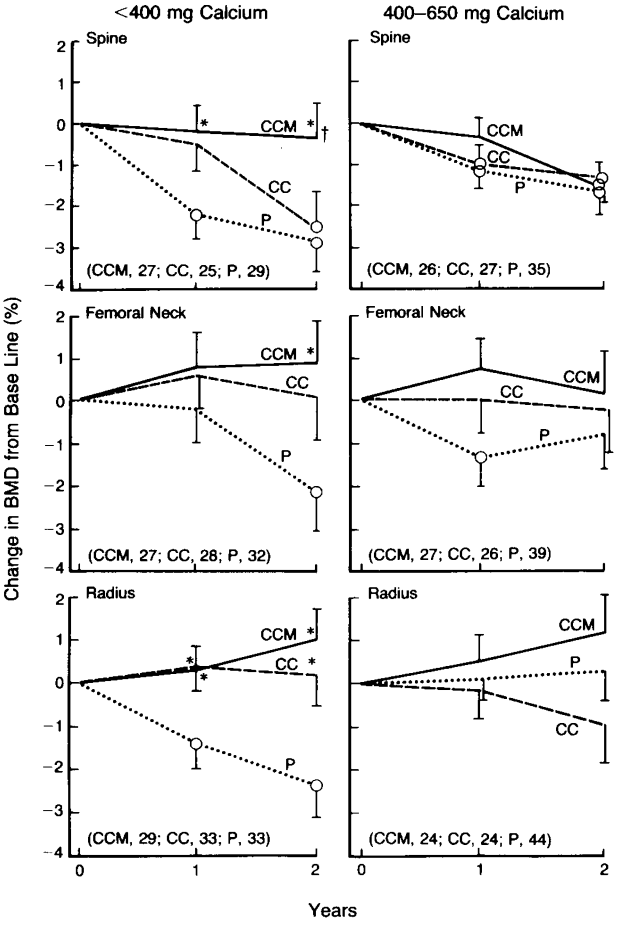

Figure 1. Effect of Calcium on Mean Adjusted Rates of Change in Bone-Mineral Density (BMD) in Late-Postmenopausal Women.

The rates were adjusted for base-line bone-mineral density and body-mass index and for dietary calcium intake during the study for each scan site and calcium-intake category. The left-hand panels show women with calcium intakes of <400 mg per day, and the right-hand panels those with intakes of 400 to 650 mg per day. The sample sizes are shown in parentheses (CCM denotes calcium citrate malate, CC calcium carbonate, and P placebo). The results in the calcium citrate malate group are indicated by solid lines, those in the calcium carbonate group by dashed lines, and those in the placebo group by dotted lines. Within each panel, mean values labeled with asterisks differed significantly from those for the placebo group ($P<0.05$); the dagger indicates a difference from the calcium carbonate group that is of borderline significance ($P = 0.081$). The open circles indicate values that differed significantly from the base-line values ($P\leq0.05$ by repeated-measures analysis of variance). The T bars indicate the SE.

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Table 4. Changes in Laboratory Values in Late-Postmenopausal Women for Whom Complete Spinal Data before and after Two Years of Supplementation with Calcium or Placebo Were Available.*

Index and Dietary Calcium-Intake Category	Treatment	Base Line	After 2 Years	SED
Serum ionized Ca (mmol/liter)				
Lower and higher	CCM and CC	1.27	1.30†	0.01
	P	1.27	1.28‡	0.01
PTH (ng/liter)				
Lower and higher	CCM and CC	32	28†	1
	P	32	33	1
Alkaline phosphatase (μkat/liter)				
Lower and higher	CCM and CC	1.24	1.10†	0.02
	P	1.30	1.23‡	0.03
Plasma $1,25(OH)_2D$ (pmol/liter)				
Lower and higher	CCM and CC	85	75†	2
	P	89	88	3
24-Hr urinary Ca:Cr ratio (mmol/mol)				
Lower	CCM	364	592†	48
	CC	450	479	52
	P	354	370	26
Higher	CCM	318	431‡	47
	CC	366	462‡	44
	P	342	374	33

*SED denotes standard error of the difference, Ca calcium, CCM calcium citrate malate, CC calcium carbonate, P placebo, PTH parathyroid hormone, $1,25(OH)_2D$ 1,25-dihydroxyvitamin D, and Cr creatinine. Lower dietary calcium intake was defined as <400 mg per day, and higher intake from 400 to 650 mg per day.

†$P \leq 0.001$ for the comparison with base-line values.

‡$P < 0.05$ for the comparison with base-line values.

els did not vary among the treatment groups. The limited decreases in serum alkaline phosphatase levels that occurred during the period of supplementation suggest that the rate of bone turnover was reduced.

No controlled studies of calcium supplementation in women or men with a dietary intake this low are available for comparison. In controlled studies in early-postmenopausal women with a higher dietary calcium intake, supplementation with 1000 to 2000 mg of calcium daily retarded bone loss from the radius[4,8,9] and reduced the loss of metacarpal cortical area.[5] Calcium supplementation had no effect on the density of the radius in the early-postmenopausal women in this study, perhaps because of the small number of subjects. Our results agree with those of other controlled studies,[8,9] which showed that bone loss from the spine in early-postmenopausal women is unresponsive to calcium supplementation. We also confirmed an earlier report[1] that supplementation with calcium retards bone loss from the radius in late-postmenopausal women. Less information is available on the relation between calcium supplementation and rates of bone loss from the spine in older women. We found that supplementation with calcium citrate malate decreased the rate of loss of bone mineral from the spine in late-postmenopausal women with a low dietary calcium intake. In men with a relatively high intake of calcium (1159 mg daily), supplementation with 1000 mg of calcium, along with vitamin D, did not retard bone loss from the spine or radius.[33]

The two supplements studied were not equally effective in retarding bone loss in late-postmenopausal women with the lower dietary calcium intake. Both supplements were absorbed in adequate amounts to suppress serum parathyroid hormone and plasma $1,25(OH)_2D$ concentrations (to similar levels); however, calcium citrate malate appeared to be absorbed better, as indicated by the greater increment in urinary calcium excretion in the women with the lower calcium intake. Although calcium carbonate has been found to be poorly absorbed in the fasting state by subjects with achlorhydria,[34] we did not evaluate the importance of this factor, since only 4 percent of the subjects had biochemical evidence of decreased gastric acid secretion (an elevated serum gastrin level and a pepsinogen I:pepsinogen II ratio of less than 2.9),[35] and they were evenly distributed among the treatment groups.

Reports on the effect of dietary calcium on both the rates of hip fracture[36-38] and bone loss[6,7,39] are mixed. In general these studies have examined subjects with a wide range of dietary calcium intakes but have not included many subjects with a low intake. The positive effect of diet alone on the density of the radius in this study and on the density of the spine in the pilot study[10] is probably attributable to the low usual calcium intake of the subjects. The detection of a benefit of calcium from food and supplements in postmenopausal women with low usual intakes is important, because intakes of less than 400 mg of calcium daily are common in this country. The National Health and Nutrition Examination Survey II in 1976 through 1980 found that the median daily calcium intake of women over 44 years of age was 475 mg.[40]

The women in this study who had undergone menopause five or fewer years earlier had accelerated rates of loss of bone from the spine. Although it has not been a consistent finding,[41,42] increased rates of bone loss have been reported to occur for two[43] to five[44,45] years after menopause. There were too few women in the early-postmenopausal group in this study for us to draw conclusions about the effect of dietary calcium on their rates of bone loss.

In summary, within this healthy population, bone loss from the spine in early-postmenopausal women was not affected by supplementation with 500 mg of calcium, despite biochemical changes suggesting increased calcium absorption. Among late-postmenopausal women who received placebo, a higher dietary calcium intake was associated with reduced bone loss from the radius, with similar trends at the spine and femoral neck. The late-postmenopausal women with a dietary calcium intake of less than 400 mg daily benefited from supplementation up to a total intake of approximately 800 mg of calcium per day. Among these women, only calcium citrate malate prevented bone loss from the spine, whereas both calcium citrate malate and calcium carbonate prevented bone loss from the femoral neck and the radius. In addition, the effect of calcium citrate malate differed significantly from that of placebo at all three bone sites, whereas the effect of calcium carbonate was significantly different

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from that of placebo only at the radius. The late-postmenopausal women with dietary calcium intakes of 400 to 650 mg daily maintained bone-mineral density at the hip and radius but lost bone from the spine despite supplementation and the biochemical changes associated with it.

On the basis of this study, we recommend that healthy postmenopausal women whose usual dietary calcium intake is low be urged to increase their calcium intake to 800 mg per day, the current recommended dietary allowance, in order to limit bone loss. At the dose evaluated here, calcium citrate malate was a better source of calcium than calcium carbonate for augmenting dietary calcium intake.

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