Effects of Calcium Supplementation on Clinical Fracture and Bone Structure

Results of a 5-Year, Double-blind, Placebo-Controlled Trial in Elderly Women

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Background: Increased dietary calcium intake has been proposed as a population-based public health intervention to prevent osteoporotic fractures. We have examined whether calcium supplementation decreases clinical fracture risk in elderly women and its mechanism of action.

Methods: Five-year, double-blind, placebo-controlled study of 1460 women recruited from the population and older than 70 years (mean age, 75 years) who were randomized to receive calcium carbonate, 600 mg twice per day, or identical placebo. The primary end points included clinical incident osteoporotic fractures, vertebral deformity, and adverse events ascertained in 5 years. Bone structure was also measured using dual x-ray absorptiometry of the hip and whole body, quantitative ultrasonography of the heel, and peripheral quantitative computed tomography of the distal radius.

Results: Among our patients, 16.1% sustained 1 or more clinical osteoporotic fractures. In the intention-to-treat analysis, calcium supplementation did not significantly reduce fracture risk (hazard ratio, 0.87; 95% confidence interval, 0.67-1.12). However, 830 patients (56.8%) who took 80% or more of their tablets (calcium or placebo) per year had reduced fracture incidence in the calcium compared with the placebo groups (10.2% vs 15.4%; hazard ratio, 0.66; 95% confidence interval, 0.45-0.97). Calcium-treated patients had improved quantitative ultrasonography findings of the heel, femoral neck and whole-body dual x-ray absorptiometry data, and bone strength compared with placebo-treated patients. Of the 92 000 adverse events recorded, constipation was the only event increased by the treatment (calcium group, 13.4%; placebo group, 9.1%).

Conclusion: Supplementation with calcium carbonate tablets supplying 1200 mg/d is ineffective as a public health intervention in preventing clinical fractures in the ambulatory elderly population owing to poor long-term compliance, but it is effective in those patients who are compliant.

Arch Intern Med. 2006;166:869-875

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RECENT CLINICAL, ANIMAL, and cell studies have confirmed that an important physiological effect of estrogen is increased calcium transport across the bowel wall and kidney tubule.[1,2] Thus, the reduction in circulating estrogen concentration after menopause results in a small daily negative calcium balance.[3] This negative calcium balance can be partly corrected by increasing dietary calcium intake as demonstrated by the beneficial effects of calcium supplementation on bone density in postmenopausal women.[3-7] The unresolved critical issue for patient care is whether the effect size is sufficient to reduce clinical fracture rates.

Reducing the population risk of fracture is likely to require a public health intervention for all in addition to treatment of high-risk individuals with pharmaceutical intervention.[8] Therefore, the current study was planned as a study of calcium supplementation in a relatively healthy, vitamin D–sufficient, and ambulatory elderly population in which the whole population rather than those with low bone mass were studied. The study also examines the biochemical and structural effects of calcium supplementation to provide an understanding of the mechanism of the effect on fracture reduction.

METHODS

PATIENTS

We recruited 1460 women during 1 year using a population-based approach in which a random selection of women (n=24 800) older than 70 years on the electoral roll in Western Australia received a letter inviting them to join the study. Of these, 4312 individuals responded and were contacted by telephone (**Figure 1**). More than 98% of women of this age are on the electoral roll (n=33 366). Although the patients entering the study were weighted in favor of those in higher socioeconomic categories, disease bur-

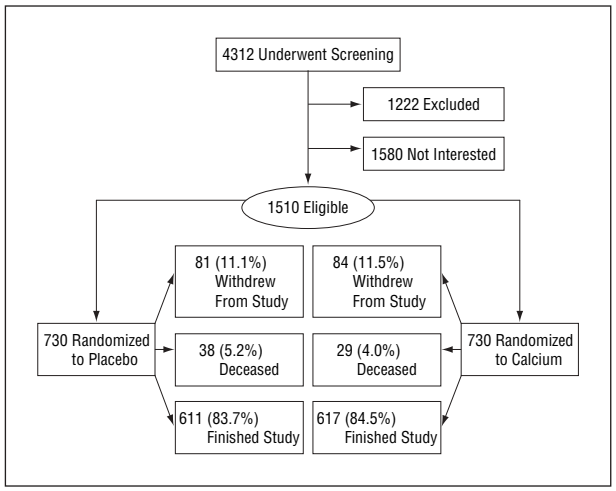

Figure 1. Details of the recruitment procedure. Finished study indicates the number of people in the placebo and calcium groups who remained in the study for the entire 60 months.

den and pharmaceutical consumption were similar to data obtained from whole populations of this age.[9] Informed consent was obtained, and the Human Rights Committee of the University of Western Australia, Perth, Australia, approved the study.

BASELINE DEMOGRAPHICS

A prevalent fracture was recorded if it occurred after the age of 50 years, was due to minimal trauma as defined by falling from a height of less than 1 m, and was not of the face, skull, or phalanges (**Table 1**). The number of years since menopause was calculated for each patient using reported age at last menstrual period, hysterectomy and ovariectomy, or onset of hot flushes. A positive smoking history was reported if at least 1 cigarette per day had been smoked for 3 months or longer at any time. Daily intake of protein, calcium, and alcohol was determined from a self-administered semiquantitative food frequency questionnaire.[10,11]

CLINICAL MEASUREMENTS

Grip strength of the dominant hand was recorded as the highest of 3 attempts[12] using a handheld dynamometer (Hand Grip Dynamometer; TEC, Clifton, NJ). Body mass index was calculated as weight in kilograms divided by the square of height in meters.

Activity levels were calculated in kilocalories per day using a validated method[13] that combines body weight, answers to questions on the number of hours and type of physical activity, and energy costs of such activities,[14,15] with a response of no to the activity questions resulting in a 0 score.

Mobility functioning was measured by the timed Up & Go test, which required that patients be timed while getting up, walking 3 m, turning, returning to the chair, and sitting down again.[16] Results of the standing Rhomberg Balance Test[17] were classified as to whether the patient was able to maintain a tandem stance for at least 10 seconds.

BONE MEASUREMENTS

Calcaneal quantitative ultrasonography (QUS) measurements of the left foot were obtained using an ultrasound densitometer (Lunar Achilles; GE Lunar Corp, Madison, Wis) at baseline and 5 years; the coefficients of variation (CV) for speed of sound and broadband ultrasound attenuation were 0.43% and 1.59%, respectively. Dual x-ray absorptiometry (DXA) bone density was measured at the hip and whole body on a fan-beam densitometer (Hologic Acclaim 4500A; Hologic Corp, Waltham, Mass) at 1 and 5 years. The CVs at the total hip, femoral neck, and whole body were 1.2%, 1.4%, and 0.8%, respectively.[18] Peripheral quantitative computed tomography bone structure and density were measured in the radius at a site 4% of the length of the radius distal to the wrist joint, using a peripheral quantitative computed tomography device (XCT-2000; StraTec Medizintechnik GmbH, Pforzheim, Germany). The voxel size was set at 150 μm in the x and y directions and 1000 μm in the z direction. The CVs for trabecular and cortical bone mineral density were 4.0% and 8.0%, respectively. The cross-sectional area of cortical bone was measured using a threshold of periosteal and endosteal bone density of 710 and 169 mg/cm^3, respectively. The Stress Strain Index was calculated as the product of the section modulus and cortical density normalized to the maximal physiological cortical density of human bones (1200 mg/cm^3) for the polar moment and the bending moments in the x and y directions, where the y direction is the widest part of the radius and the x direction is perpendicular to this.[19]

BIOCHEMICAL MEASUREMENTS

Serum intact parathyroid hormone (PTH) level was measured using an immunochemiluminometric method with intra-assay and interassay CVs of 3.6% and 6.2%, respectively.[20] Total serum 25-hydroxyvitamin D level was measured using an extraction technique, followed by a competitive binding assay using diluted human serum that measures 25-hydroxycholecalciferol and ergocalciferol levels equally. Intra-assay and interassay CVs were 8% and 16%, respectively.[21]

RANDOMIZATION TO STUDY TREATMENT AND COMPLIANCE

Patients received calcium carbonate tablets, 600 mg twice per day (with morning and evening meals), or identical placebo tablets (Wyeth Consumer Healthcare, Baulkham Hills, Australia). The randomization list was produced by generating 150 blocks of 10 numbers. In each block, 5 positions representing placebo and 5 positions representing calcium treatment were ordered using a letter code according to a random number generator. The numbered blocks were ordered according to randomly generated numbers, and an identification number was assigned in order to each letter code in the randomized list. The Pharmacy Department of the Sir Charles Gairdner Hospital, Nedlands, Australia, assigned a treatment to the letter code and assigned the appropriate medications to the patient according to this list. The randomization was stratified by allocating patients to blocks according to whether a prevalent nontraumatic fracture had occurred after age 50 years, ensuring that an equal number of patients with and without a prevalent fracture received placebo or calcium. Medication compliance was checked by counting returned tablets at each 12-month review and was calculated as a percentage of the optimum. Average yearly compliance of less than 80% was classified as noncompliant.

INCIDENT FRACTURES AND ADVERSE EVENTS

Adverse events resulting in attendance to a health care professional were recorded in a diary at 4-month intervals and coded using the International Classification of Primary Care, Version 2-Plus, system database of disease coding (Family Medicine Research Unit, Department of General Practice, University of Sydney, Sydney, Australia). Adverse events were grouped according to 17 categories identified by the International Classification of Primary Care, Version 2-Plus, system.[22] Atrau-

Table 1. Baseline Details of the Subjects by Compliance and Treatment*

Characteristic	Patients Compliant With Medication Regimen by Treatment		Patients Noncompliant With Medication Regimen by Treatment		*P* Value Between Compliance Groups
	Placebo	Calcium	Placebo	Calcium	
Demographic Data					
No. of subjects	410	420	320	310	
Age, y	75.1 ± 2.7	74.9 ± 2.5	75.2 ± 2.8	75.6 ± 2.9	.006
Time since menopause, mean (range), y	26 (23-31)	26 (22-29)	26 (23-31)	27 (24-29)	.02
Weight, kg	68.7 ± 12.2	68.7 ± 12.1	68.8 ± 12.5	68.4 ± 14.0	.43
Height, cm	158.7 ± 6.0	159.1 ± 5.8	158.2 ± 6.0	159.3 ± 6.0	.95
Prevalent fractures since age 50 y, %†	25.2	26.2	31.6	27.7	.09
Smoked ever, %‡	34.2	36.1	37.2	42.2	.09
Recreational activity, %	75	76	73	76	.57
Timed Up & Go test, s	9.6 ± 2.6	9.7 ± 2.3	10.5 ± 3.7	10.7 ± 3.5	.001
Grip strength, kg	20.8 ± 4.5	20.6 ± 4.7	20.0 ± 4.7	20.0 ± 4.7	.002
Passed Rhomberg Balance Test, %	76.6	74.3	70.8	69.8	.006
Food Frequency Analysis					
No. of subjects	390	400	302	293	
Protein intake, mean (interquartile range), g/d	76 (60-94)	78 (62-97)	76 (77-93)	77 (76-95)	.10
Calcium intake, mean (interquartile range), mg/d	897 (704-1146)	915 (711-1196)	950 (761-1173)	903 (685-1146)	.46
Alcohol consumption, %§	19	22	27	19	.31
Heel QUS					
No. of subjects	394	407	304	296	
BUA, dB/MHz	100.5 ± 8.2	101.1 ± 7.9	99.6 ± 8.1	100.3 ± 7.5	.046
SOS, m/s	1514 ± 26	1515 ± 24	1510 ± 27	1511 ± 26	.004
Heel QUS stiffness, % of that of young adult	70.8 ± 11.7	71.6 ± 11.0	69.2 ± 11.7	69.9 ± 11.2	.007
Hip DXA BMD‖					
No. of subjects	361	352	198	188	
Total hip BMD, mg/cm^2	817 ± 120	819 ± 123	813 ± 119	818 ± 122	.17
Femoral neck BMD, mg/cm^2	692 ± 98	695 ± 102	693 ± 114	680 ± 111	.29
Whole-Body BMD¶					
No. of subjects	120	98	44	46	
Whole-body BMD, mg/cm^2	866 ± 91	863 ± 102	861 ± 114	835 ± 80	.17

Abbreviations: BMD, bone mineral density; BUA, broadband ultrasound attenuation; DXA, dual x-ray absorptiometry; QUS, quantitative ultrasonography; SOS, speed of sound.

*Unless otherwise indicated, data are expressed as mean ± SD.

†Indicates percentage of the patients with 1 or more prevalent fracture after 50 years of age.

‡Indicates percentage of patients who reported smoking 1 cigarette per day for at least 3 months.

§Indicates more than 2 standard drinks/week.

‖Measured at 1 year.

¶Excludes the head.

matic incident clinical fractures and atraumatic symptomatic vertebral fractures were reported in the diary. The diagnosis and classification of vertebral and nonvertebral fractures were confirmed by radiographic reports.

Vertebral deformities were assessed using morphometric x-ray absorptiometry software on a densitometer (software version 9.1, Hologic 4500A; Hologic Corp) at years 1 and 5. The positions of 6 reference markers for each vertebra were placed at the corners and in the middle of the upper and lower surface of each vertebra. The mean CVs in morphometric x-ray absorptiometry measurements of the anterior, middle, and posterior heights of vertebrae varied from 5.8% at T6 to 3.1% at L4. Vertebral heights reference data and values for deformities were calculated according to a modification of the procedure described by McCloskey et al.[23] Incident vertebral deformities were defined as vertebral deformities not present at year 1, with a reduction in posterior, middle, or anterior heights of 20% or more.

STATISTICS AND POWER CALCULATIONS

Statistical procedures were performed with SPSSPC for Windows version 11.5 (SPSS, Inc, Chicago, Ill). The time to first clinical event was analyzed using the Cox proportional hazards model with and without adjustment for covariates. Differences between normally distributed characteristics of the treatment groups were determined by univariate analysis of variance with adjustments for covariates. The Mann-Whitney test was used to determine the differences between the groups for nonnormally distributed variables. All statistical tests were 2-tailed, and $P<.05$ was considered significant.

Power calculations were conducted before study commencement, assuming a fracture rate of 3.5% per year in the placebo group and assuming that calcium would reduce the event rate by 35%. At a power of at least 80%, at an α of .05, and allowing for a 30% noncompliance rate during the 5-year study, recruitment of 737 patients per group was required.

RESULTS

Patient recruitment for the study and their final categorization is shown in Figure 1. Of the 1222 women excluded, 977 (80.0%) were taking medications that could affect bone mass, 199 (16.3%) had medical conditions that

Table 2. Patients Sustaining 1 or More Incident Fractures or Vertebral Deformities During 60 Months at the Skeletal Sites Shown

Variable	No. (%) of Patients by Treatment		HR (95% CI)
	Placebo	Calcium	
All subjects (N = 1460)			
Upper limb	31 (4.2)	29 (4.0)	0.93 (0.56-1.54)
Wrist or hand	20 (2.7)	21 (2.9)	1.10 (0.60-2.02)
Rib or pelvis	17 (2.3)	17 (2.3)	0.99 (0.55-1.78)
Proximal femur	6 (0.8)	11 (1.5)	1.84 (0.68-4.96)
Lower limb	31 (4.2)	18 (2.5)	0.58 (0.32-1.03)
Any appendicular site	94 (12.9)	83 (11.4)	0.88 (0.65-1.18)
Spine	39 (5.3)	38 (5.2)	0.98 (0.63-1.54)
Any site	126 (17.3)	110 (15.1)	0.87 (0.67-1.12)
Vertebral deformity* (n = 883)	50 (11.1)	44 (10.2)	0.95† (0.78-1.17)
Compliant with medication (n = 830)			
Upper limb	22 (5.4)	10 (2.4)	0.44 (0.21-0.92)
Wrist or hand	12 (2.9)	10 (2.4)	0.81 (0.35-1.88)
Rib or pelvis	13 (3.2)	8 (1.9)	0.71 (0.33-1.55)
Proximal femur	3 (0.7)	5 (1.2)	1.64 (0.39-6.87)
Lower limb	18 (4.4)	10 (2.4)	0.54 (0.25-1.18)
Any appendicular site	58 (14.1)	39 (9.3)	0.65 (0.43-0.97)
Spine	8 (2.0)	9 (2.1)	1.10 (0.42-2.84)
Any site	63 (15.4)	43 (10.2)	0.66 (0.45-0.97)
Vertebral deformity* (n = 609)	32 (10.5)	22 (7.2)	0.83† (0.65-1.05)
Noncompliant with medication (n = 630)			
Upper limb	9 (2.8)	19 (6.1)	2.17 (0.98-4.80)
Wrist or hand	8 (2.5)	11 (3.5)	1.54 (0.63-3.78)
Rib or pelvis	4 (1.3)	9 (2.9)	1.59 (0.62-4.10)
Proximal femur	3 (0.9)	6 (1.9)	2.01 (0.50-8.05)
Lower limb	13 (4.1)	8 (2.6)	0.62 (0.26-1.49)
Any appendicular site	36 (11.3)	44 (14.2)	1.27 (0.82-1.98)
Spine	31 (9.7)	29 (9.4)	0.95 (0.58-1.59)
Any site	63 (19.7)	67 (21.6)	1.09 (0.77-1.54)
Vertebral deformity* (n = 97)	18 (12.4)	22 (17.1)	1.21† (0.84-1.73)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Indicates incident vertebral deformities assessed using morphometric x-ray absorptiometry at years 1 and 5.
†Expressed as relative risk.

made it unlikely they would survive the 5 years of the study, 44 (3.6%) were participating in another clinical trial, and 2 (0.2%) were not prepared to be assigned to the placebo. Another 1580 individuals were not interested. Therefore, 1510 women were eligible for the study, of whom the first 1460 were recruited. There were no differences in baseline demographic characteristics between the placebo and calcium groups. In a randomly selected subset of patients (n=81), 25-hydroxyvitamin D levels were generally above the deficient range because only 6.1% (during winter) and 2.8% (during summer) of patients had vitamin D concentrations below 12 ng/mL (<30 nmol/L) (mean±SD winter level, 27±14 ng/mL [67±35 nmol/L]; mean±SD summer level, 35±12 ng/mL [87±30 nmol/L]). No PTH concentrations were above the upper limit of the reference range (mean±SD winter level, 37±11 pg/mL; mean±SD summer level, 37±11 pg/mL; n=81).

The risks of withdrawal and death were the same in the calcium group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.63 -1.16) compared with the placebo group (HR, 0.76; 95% CI, 0.47-1.23) (Figure 1). Eight hundred thirty patients (56.8%) complied with the medication regimen throughout the study, with no significant difference in compliance failure in the calcium group (310 patients) compared with the placebo group (320 patients) (χ^2=0.28; P=.60). Compared with compliant patients, noncompliant persons were slightly older, weaker, and slower and had lower QUS measures (Table 1), but there were no differences related to the original randomization to calcium or placebo.

INCIDENT FRACTURE

Table 2 and **Figure 2** show the fracture outcomes. A total of 236 individuals (16.2%) sustained 297 incident osteoporotic fractures. The intention-to-treat analysis did not demonstrate an effect of calcium to reduce fracture risk, recorded as time to first fracture at any site (HR, 0.87; 95% CI, 0.67-1.12), time to first fracture of the appendicular skeleton (HR, 0.88; 95% CI, 0.65-1.18), time to first vertebral fracture (HR, 0.98; 95% CI, 0.63-1.54), or incident morphometric x-ray absorptiometry vertebral deformity.

A preplanned per protocol analysis restricted to the 830 patients (56.8%) who consumed 80% of tablets (Figure 2 and Table 2) demonstrated a reduction in all-site clinical fractures (HR, 0.66; 95% CI, 0.45-0.97), appendicular fractures (HR, 0.65; 95% CI, 0.43-0.97), and upper limb fractures (HR, 0.44; 95% CI, 0.21-0.92) in the calcium group before and after adjustment for age, body mass index, and prevalent baseline fracture entered as covariates. Baseline dietary calcium intake did not influence any of the HRs obtained. Although analysis of the baseline structural assessment of the skeleton using heel QUS (broadband ultrasound attenuation or speed of sound) adjusted for treatment status showed that individuals with higher measurements had reduced incident fracture risk (HR per 1-SD increase in speed of sound, 0.67; 95% CI, 0.58-0.77; HR per 1-SD increase in broadband ultrasound attenuation, 0.70; 95% CI 0.61-0.80), the addition of baseline QUS bone structural measures did not substantially alter any of the fracture HRs examined.

An analysis of fractures in the noncompliant population showed no difference in the number or type of fractures sustained between placebo- and calcium-treated patients.

BONE STRUCTURE AND BIOCHEMISTRY

There was no difference in any bone factors between calcium- and placebo-treated patients at baseline (QUS) and 1 year (DXA) (Table 1). The changes in bone structure are shown in **Figure 3**. The QUS measurements from baseline to 5 years, adjusted for body mass index, age, and tablet compliance, show significant improvement in calcium-treated patients for broadband ultrasound attenuation and stiffness, but not speed of sound. A reduction in the loss of bone content and area but not bone mineral density was seen at the femoral neck and whole-

body sites but not other hip sites, in the calcium-treated patients before and after adjustment for body mass index, age, and tablet compliance during the study. The cross-sectional radius peripheral quantitative computed tomography data measured at 5 years show a larger cortical volume in the calcium group compared with the placebo group, which had a favorable effect on the bone strength factors of the polar Stress Strain Index and Stress Strain Index in the x and y directions.

The PTH level decreased from baseline to year 5 (107 placebo- and 103 calcium-treated patients) in the calcium compared with the placebo group (mean ± SD change, –8.9±13.2 and –2.0±13.2 pg/mL, respectively; $P<.001$).

ADVERSE EVENTS

Of the 92 000 adverse events recorded, only constipation was higher in the calcium group (13.4%) compared with the placebo group (9.1%), with no difference between groups in the percentage of patients who stopped study medication therapy because of constipation. Two patients in each treatment group had kidney stones during the study. Incident ischemic heart disease was diagnosed in 56 patients (7.7%) in the calcium group and in 51 patients (7.0%) in the placebo group, with no difference in the relative risk for the calcium compared with placebo group (HR, 1.12; 95% CI, 0.77-1.64).

COMMENT

The patients recruited for the study were representative of non–vitamin D–deficient ambulatory women older than 70 years who have a 5-year risk of fracture greater than 15%. The principal finding was that randomization to a calcium supplement for 5 years failed to show a significant preventive effect on fracture, with results similar to those of a previous meta-analysis[24] of a number of small studies of appendicular fracture (relative risk, 0.86; 95% CI, 0.67-1.12) and a recently reported study[25] of patients with a previous fracture (HR, 0.94; 95% CI, 0.81-1.09). They are divergent from previous reports[26,27] of beneficial effects of combined calcium and cholecalciferol (vitamin D) treatment in patients who may have been vitamin D deficient and studies[28,29] showing a reduction in spine fracture with calcium supplementation in osteoporotic patients.

The lack of significance of calcium therapy in the intention-to-treat analysis is likely due to the lack of compliance with the medication regimen, which in the power calculation before commencement of the study was predicted to be 30%, but was in fact 43%. This is a limitation of the study but reflects the difficulties of implementation of preventive health practice in all such studies. Another possible cause for this relative lack of efficacy may be that the vitamin D status of the population, although substantially better than that encountered in studies in higher latitudes, may have been insufficient to allow optimal absorption and disposal of calcium to the skeleton.

In the per-protocol analysis of the 56.8% of patients who took 80% or more of their assigned medication, the risk of any clinical osteoporotic fracture was reduced by a factor of 0.34 (absolute risk reduction, 15.4%-10.2%). The maintenance of or improvement in QUS and DXA measures with calcium supplementation supports an effect to improve bone mass and possibly architecture. The peripheral quantitative computed tomography data showed that the effect of calcium was principally to maintain cortical bone in the endocortical area. At the radial site, it was possible to demonstrate an increase in cortical volume and therefore mass and calculated resistance to torsional and bending forces by calcium, an expected result of increased cortical bone mass. The lack of effect on trabecular bone density was surprising but may relate to a substantially damaged trabecular structure in these individuals or a site-specific effect of reduced bone resorption via effects on reducing the PTH level.[5] This was supported by

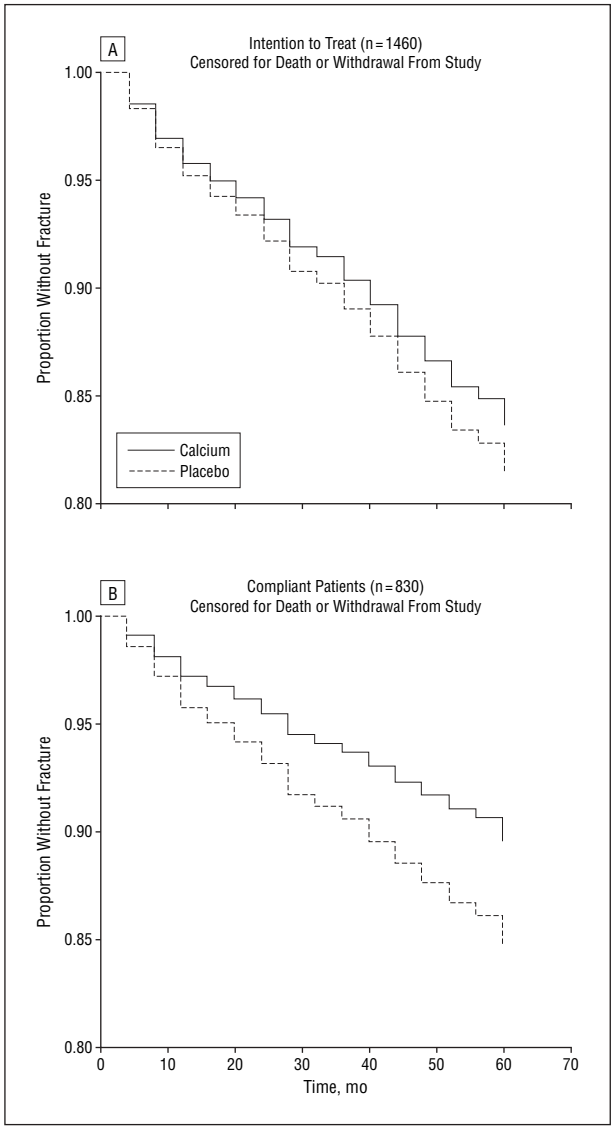

Figure 2. Cox proportional hazards analysis of the occurrence of the first incident fracture in patients taking calcium compared with patients taking the placebo. A, Intention-to-treat analysis, adjusting for tablet compliance (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.67-1.12). After further adjustment for body mass index (BMI), age, and prevalent fracture occurring after 50 years of age, the HR was 0.86 (95% CI, 0.67-1.11); after adjustment for calcium and tablet compliance interaction, the HR was 0.60 (95% CI, 0.30-1.01). B, Subset analysis of patients consuming 80% or more of tablets (HR, 0.66; 95% CI, 0.45-0.97). After adjustment for BMI, age, and prevalent fracture occurring after 50 years of age, the HR was 0.67 (95% CI, 0.45-0.99).

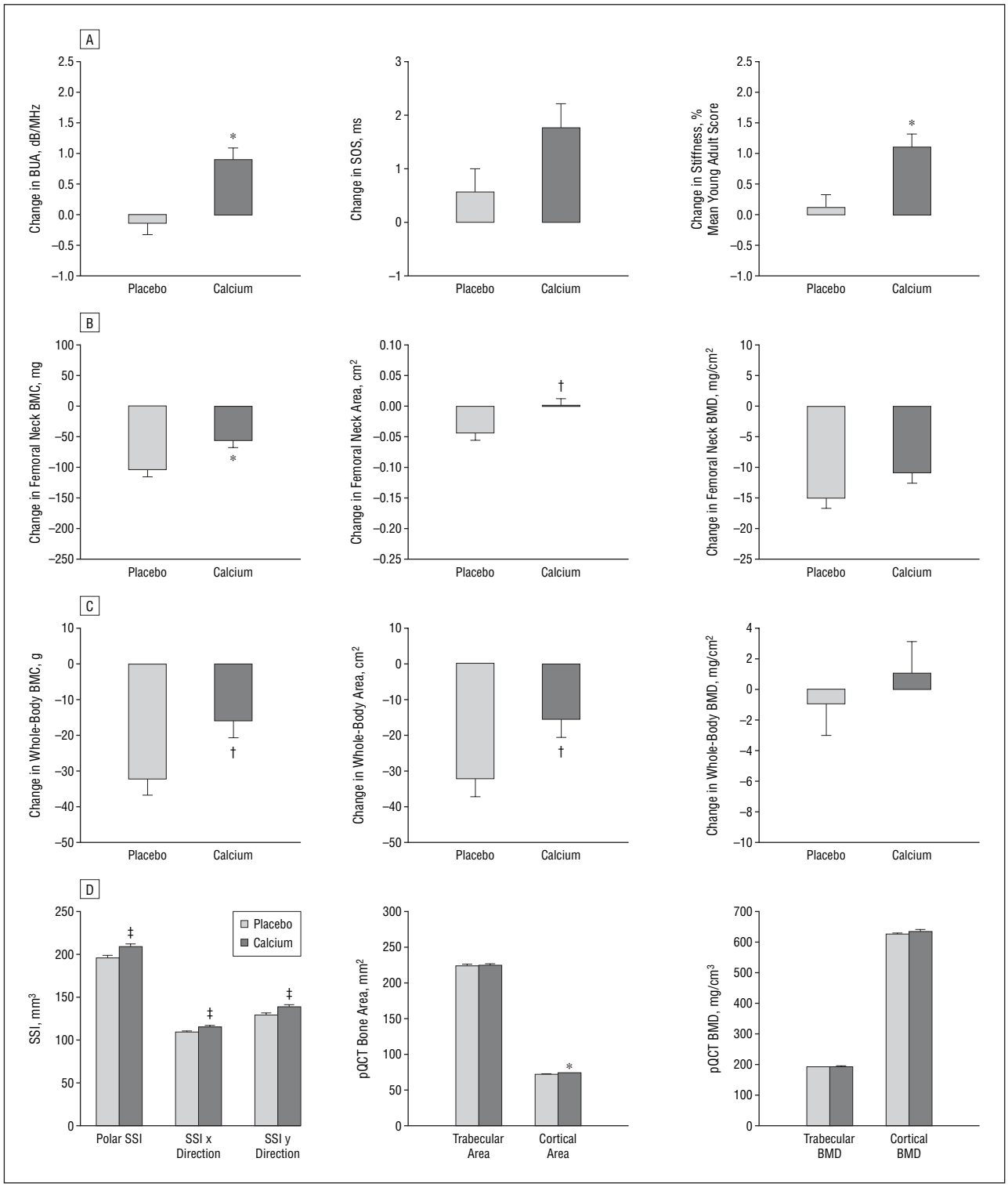

Figure 3. Effects of treatment on bone structural variables. Results are expressed as mean ± SEM after adjustment for baseline age, baseline body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), and tablet compliance. A, Change in quantitative ultrasonography (QUS) of the heel from baseline to year 5. B, Change in femoral neck bone mineral content (BMC), area, and bone mineral density (BMD) from years 1 to 5. C, Change in whole-body BMC, area, and BMD from years 1 to 5. D, Peripheral quantitative computed tomography (pQCT) findings of the distal forearm at year 5. Changes in QUS, BMD, and pQCT factors were adjusted to a mean age of 75 years, mean BMI of 27, and tablet compliance. BUA indicates broadband ultrasound attenuation; SOS, speed of sound; SSI, Stress Strain Index. *$P<.001$. †$P<.05$. ‡$P<.01$.

our biochemical data showing significant suppression of PTH with calcium supplementation.

In patients compliant with the medication regimen, baseline dietary calcium intake, baseline heel QUS, or 1-year hip DXA were not significant covariates in the fracture analysis. Thus, the effect of 1.2 g of calcium appears to be sufficiently large to be applicable to compliant individuals, irrespective of dietary calcium intake, with no signifi-

cant modifying effect of baseline bone structure. To date, studies of the effectiveness of pharmacologic agents other than hormone replacement therapy[30] in reducing fracture rates has been restricted to high-risk populations with low DXA bone mineral density.[31] When patients have not been selected on the basis of low DXA bone mass density, no hip fracture reduction has been found.[32]

The per-protocol analysis potentially violated the original randomization. Compared with compliant patients, noncompliant individuals were slightly older, weaker, and slower and had lower QUS measures, but these effects did not operate differentially in the 2 treatment groups. We also evaluated differences between treatment groups in fracture in the noncompliant patients in addition to the compliant patients. The analysis of fracture rates in the noncompliant patients showed no difference in risk of fracture related to treatment group, thus making it unlikely that patients had become noncompliant owing to treatment status.

Because it is important for a public health intervention to be safe, we conducted a careful evaluation of adverse events. Our evaluation showed that, although constipation increased with calcium treatment, the risk of kidney stones, ischemic heart disease, or other adverse events was not increased.

In conclusion, the calcium supplementation regimen tested currently cannot be recommended as a public health approach to fracture prevention because of the lack of long-term compliance. These data should give pause to those who consider that public health policy in this area should be based on epidemiological or surrogate endpoint data. However, these data support the continued use of calcium supplements by women who are able to remain compliant with their use. In these individuals, especially if they are under the care of a clinician, calcium supplementation is a safe and effective therapy for reducing the risk of osteoporotic fracture.

Accepted for Publication: September 11, 2005.
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Author Contributions: Drs Prince, Devine, and Dick had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: None.
Funding/Support: This study was supported by a research grant from the Healthway Health Promotion Foundation of Western Australia and by project grant 254627 from the National Health and Medical Research Council of Australia.
Disclaimer: Neither of the funding agencies had any input into any aspect of the design and management of this study.

REFERENCES

1. Prince RL. Counterpoint: estrogen effects on calcitropic hormones and calcium homeostasis. *Endocr Rev*. 1994;15:301-309.
2. Christakos S, Prince R. Estrogen, vitamin D, and calcium transport. *J Bone Miner Res*. 2003;18:1737-1739.
3. Nordin BEC. Calcium and osteoporosis. *Nutrition*. 1997;13:664-686.
4. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. *N Engl J Med*. 1991;325:1189-1195.
5. Prince R, Devine A, Dick I, et al. The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. *J Bone Miner Res*. 1995;10:1068-1075.
6. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med*. 1995;98:331-335.
7. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton J. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *J Bone Miner Res*. 1998;13:168-174.
8. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med*. 2004;164:1108-1112.
9. Bruce DG, Devine A, Prince RL. Recreational physical activity levels in healthy older women: the importance of fear of falling. *J Am Geriatr Soc*. 2002;50:84-89.
10. Ireland P, Jolley D, Giles G, et al. Development of the Melbourne FFQ. *Asia Pac J Clin Nutr*. 1994;1:19-31.
11. Hodge A, Patterson AJ, Brown WJ, Ireland P, Giles G. The Anti Cancer Council of Victoria FFQ. *Aust N Z J Public Health*. 2000;24:576-583.
12. Kallman DA, Plato CC, Tobin JD. The role of muscle loss in the age-related decline of grip strength. *J Gerontol*. 1990;45:M82-M88.
13. Devine A, Dhaliwal SS, Dick IM, Bollerslev J, Prince RL. Physical activity and calcium consumption are important determinants of lower limb bone mass in older women. *J Bone Miner Res*. 2004;19:1634-1639.
14. McArdle WD, Katch FI, Katch VL. *Energy, Nutrition and Human Performance*. Philadelphia, Pa: Lea & Febiger; 1991.
15. Pollock ML, Wilmore JH, Fox SM. *Health and Fitness Through Physical Activity*. New York, NY: John Wiley & Sons Inc; 1978.
16. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142-148.
17. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332:556-561.
18. Henzell S, Dhaliwal S, Pontifex R, et al. Precision error of fan-beam dual X-ray absorptiometry scans at the spine, hip, and forearm. *J Clin Densitom*. 2000; 3:359-364.
19. Schoenau E, Neu CM, Rauch F, Manz F. The development of bone strength at the proximal radius during childhood and adolescence. *J Clin Endocrinol Metab*. 2001;86:613-618.
20. St. John A, Davies C, Riley WJ, et al. Comparison of the performance and clinical utility of a carboxy-terminal assay and an intact assay for parathyroid hormone. *Clin Chim Acta*. 1988;178:215-223.
21. Dean B, Kolavcic MS, Wark JD, Harrison LC. Chromatography of serum on Sep-pak C18 corrects falsely elevated vitamin D metabolite levels measured by protein binding assay. *Clin Chim Acta*. 1988;176:169-178.
22. Britt H. A new coding tool for computerised clinical systems in primary care—ICPC plus. *Aust Fam Physician*. 1997;26:S79-S82.
23. McCloskey EV, Spector TD, Eyres KS, et al. The assessment of vertebral deformity. *Osteoporos Int*. 1993;3:138-147.
24. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis, VII: meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev*. 2002;23:552-559.
25. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D_3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or Vitamin D, RECORD). *Lancet*. 2005;365:1621-1628.
26. Chapuy MC, Arlot MF, Duboeuf F, et al. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *N Engl J Med*. 1992;327:1637-1642.
27. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337:670-676.
28. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res*. 1996; 11:1961-1966.
29. Riggs BL, Seeman E, Hodgson SF, Taves DR, O'Fallon WM. Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. *N Engl J Med*. 1982;306:446-450.
30. Bagger YZ, Tanko LB, Alexandersen P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone*. 2004;34:728-735.
31. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*. 1998;280:2077-2082.
32. McClung MR, Geusens P, Miller PD, et al; Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med*. 2001;344:333-340.