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Correcting Calcium Nutritional Deficiency Prevents Spine Fractures in Elderly Women*

ROBERT R. RECKER, SHARILYN HINDERS, K. MICHAEL DAVIES, ROBERT P. HEANEY, MARY RUTH STEGMAN, JOAN M. LAPPE, and DONALD B. KIMMEL

ABSTRACT

We tested the spine antifracture and bone sparing efficacy of 1.2 g/day of oral calcium as carbonate in two groups of elderly women, one with prevalent fractures (PF, $n = 94$) on entry and the other without (NPF, $n = 103$). It was a prospective randomized, double-blind, placebo-controlled trial in mostly rural communities in women over age 60 who were living independently and were consuming <1 g/day of calcium. We obtained annual lateral spine radiographs and semiannual forearm bone density over 4.3 ± 1.1 years and determined vertebral fractures by radiographic morphometry augmented by physician assessment. In the PF group, 15 of 53 subjects on calcium had incident fractures, compared with 21 of 41 on placebo ($p = 0.023$, χ^2). Calcium did not reduce the rate of incident fractures in the NPF group. Those with a prevalent fracture on entry and not treated with calcium were 2.8 times more likely to experience an incident fracture than all others. Change in the forearm bone mass on placebo in the PF group was −1.24 ± 2.41%/year compared with +0.31 ± 1.80%/year on calcium ($p < 0.001$). In the NPF group, the difference was less: −0.39 ± 2.08%/year versus 0.00 ± 1.64%/year ($p = 0.2$). We conclude that in elderly postmenopausal women with spine fractures and selfselected calcium intakes of <1 g/day, a calcium supplement of 1.2 g/day reduces the incidence of spine fractures and halts measurable bone loss. (J Bone Miner Res 1996; 11:1961–1966)

INTRODUCTION

CALCIUM INTAKE is an important determinant of bone health.[1–8] All postmenopausal calcium intervention studies reported since 1988 in which the investigator controlled the calcium intake of a test group and excluded women within 5 years of menopause have demonstrated a bone sparing effect by serial measurement of bone mass.[1] Nevertheless, self-chosen calcium intakes remain generally below recommended levels[9] for women of all ages, and physicians seem to regard increasing calcium intake as a minor modality in the management of the bone health of elderly women.

We report here the spine antifracture and bone-sparing efficacy results of a calcium intervention trial between two groups of elderly women, those with and without pre-existing spine fractures, who had low self-chosen calcium intakes and were fully ambulatory and living independently.

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MATERIALS AND METHODS

Subjects

The subjects were healthy white women volunteers of European ancestry, aged 73.5 ± 7.1 years, who were ambulatory and living independently. The study was approved by the Creighton University Institutional Review Board. All subjects gave informed consent. Recruitment began in November 1987, and ended in January 1990. Fifty-five study sites, most of which were government-sponsored meal sites established for the elderly, were used. About 75% of the subjects lived in rural communities, and 25% lived in Omaha. Enrollment was limited to healthy postmenopausal women over age 60 whose usual calcium intakes were estimated to be <1 g/day. There was no upper age limit.

Osteoporosis Research Center, The Department of Medicine, Creighton University, School of Medicine, Omaha, Nebraska, U.S.A.

We designed the study to evaluate spine fracture incidence and forearm bone mass changes in two groups; those with prevalent spine fractures (PF) and those without prevalent fractures (NPF) on entry. Subjects with other diagnoses or with treatments known to affect the skeleton were excluded. However, there was a wide variety of mild chronic illness in members of the study population, precisely the universe of people affected most by osteoporosis. Of 750 candidates screened for entry, 251 were entered. About half of the 499 who were screened but not enrolled were rejected because calcium intake levels were above 1 g/day (see below). The other half chose not to enroll when the details of the protocol were explained. No baseline bone density or spine fracture data were obtained from the 499 who were not enrolled. Of the 251 subjects who were entered, 54 were excluded from analysis because they underwent less than 1 year of observation. Forty-seven withdrew after screening before any serial data were obtained, and seven remained on the study for less than a year. They yielded few serial bone density data and no fracture data. Because of the small amount of treatment data and the short term of treatment, all 54 were simply considered to be in the same category as those who declined to participate after screening. Of the 197 who were entered into the analysis, there were 12 deaths after 1–3.5 years of observation and 6 who moved out of the area after 1–4.5 years of observation.

Protocol

This was a prospective, randomized, double-blind, placebo-controlled trial. As predicted from previous data, (L.J. Melton, personal communication)[10] the PF and NPF groups were of nearly equal size, at $n = 94$ and 103, respectively. For logistical reasons, it was not practical to randomize treatment according to prevalent fracture status. The subjects were thus randomized without regard to prevalent fracture status to receive either calcium carbonate tablets (Caltrate, Lederle Laboratories, Wayne NJ, U.S.A.) or identical appearing placebo, twice daily with each of two meals. The calcium tablets each contained 600 mg of calcium. The treatment code was not broken until all the experimental data were obtained.

Each study site was visited at intervals of 6 months. Visits were made with a customized van equipped with an X-ray unit, film processor, and a single photon absorptiometer (SPA) (Model 2780, Norland Corporation, Fort Atkinson, WI, U.S.A.). At each visit, interim history was obtained, pills were dispensed, and bone density was measured. Lateral spine radiographs were obtained at intervals of 1 year. Compliance was expressed as the percentage of pills prescribed that were not returned on a subsequent visit. Lateral thoracic and lumbar spine films were taken in the upright position inside the mobile unit under standardized conditions with a tube-to-film distance of 40 in.

Vertebral morphometry

Quantitative classification, prevalent fractures: Vertebral morphometry was performed on each film according to methods previously described in our laboratory.[11,12] Vertebral deformity or fracture was defined morphometrically as vertebral heights >2.5 and >4 standard deviations (SD) below the reference population mean, for wedge and compression deformities, respectively. A vertebra was called deformed if either or both of these criteria were met. These values are the empirically determined thresholds of detection of vertebral deformity by an experienced clinician.[11–13]

Qualitative classification, prevalent fractures: After completion of the morphometric measurements, the films of each individual were reviewed as a group by a clinician (R.R.R.), and all vertebrae were scrutinized. Positive and negative calls of prevalent fracture by the algorithm were judged against the clinician's assessment, which was taken as the standard.

Quantitative classification, incident fractures: Incident deformities of vertebrae were defined morphometrically as >20% reduction in anterior or posterior height relative to earlier measured values.[14,15]

Qualitative classification, incident fractures: During the review of the entire set of films of each subject, after completion of the morphometric measurements, the clinician (R.R.R.) also scrutinized all vertebrae for incident fractures. Positive and negative calls of incident fractures by the algorithm were judged against the clinician's assessment, which was again taken as the standard.

All the morphometric and clinician evaluations were performed before the blind was broken. The final decision on all prevalent and incident fractures was made by the clinician during visualization of the films, with the morphometric results available at the time of the evaluation. Since the quantitative algorithms seemed to overdiagnose both prevalent and incident vertebral deformity, the more conservative results obtained by the clinician's reading of the films were used in the analysis. This approach, combining morphometry with confirmation by a trained expert, has been recommended by an expert panel[14,15] as an acceptable method of eliminating false positives and false negatives produced by radiographic morphometry.

Single photon absorptiometry

Bone mass was measured by ^{125}I-based SPA, expressing bone mineral content (BMC, g) measured at a site on the radius one-third the distance from the styloid to the olecranon. Precision was 2.0%. Since we were interested in within-person changes and had no need to minimize inter-individual variation, and since BMC is a more precise measure than BMC/BW with this instrument, we report here only BMC.

A value for the annual rate of bone loss for each subject was derived from densitometry measurements as follows. The complete set of values from each subject was averaged, and each individual measurement was expressed as a fraction of the subject's mean. A slope was calculated for each subject with the resulting normalized BMC as the dependent variable and the time of observation as the independent variable. Change was then expressed as a rate.

TABLE 1. BASELINE COMPARISON

	Prevalent fracture group				*Nonprevalent fracture group*			
	Calcium (n = 51)		*Placebo (n = 41)*		*Calcium (n = 40)*		*Placebo (n = 59)*	
	mean	*SD*	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*
Age	75.4	7.3	74.2	6.9	72.8	6.1	72.1	7.5
BMC (g)*	0.706	0.118	0.694	0.126	0.724	0.151	0.783	0.150
Calcium intake (mg/day)	451	179	447	196	386	218	442	184

* Six subjects did not have baseline BMC measurements, thus differing from *n* for fractures (see Table 3). SD, standard deviation.

Dietary calcium intake

An estimate of calcium intake from food, medication, and supplements was made for each person prior to entry by an abbreviated questionnaire[9] administered by the research nurse in charge of the project (S.H.). Candidates were invited to volunteer for the study only if calcium intake was estimated to be <1 g/day. Whenever there was uncertainty about the validity of a given response, volunteers were instructed to keep a diary of all food and liquid intake over a 7-day period. The completed diaries and questionnaires were analyzed by a dietitian using Nutripractor software (Practorcare, San Diego, CA, U.S.A.).

Serum 25 hydroxyvitamin D

Blood specimens were obtained from a randomly chosen subset of 38 members of the cohort at the beginning of observation, at the end of 2 years, and again at the end of the study. The serum 25 hydroxyvitamin D (25OHD) concentration was measured by a competitive binding assay kit (Nichols Institute Diagnostics, San Juan Capistrano, CA, U.S.A.). The sensitivity of this assay is 2.2 ng/ml.

Statistics

The study was designed in advance to permit independent analysis of the PF and NPF groups. We analyzed incident fracture and bone density changes in the PF and NPF groups by "intention-to-treat." The difference in the numbers of subjects with incident vertebral deformities between treated and untreated subjects in the PF and NPF groups was tested by the Chi square with Yates' correction.

Then, to examine the relative contributions of the variables (prevalent deformity, initial bone mass, and treatment) to vertebral fracture incidence, we used the Cox proportional hazards regression model for both univariate and multivariate survival analysis in the entire cohort. Model determination was made according to the methods described by Kleinbaum, Kupper, and Morgenstern.[16] The assumptions for the use of this survival analysis were met, as determined by the Kaplan-Meier method of comparison of survival curves. Each vertebral fracture was estimated to have occurred half way between the date of the visit at which the incident fracture was visualized and the previous visit. Hazard ratios were calculated from the beta coefficients derived from the Cox proportional hazards regression model and were calculated for each standard deviation decrement of the variable.[17] These analyses were computed using the Statistical Analysis System (SAS, Cary, NC, U.S.A.) procedures LIFETEST and PHREG.[18] Differences in the rates of change in bone mass between treated and untreated subjects in the PF and NPF groups were compared by *t*-tests of means.

RESULTS

Baseline characteristics of study population

Table 1 presents a summary of several pertinent variables at entry into the study. The four subgroups, (1) prevalent fracture-calcium (PF-calcium), (2) prevalent fracture-placebo (PF-placebo), (3) nonprevalent fracture-calcium (NPF-calcium), and (4) nonprevalent fracture-placebo (NPF-placebo), were similar in age and customary calcium intake. Of the 94 PF subjects, 53 had one prevalent fracture, 26 had two, 11 had three, and 4 had more than three. As expected,[19] the baseline BMC was significantly greater in the NPF group than in the PF group ($0.760 \pm 0.152, n = 99$, vs. 0.701 ± 0.120, $n = 92$; $p < 0.002$). Serum 25OHD, measured on a subset of 38 individuals, was 62.5 ± 15 and 65.0 ± 22.5 nmol/ml, respectively, in the calcium and placebo-treated subjects (NS).

Incidence of spine fracture

During the 4.3 ± 1.1 years of observation, 36 persons in the PF group ($n = 94$) had 86 incident vertebral deformities. Sixty-two involved previously normal vertebrae, and 24 involved 18 previously deformed vertebrae. In the NPF group ($n = 103$), 25 persons had 59 incident vertebral deformities. Fifty-two involved previously normal vertebrae, and seven involved six previously deformed vertebrae. The number of persons with and without incident fractures in each of the four subgroups is shown in Table 2. In the PF group, calcium supplementation significantly reduced the rate of incident fractures ($p = 0.023$). In the NPF group, calcium supplementation did not affect the rate of incident

TABLE 2. EFFECT OF CALCIUM SUPPLEMENT ON INCIDENT FRACTURES*

	Prevalent Fracture Group (P = 0.023)†			*Nonprevalent Fracture Group (P = 0.435)*		
Fracture Status	*Calcium*	*Placebo‡*	*Total*	*Calcium*	*Placebo*	*Total*
Incident fractures	15	21	36	12	13	25
No incident fractures	38	20	58	30	48	78
Totals	53	41	94	42	61	103

* The number in each cell represents the number of subjects.
† Prevalent calcium vs. prevalent placebo (χ^2).
‡ $p = 0.002$ (χ^2), prevalent fracture-placebo vs. nonprevalent fracture-placebo.

TABLE 3. ESTIMATED HAZARD RATIOS OF INCIDENT VERTEBRAL FRACTURES

Variable	*Hazard ratio*	*95% confidence intervals*
Univariate analysis		
Prevalent fracture	1.9	1.14–3.18
Initial BMC*	1.43	1.10–1.87
Treatment effect	1.23	0.74–2.04
Multivariate analysis†		
Nontreatment × prevalent fracture (unadjusted)	2.8	1.64–4.76
Nontreatment × prevalent fracture (adjusted for initial BMC)	2.45	1.42–4.20

* Hazard ratio for each standard deviation decrement of BMC.
† First-order interaction model included the variables: nontreatment, prevalent fracture, and treatment × prevalent fracture.

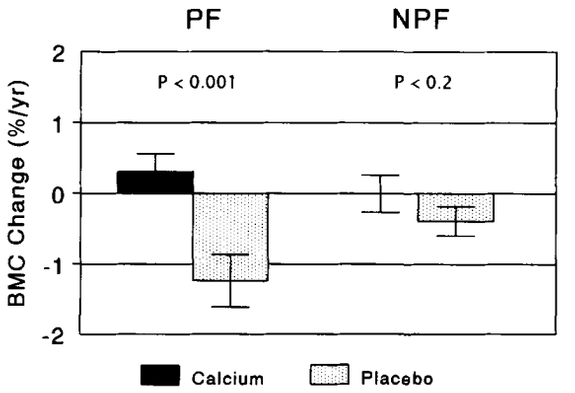

FIG. 1. Treatment effects on rates of change (mean ± SEM, %/year) in forearm bone mass. The treatment effect was significant in the PF group (0.31 ± 0.25 vs. −1.24 ± 0.38, $p < 0.001$) but not in the NPF group (0.00 ± 0.26 vs. −0.39 ± 0.27, $p < 0.2$). Among placebo-treated subjects, the rate of bone loss was greater in the PF group than in the NPF group (−1.24 ± 0.38 vs. −0.39 ± 0.27, $p = 0.03$). The rate of bone loss in the PF-placebo group was different from zero ($p < 0.01$), while that in the NPF-placebo group was marginally significant ($p < 0.1$).

fractures ($p = 0.435$). Incident fracture was greater in the PF-placebo group than in the NPF-placebo group (51% in PF vs. 21% in NPF; $p = 0.002$, χ^2).

Contribution of prevalent fracture status, initial BMC, and calcium supplementation to incident fracture (Cox proportional hazards model)

Table 3 shows the univariate and multivariate Cox proportional hazards regression analyses. Three components to the risk of incident vertebral fracture were tested: prevalent fracture, initial BMC, and treatment effect. Subjects with prevalent fracture were 1.9 times more likely to experience incident fracture than those without prevalent fracture (95% confidence interval [CI], 1.14–3.18). For each standard deviation decrement of initial BMC, the risk of incident fracture was increased by 1.43 (95% CI, 1.10–1.87). Though treatment itself was not associated with incident vertebral fracture, the first-order interaction model showed a strong interaction of treatment and prevalent fracture. Subjects in the PF-placebo group were 2.8 times more likely to experience incident fracture than all others (95% CI, 1.64–4.76). Adjustment for initial BMC accounted for a minor amount of the risk of incident fracture, reducing the hazard ratio from 2.8 to 2.45.

Change in forearm bone mass

Figure 1 presents the data for change in forearm bone mass. Two subjects in the PF group and four subjects in the NPF group did not have initial BMC measurements because of technical problems and are not included either here or in Tables 1 and 3. The PF-placebo group was losing bone at a substantially greater rate than the NPF-placebo group (−1.24 ± 0.38 vs. −0.39 ± 0.27; $p = 0.03$). In both groups, calcium supplementation completely abolished loss. The difference was highly significant for the PF group ($p < 0.001$), and not significant for the NPF group ($p < 0.2$), likely because the untreated loss rate was much less and the treatment-induced difference correspondingly smaller.

Compliance and side effects

Median compliance was 64%, but the distribution was bimodal, with 5% of each group refusing to accept pills *after* they had agreed to the study and been entered into the randomization. For the intention-to-treat analysis, they were retained in their respective groups.

Side effects were minor, although eight subjects complained of constipation, seven in the treatment group and one in the placebo group. In none of the subjects did the constipation result in dropping out of the study, and in all cases the constipation was managed by diet or stool softeners. No instances of urolithiasis occurred.

DISCUSSION

Our study showed that supplemental calcium in a group of elderly women with low self-selected calcium intakes reduces the risk of incident spine fractures in those who already have them and halts measurable bone loss for at least 4 years. This effect was evident despite a median compliance rate of only 64%.

The majority of U.S. women of all ages have calcium intakes that are below the 1989 RDA[20] and far below the recent recommendations of the Optimal Calcium Intake Consensus Conference.[21] We enrolled only women whose self-selected calcium intakes were <1 g/day; mean intakes at baseline for all four of our subgroups were <500 mg/day. This selection criterion was intended to enrich all four subgroups with persons having nutritional calcium deficiency, thus offering a better chance to demonstrate a calcium effect. The data of this study thus add to the body of evidence demonstrating that suboptimal calcium nutrition contributes to the increasing vertebral fracture burden of aging women.[8,22,23]

We observed antifracture efficacy of calcium only in the PF group. The likely reason is that the PF group itself concentrated individuals with nutritional calcium deficiency. This is suggested by the greater rate of loss of forearm BMC and the greater effect of calcium supplementation on BMC loss in this group. Also, initial bone mass in the PF group was less than that in the NPF group. The positive response to calcium supplementation observed in this study, as in most studies of calcium supplementation, will tend to be dominated by those members of a treatment group who have nutritional calcium deficiency. There is no test for such deficiency beyond a response to calcium. Concentration of such individuals in the PF group is therefore not surprising. Our subjects were already at the age when fractures typically occur. Those with two risk factors (age-related loss and calcium deficiency) would be expected to exhibit more fractures than those who have only one.

While we used calcium carbonate, we believe that the results of this study can be generalized to nearly any form of calcium, including food calcium, since nearly all are equally bioavailable[24] if taken with meals.[25,26] Also, because low calcium intake is a marker for several dietary deficiencies,[27] and because calcium supplements may aggravate certain of them,[28] food sources of calcium are preferable to supplements to the extent that it is possible or practical to achieve recommended intakes of 1500 mg/day.

These data provide the clinician with evidence that the presence of pre-existing spine fractures is a marker that identifies older patients who will benefit most by increased calcium intake. In such patients, calcium supplementation produces both a decline in incidence of vertebral deformity and a slower rate of bone loss. Elderly women without vertebral deformity also benefit by experiencing a mild slowing in the rate of bone loss. Thus, one should not wait until fracture occurs in an elderly woman to begin calcium prophylaxis, because an increase in calcium intake to a level at or above the NIH recommendations benefits all.

The failure to observe antifracture efficacy of calcium in the NPF group was probably related both to their lower rate of incident fractures, significantly less than in the PF group ($p = 0.023$), and to the concentration of the calcium-dependent subjects in the PF group (see above). Given the number of subjects in the NPF group, in order to have observed a significant calcium effect on fracture incidence, a 77% reduction in the number of individuals with incident fractures would have been required. No existing treatment for osteoporosis produces such a marked antifracture effect. Thus, the data from our NPF group are useful in planning antifracture efficacy studies. They demonstrate in a real world setting the impact on the statistical power to detect treatment effects in NPF individuals compared with PF individuals because of their lower incidence of fractures. Since about two-thirds of elderly women are represented by the NPF group,[10] we suggest that a properly powered study of the effect of calcium supplementation on incident vertebral deformity in elderly women without prevalent fractures is needed.

At entry, vertebral fractures were already present in 48% of our subjects. This value is only slightly higher than the smoothed prevalence value (38%) among Olmstead County women over age 60.[10] Our population was older than the Olmstead County group, 68% being over age 70. The prevalence of vertebral fracture in women over age 70 in Olmstead County was 42%. Furthermore, unlike the Olmstead County study, our subjects were chosen for low calcium intake, something that is potentially associated with higher prevalent vertebral fracture. Thus, making allowance for somewhat different age distributions and our restrictive calcium intake selection criteria, our fracture prevalence value was compatible with existing data from Olmstead county.[10]

The presence of vertebral fractures is a powerful marker for increased risk of incident vertebral fracture.[29] Our data show that prevalent fracture is such a powerful marker predisposing to incident fracture (Cox Hazard ratio 1.9) that its presence might overwhelm a treatment effect. We suggest that osteoporosis treatment trials involving elderly women take into account their prevalent fracture status at study onset.

The bone sparing and antifracture efficacy of supplemental calcium demonstrated here may rival that demonstrated for some of the currently approved prescription-only agents that are used in the treatment of established osteoporosis.[30,31] Thus, in osteoporosis treatment trials that com-

pare "agent" to "control" when the control group has received calcium supplementation, the failure to demonstrate a difference is not necessarily to be taken as "no effect" of the treatment agent.

In summary, our study showed that calcium supplementation of a group of elderly women with low selfselected calcium intake not only reduces the risk of incident spine fractures in those who already have them, but also halts measurable bone loss.

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Address reprint requests to:
Robert R. Recker, M.D.
601 North 30th Street
Omaha, NE 68131, U.S.A.

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