EFFECT OF CALCIUM SUPPLEMENTATION ON BONE LOSS IN POSTMENOPAUSAL WOMEN

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Abstract *Background.* The use of calcium supplements slows bone loss in the forearm and has a beneficial effect on the axial bone density of women in late menopause whose calcium intake is less than 400 mg per day. However, the effect of a calcium supplement of 1000 mg per day on the axial bone density of postmenopausal women with higher calcium intakes is not known.

Methods. We studied 122 normal women at least three years after they had reached menopause who had a mean dietary calcium intake of 750 mg per day. The women were randomly assigned to treatment with either calcium (1000 mg per day) or placebo for two years. The bone mineral density of the total body, lumbar spine, and proximal femur was measured every six months by dual-energy x-ray absorptiometry. Serum and urine indexes of calcium metabolism were measured at base line and after 3, 12, and 24 months.

Results. The mean (±SE) rate of loss of total-body bone mineral density was reduced by 43 percent in the calcium group (−0.0055±0.0010 g per square centimeter per year) as compared with the placebo group (−0.0097±0.0010 g per square centimeter per year, P = 0.005). The rate of loss of bone mineral density was reduced by 35 percent in the legs (P = 0.02), and loss was eliminated in the trunk (P = 0.04). Calcium use was of significant benefit in the lumbar spine (P = 0.04), and in Ward's triangle the rate of loss was reduced by 67 percent (P = 0.04). Calcium supplementation had a similar effect whether dietary calcium intake was above or below the mean value for the group. Serum parathyroid hormone concentrations tended to be lower in the calcium group, as were urinary hydroxyproline excretion and serum alkaline phosphatase concentrations.

Conclusions. Calcium supplementation significantly slowed axial and appendicular bone loss in normal postmenopausal women. (N Engl J Med 1993;328:460-4.)

THE value of supplementation of calcium intake in the prevention of osteoporosis remains uncertain.[1,2] Calcium intake is positively related to calcium balance,[3,4] and calcium supplementation benefits appendicular cortical bone mass.[5-9] The axial skeleton, however, is the site at which two of the most important osteoporotic fractures, those of the spine and hip, occur. Some but not all studies have found a relation between calcium intake and the incidence of hip fractures.[10-13] The value of calcium in slowing bone loss from the spine in women soon after menopause remains uncertain,[14-16] possibly because the dominant factor affecting bone metabolism in these women is their recent decline in estrogen secretion.

Recently, Dawson-Hughes et al.[17] examined the effect of calcium supplementation on axial bone loss in postmenopausal women. The supplementation had beneficial effects in the women who had reached menopause more than five years earlier and whose dietary calcium intake was less than 400 mg per day. Although their study provided important evidence of a role of calcium intake in the prevention of bone loss in postmenopausal women, it did not have the statistical power to rule out small but biologically important effects of calcium supplementation in women with dietary intakes of 400 to 650 mg per day, the dose of calcium was small (500 mg per day), and women with a dietary calcium intake of more than 650 mg per day were not studied. We undertook the current study to determine the effect of calcium, in a dose of 1000 mg per day, on bone mineral density in women who had reached menopause at least three years earlier and who had a wide range of calcium intakes.

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Supported by grants from the Health Research Council of New Zealand, the Arthritis Foundation, the Paykel Trust, the ASB Charitable Trust, and the New Zealand Lottery Board.

METHODS

Subjects

Through newspaper advertisements, we recruited white women who had reached menopause more than three years earlier. The 215 respondents completed a questionnaire about their medical history. The exclusion criteria were a history of disorders of calcium metabolism, including symptomatic vertebral fractures; renal, thyroid, or hepatic dysfunction; current systemic disease; the use of hormone-replacement therapy within the previous three years; the use of supraphysiologic doses of any glucocorticoid for more than six months at any time; and the current use of any glucocorticoid, anticonvulsant medication, or thiazide diuretic agent. A total of 135 women met none of these criteria and were enrolled in the study.

Study Protocol

The women were randomly assigned to receive 1000 mg of elemental calcium in the form of 5.24 g of calcium lactate–gluconate and 0.8 g of calcium carbonate, formulated as an effervescent tablet, taken with water in a divided dose twice daily, or identical effervescent tablets containing sucrose, for two years. All the tablets were provided by Sandoz (Auckland, New Zealand). Neither the women nor the investigators were aware of the treatment assignment. The study was approved by the Auckland Hospital Research Ethics Committee, and all the women gave written informed consent.

The women were seen at three and six months, and then every six months thereafter; their medical history in the intervening period and their compliance with treatment (as assessed by tablet counts) were recorded at each visit. The mean (±SD) rate of compliance during the two-year study period was 84±7 percent in the calcium group and 83±10 percent in the placebo group.

During the course of the study, three women left the country, three were given hormone-replacement therapy by their personal physicians, one withdrew for personal reasons, and six withdrew because of intercurrent illness. Four of the six illnesses were judged to be unrelated to the study treatment (nasopharyngeal carcinoma, thyrotoxicosis, rheumatoid arthritis, and chronic lymphatic leukemia). A renal calculus developed in one woman in the calcium group at six months. Her rate of urinary calcium excretion was 148

mg per day (3.7 mmol per day) before treatment. A second woman, also in the calcium group, had an exacerbation of preexisting dyspeptic symptoms. Thus, 122 women completed the two-year study.

Measurements

Bone mineral density was measured with a dual-energy x-ray absorptiometer (DPX, Lunar Radiation, Madison, Wis.). Scans of the whole body, lumbar spine (L2 to L4), and proximal femur were performed every six months. For each scan, the mass of bone mineral was determined and was expressed in the form of a ratio to the projected area of the scanned region. In the whole-body scans, the densities of subregions (arms, legs, and trunk) were calculated as well as the whole-body bone mineral density. The densitometer software changed between the first two visits, so the base-line scans were reanalyzed with the new software. The precision of these measurements of bone density in our laboratory was as follows: total body, 0.4 percent; lumbar spine, 1.0 percent; femoral neck, 1.4 percent; Ward's triangle, 2.9 percent; and trochanter, 1.6 percent. Lateral spinal radiographs were performed at study entry. In one woman there was residual contrast medium from myelography performed many years earlier, and in another woman there was a fracture of the second lumbar vertebra. In the first woman, data on the lumbar spine were excluded, and in the second, data on the affected vertebra were excluded. The severity of osteophytosis in the scanning region was graded according to the system of Orwoll et al.[18]; it was absent or mild in 83 percent of the women. Ten women in each group had osteophytes present at two vertebral levels, but none had severe osteophytosis.

Calcium intake was determined from four-day diet diaries at base line and at two years. Physical activity was assessed by questionnaire.[19] We collected fasting blood samples (for the measurement of serum ionized calcium, creatinine, intact parathyroid hormone [with an Allegro assay, Nichols Institute, San Juan Capistrano, Calif.], 25-hydroxyvitamin D, and alkaline phosphatase), second-urination fasting urine samples (for the measurement of hydroxyproline and creatinine), and 24-hour urine samples (for the measurement of calcium and creatinine) at base line, three months, and two years. The methods used for these measurements have been described elsewhere.[20]

Statistical Analysis

We analyzed the results for bone mineral density by calculating the slope of the regression line of bone mineral density against time for each woman at each measurement site. The mean slopes at each site were compared between the treatment groups by analysis of covariance, with age, base-line bone mineral density, dietary calcium intake, and compliance as covariates. These covariates were chosen because they were likely to influence either the rate of bone loss or the response to calcium supplementation. The values for the slopes presented are the least-squares means adjusted for these covariates. When appropriate, the results were analyzed by repeated-measures multivariate analysis. Significance was evaluated with the F approximation to the Hotelling–Lawley trace. Other results were compared with the use of t-tests. The programs of the SAS Institute (Cary, N.C.) were used for all analyses.[21] Since all comparisons were made a priori, no adjustment of alpha (0.05) was made. All tests were two-tailed. Only the results in the 122 women who completed the study were included in the analyses. Results are presented as means ±SE, unless otherwise indicated.

Results

The base-line characteristics of the women are shown in Table 1. There was no significant difference between the groups in any characteristic.

Bone Mineral Density

The initial mean values for bone mineral density at all sites were similar in the two groups (Table 2). The changes in total-body bone mineral density during the study are shown in Figure 1, and the rate of change in bone mineral density as a function of time is shown in Table 3. Bone mineral density declined in both groups ($P<0.001$), but the decline was significantly greater in the placebo group ($P = 0.005$). The beneficial effects of calcium supplementation were comparable throughout the subregions of the total-body scans (Table 3).

The changes in bone mineral density of the lumbar spine are shown in Figure 2 and Table 3. There was no net change in bone mineral density in the placebo group, but it increased in the calcium group ($P<0.001$), and there was a significant difference between the two groups ($P = 0.04$). In the femur (Fig. 3), the bone mineral density tended to decline less in the calcium group, but a significant treatment effect was found only in Ward's triangle ($P = 0.04$).

To determine whether the beneficial effects of calcium were attributable mainly to a reduction in

Table 1. Base-Line Clinical Characteristics of Postmenopausal Women Given Calcium Supplementation or Placebo for Two Years.*

Characteristic	Calcium Group (N = 61)	Placebo Group (N = 61)
Age (yr)	58±5	58±5
Years since menopause	9±4	10±6
Weight (kg)	65±9	66±9
Height (m)	1.62±0.05	1.63±0.06
Physical activity (MJ/day)	4.5±1.8	4.8±1.9
Dietary calcium intake (mg/day)	760±300	730±290
No. of smokers	7	4
Alcohol intake (g/day)	2.6±1.1	2.6±1.0

*Plus–minus values are means ±SD. There were no significant differences between the groups.

Table 2. Base-Line Values for Bone Mineral Density in Postmenopausal Women Given Calcium Supplementation or Placebo for Two Years.*

Site	Calcium Group (N = 61)	Placebo Group (N = 61)
	g/cm^2	
Total body	1.06±0.09	1.06±0.08
Arms	0.75±0.06	0.74±0.06
Legs	1.09±0.10	1.10±0.09
Trunk	0.85±0.08	0.86±0.08
Lumbar spine	1.02±0.14	1.05±0.14
Femoral neck	0.85±0.09	0.86±0.10
Ward's triangle	0.73±0.12	0.72±0.13
Trochanter	0.73±0.11	0.76±0.11

*Plus–minus values are means ±SD. There were no significant differences between the groups.

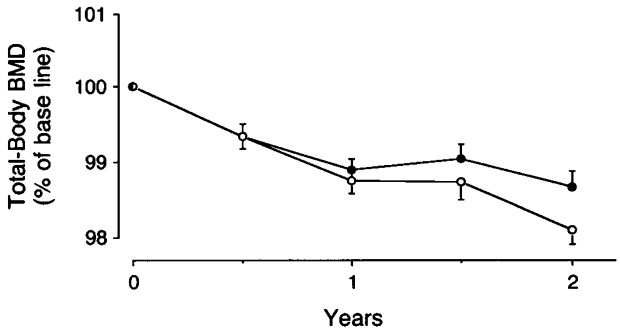

Figure 1. Mean (±SE) Total-Body Bone Mineral Density (BMD) in Postmenopausal Women Given Calcium Supplementation (●) or Placebo (○) for Two Years.

The results are expressed as a percentage of the base-line values. The loss of bone mineral density was significantly greater in the placebo group during the two-year study period (P = 0.005).

bone turnover, the rates of total-body bone loss during the second year alone were compared. The mean (±SE) rate of bone loss in the calcium group was −0.0023±0.0017 g per square centimeter per year, as compared with −0.0070±0.0017 g per square centimeter per year in the placebo group (P = 0.05).

There were five symptomatic fractures in the placebo group and two in the calcium group.

Dietary Calcium Intake

The mean (±SD) dietary calcium intake in all the women was 750±290 mg per day at base line and 740±260 mg per day at two years. The rates of loss of total-body bone mineral density were similar in the women whose base-line intake was above the mean and in those in whom it was below the mean (data not shown).

Biochemistry

Figure 4 shows the principal biochemical indexes of calcium metabolism measured during the study. The results in the two groups were similar at base line. The mean serum parathyroid hormone concentration was lower in the calcium group than in the placebo group at three months (P<0.05), and it remained slightly but not significantly lower at subsequent visits. Urinary hydroxyproline excretion decreased during the first three months in the calcium group (P<0.001), and it was significantly lower than in the placebo group. The mean serum alkaline phosphatase concentration also declined between base line and month 3 in the calcium group (P<0.001), but the difference between groups was not significant. Urinary calcium excretion was higher in the calcium group than in the placebo group at both 3 and 12 months. The mean serum ionized calcium concentrations were normal and did not change in the two groups throughout the study period (mean values, 4.9 to 5.0 mg per deciliter [1.22 to 1.24 mmol per liter]).

The mean (±SE) serum 25-hydroxyvitamin D concentrations at base line were 38±2 ng per milliliter (95±5 nmol per liter) in the placebo group and 37±2 ng per milliliter (93±5 nmol per liter) in the calcium group. The mean creatinine clearance at base line was 76±2 ml per minute in the placebo group and 78±2 ml per minute in the calcium group, and it did not change significantly in either group during the study (at two years the value was 78±3 ml per minute in both groups).

Table 3. Rates of Change in Bone Mineral Density in Postmenopausal Women Given Calcium Supplementation or Placebo for Two Years.*

Site	Calcium Group (N = 61)	Placebo Group (N = 61)	P Value
	g/cm²/yr		
Total body	−0.0055±0.0010†	−0.0097±0.0010†	0.005
Arms	−0.0039±0.0012‡	−0.0068±0.0012†	0.10
Legs	−0.0083±0.0014†	−0.0128±0.0014†	0.02
Trunk	0.0006±0.0013	−0.0031±0.0013§	0.04
Lumbar spine	0.0073±0.0021†	0.0012±0.0021	0.04
Femoral neck	−0.0013±0.0021	−0.0033±0.0020	0.50
Ward's triangle	−0.0037±0.0025	−0.0111±0.0025†	0.04
Trochanter	−0.0070±0.0022‡	−0.0115±0.0022†	0.16

*Plus–minus values are the least-squares means (±SE) for the slopes of the individual regressions of bone mineral density against time. The P values indicate the significance of the differences between groups (by analysis of covariance).

†P<0.001 for the difference of the slope from zero.

‡P<0.005 for the difference of the slope from zero.

§P<0.05 for the difference of the slope from zero.

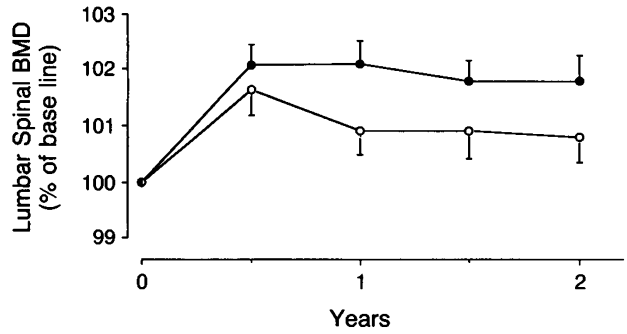

Figure 2. Mean (±SE) Lumbar Spinal Bone Mineral Density (BMD) in Postmenopausal Women Given Calcium Supplementation (●) or Placebo (○) for Two Years.

The results are expressed as a percentage of the base-line values. There was a significant difference between the groups during the two-year study period (P = 0.04).

Discussion

We found that a calcium supplement of 1000 mg per day has a beneficial effect on bone loss in normal postmenopausal women. The effect was consistent throughout the skeleton, although the differences between the placebo and treatment groups were not statistically significant at all sites. At most sites the placebo group lost bone at a rate of approximately 1 percent per year. This rate of loss was reduced by one third to one half in the calcium group, resulting at

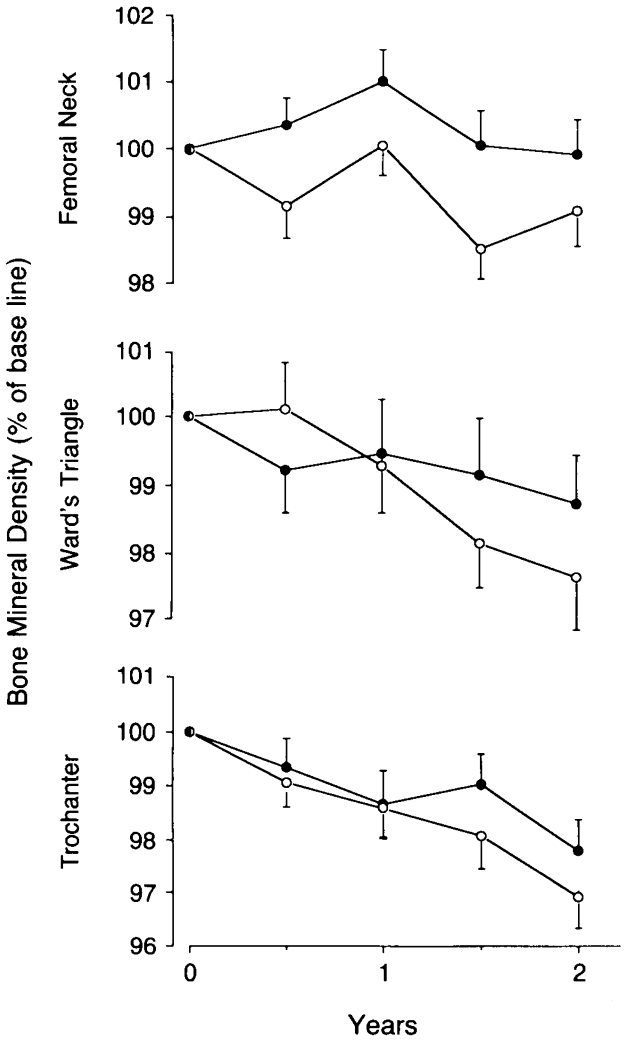

Figure 3. Mean (±SE) Bone Mineral Density in the Proximal Femur in Postmenopausal Women Given Calcium Supplementation (●) or Placebo (○) for Two Years.

The results are expressed as a percentage of the base-line values. There was a significant difference between the groups in the values for Ward's triangle during the two-year study period ($P = 0.04$).

the end of two years in differences of 0.5 to 1.1 percent between the groups in bone mineral density. Although these differences were small, they could result in a decreased risk of fracture if they were cumulative.

One aspect of our results merits comment. There was an increase in bone mineral density of the lumbar spine between base line and month 6 in both groups. There had been a change in the densitometer software between these two visits; however, reanalyzing the base-line scans with the new software did not eliminate the increases. During the same period, the bone mineral density as measured in the spinal region of the total-body scans did not change in either group of women (data not shown), suggesting that the increase in the bone mineral density of the lumbar spine was a software artifact not correctable by reanalysis. Such an artifact would affect both groups equally and not influence the comparison between them.

The effects of calcium supplementation on the indexes of bone and calcium homeostasis were as would be predicted. Serum parathyroid hormone concentrations were lower in the calcium group, which probably resulted in the decrease in urinary hydroxyproline excretion and serum alkaline phosphatase concentrations in that group. For all these biochemical indexes, the differences between the calcium and placebo groups tended to diminish with time, and no difference was significant at two years. This diminution with time was probably due to the decreases in fractional

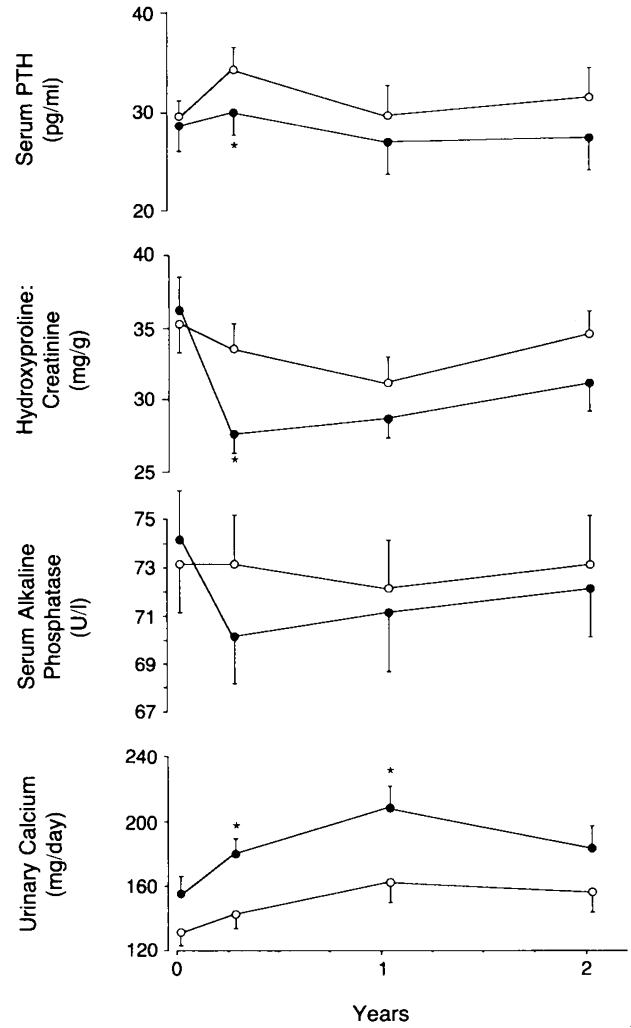

Figure 4. Mean (±SE) Biochemical Indexes of Calcium Metabolism and Bone Turnover in Postmenopausal Women Given Calcium Supplementation (●) or Placebo (○) for Two Years.

Significant differences between the groups are indicated by asterisks ($P<0.05$). PTH denotes parathyroid hormone. To convert values for PTH to picomoles per liter, multiply by 0.11; to convert values for the ratio of hydroxyproline to creatinine to micromoles per millimole, multiply by 0.87; and to convert values for calcium to millimoles per day, multiply by 0.025.

intestinal calcium absorption and renal tubular calcium reabsorption that occur during long-term calcium supplementation.

The results of this study are generally consistent with previously published results. We confirmed that appendicular bone loss slows with calcium supplementation.[5-9] There is no inconsistency between the positive effect of calcium supplementation on axial bone mineral density in this study and the negative results of Riis et al.[15] and Ettinger et al.,[14] since those studies were performed among women who had just reached menopause, whereas the women we studied had on average been postmenopausal for 10 years. Dawson-Hughes et al.[17] also found that the number of years after menopause was important in determining the effect of calcium supplementation on bone loss. It is of interest that in the studies in which calcium supplementation was beneficial,[9,16,17,22] the supplementation consisted of soluble calcium salts or dairy products, whereas calcium carbonate was not effective.[14,15,17,23] The subjects in those studies were not all comparable, so it is unlikely that the differences in effect on bone density are attributable only to the form of calcium supplementation used. However, there are clearly differences in the short-term bioavailability of different calcium preparations[24] that might cause them to have different effects on bone loss.

Our study extends that of Dawson-Hughes et al. by indicating that a larger supplement than was used in that study has beneficial effects on both axial and appendicular bone mineral density in women whose dietary calcium intake is greater than 400 mg per day. Since more than half of American women in this age group, and possibly an even larger proportion of women in other Western countries, have calcium intakes above 400 mg per day, this additional information is of practical importance. The demonstration of a benefit in the proximal femur is of particular importance because of the morbidity and costs associated with fractures at this site.

The time course of the beneficial effect of calcium supplementation is crucial to a determination of the likelihood that high intakes of calcium will result in fewer fractures. The mean values for bone mineral density in the total body and to a lesser extent in Ward's triangle and the trochanter diverged progressively in the two groups. This was not the case in the lumbar spine, however, where most of the difference between the groups became apparent during the first 6 to 12 months. Several previous studies have shown a similar transient effect of calcium on the rate of bone loss.[9,15-17] It is therefore possible that some of the treatment effects may have resulted from the fact that increased calcium intake caused a reduction in bone turnover, with a resultant filling of the bone remodeling space.[25] In this study, however, only the total-body measurements were of sufficient precision to make separate analyses of the rates of bone loss in years 1 and 2 meaningful; the results do indicate a sustained beneficial effect of calcium supplementation. Studies of considerably longer duration will be needed to determine whether the beneficial effects of calcium supplementation on the loss of bone mineral density are cumulative.

We are indebted to Tim Cundy, M.D., for his comments on the manuscript.

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