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Randomized Controlled Trial of Calcium in Healthy Older Women

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ABSTRACT

PURPOSE: Calcium has been shown to have positive effects on bone mineral density in postmenopausal women. However, these effects are small, it is unknown whether they are sustained with long-term use, they have not been shown with intention-to-treat analyses, and the evidence for fracture prevention with calcium monotherapy is inconsistent.

METHODS: A randomized controlled trial of calcium (1 g/day as the citrate) in 1471 healthy postmenopausal women (aged 74 ± 4 years) was performed to assess the effects on bone density and fracture incidence over 5 years.

RESULTS: Follow-up was complete in 90% of subjects, and average medication compliance was 55% to 58%. Calcium had a significant beneficial effect on bone density (intention-to-treat analysis), with between-groups differences at 5 years of 1.8% (spine), 1.6% (total hip), and 1.2% (total body). Effects were greater in a per-protocol analysis (5-year differences of 2.3%, 2.8%, and 1.8%, respectively). A total of 425 fractures occurred in 281 women. Hazard ratios, based on time to first fracture, were 0.90 (95% confidence interval [CI], 0.71-1.16) for any symptomatic fracture, 0.72 (95% CI, 0.44-1.18) for vertebral, 3.55 (95% CI, 1.31-9.63) for hip, and 0.65 (95% CI, 0.41-1.04) for forearm fracture. Per-protocol analysis found respective hazard ratios of 0.86 (95% CI, 0.64-1.17), 0.62 (95% CI, 0.33-1.16), 3.24 (95% CI, 0.65-16.1), and 0.45 (95% CI, 0.24-0.87). Height loss was reduced by calcium in the per-protocol population ($P = .03$). Serum alkaline phosphatase and procollagen type-I N-terminal propeptide were lower in the calcium group at 5 years, but constipation was more common.

CONCLUSIONS: Calcium results in a sustained reduction in bone loss and turnover, but its effect on fracture remains uncertain. Poor long-term compliance limits its effectiveness.

KEYWORDS: Osteoporosis; Mineral supplements; Nutrition; Falls; Tooth loss; Urinary calculi; Iron

Calcium is the principal mineral constituent of bone, and the use of calcium supplements has long been advocated for the prevention and treatment of osteoporosis. There is now clinical trial evidence that calcium has positive effects on bone mineral density in postmenopausal women.[1-3] However, these effects have been small and would only be clinically significant if they were progressive with continued use. Because most studies have lasted ≤2 years, this is not known.[4] In addition, most studies have involved modest numbers of subjects and not provided intention-to-treat analyses, so the quality of the evidence for prevention of bone loss by calcium is poor by currently accepted standards.

Several studies of calcium monotherapy have suggested that the reduced bone loss in postmenopausal women is associated with a reduction in fracture risk of up to one half,[5-7] but meta-analysis of the available studies does not demonstrate convincing evidence for fracture protection.[4] There is also evidence that combined intervention with calcium and vitamin D reduces fractures in the elderly.[8-11]

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However, a recent study of 5292 women and men with a previous fracture showed no benefit from calcium, vitamin D, or their combination.[12] Thus, there is substantial uncertainty regarding the value of both these interventions.

We previously observed increases in bone density and an apparently substantial reduction in fracture incidence among postmenopausal New Zealand women in a small trial of calcium supplementation.[3,6] The present study was designed to reassess more rigorously the effects of calcium supplementation on long-term bone loss and fracture incidence in this population.

CLINICAL SIGNIFICANCE

- Daily calcium supplements promote sustained reduction in bone loss and bone turnover in normal postmenopausal women but do not show clear anti-fracture efficacy.
- Constipation may contribute to poor long-term compliance, which may, in turn, limit the effectiveness of calcium supplements.

METHODS

This is a randomized controlled trial in healthy postmenopausal women that is designed to assess the effects of calcium on bone density and fracture incidence over a period of 5 years. The methods have been described.[13] Briefly, subjects were aged more than 55 years, not receiving therapy for osteoporosis or taking calcium supplements, and free of major ongoing disease. Serum creatinine was less than 2.3 mg/dL (0.2 mmol/L), and serum 25-hydroxyvitamin D was greater than 10 μg/L (25 nmol/L). Lumbar spine density was not below the age-appropriate normal range. Women were recruited by advertisement and mail-outs using electoral rolls. Their baseline characteristics are shown in Table 1 and were comparable between groups.

Protocol

Treatments were allocated randomly by computer. Subject numbers were allocated and medication was dispensed by staff who had no direct contact with the other study staff or the subjects. The women received either 1 g of elemental calcium daily (as citrate) or identical placebo in 2 divided doses. Compliance was assessed by tablet counts.

Subjects who had fractures during the study were advised regarding the options for prevention of future fractures, and many of these women started anti-osteoporosis therapies and took calcium supplements. In the latter case, trial interventions were discontinued, although follow-up was maintained.

Measurements

At baseline, 30 months, and 60 months, spine (L1-4), hip, and total body scans were carried out, and vertebral morphometry was performed with a Lunar Expert dual-energy x-ray absorptiometer (GE-Lunar, Madison WI,

Table 1 Characteristics of Study Subjects at Baseline

Characteristic	Placebo	Calcium	*P**
n	739	732	
Age (y)	74.3 (4.3)	74.2 (4.2)	.83
Years since menopause	25.0 (6.3)	24.6 (6.4)	.27
Weight (kg)	67.1 (11.8)	66.9 (11.5)	.25
Height (cm)	159.2 (5.9)	158.9 (5.6)	.80
Body mass index (kg/m^2)	26.4 (4.2)	26.5 (4.3)	.65
Calcium intake (mg/d)	853 (381)	861 (390)	.67
Bone mineral density (g/cm^2)			
Lumbar spine	1.05 (0.18)	1.06 (0.18)	.15
Total body	1.03 (0.09)	1.04 (0.09)	.36
Total hip	0.85 (0.13)	0.86 (0.14)	.66
Bone density T-scores			
Lumbar spine	-0.8 (1.6)	-0.9 (1.5)	.11
Total body	-1.2 (1.1)	-1.1 (1.2)	.34
Total hip	-1.2 (1.1)	-1.2 (1.1)	.64
Serum 25-hydroxyvitamin D (μg/L)†	20.8 (7.8)	20.6 (7.6)	.69
Glomerular filtration rate (mL/min/1.73m^2)§	61 (11)	61 (10)	.58
Current smokers	2.6%	3.4%	.34
Prevalent fracture‡	29.1%	28.1%	.69

Median alcohol intake was <1 drink per week ($P = .63$ between groups). Data are mean (standard deviation).

*Between-groups comparisons.

†Multiply by 2.5 to obtain nanomoles per liter.

‡Fracture resulting from minimal trauma after the age of 40 years.

§Estimated as recommended by Mathew TH; The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust.* 2005;183:138-141.

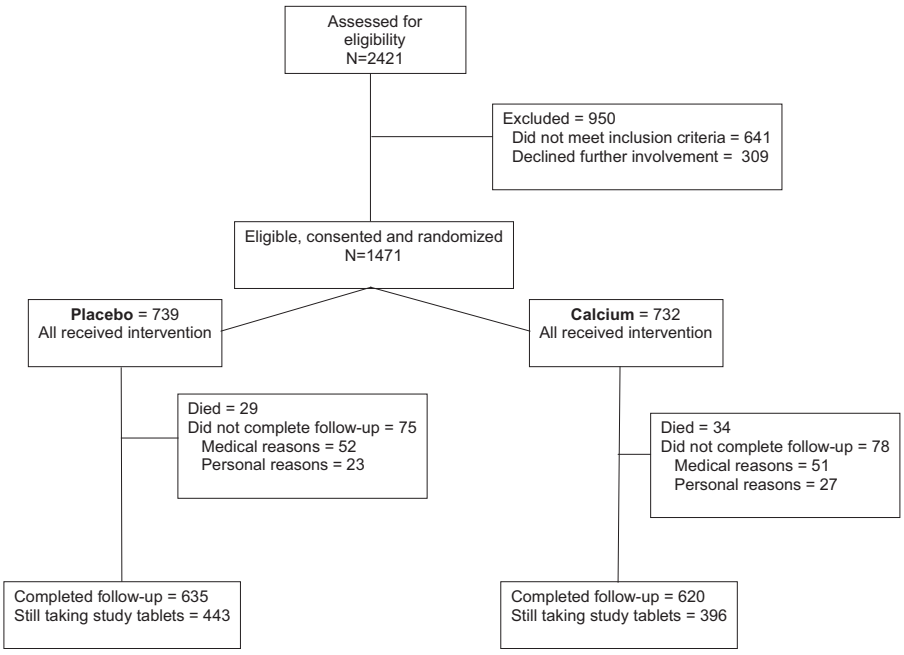

Figure 1 Subject disposition.

software version 1.7). Incident vertebral fractures were defined as a decrease in any vertebral height of more than 20%, provided that the absolute decrease was at least 4 mm. Each vertebra that met these criteria was reviewed by 2 experienced clinicians to ensure that the identification of vertebral margins was correct.

Subjects were asked at each 6-month visit about fractures. If reported, the relevant radiograph or report was obtained. If a subject reported an episode suggestive of fracture but a radiograph had not been taken, then this was arranged. Symptomatic vertebral fractures diagnosed independently of the study's assessments were classified as "clinical fractures" as long as they also met the criteria for definition of an incident vertebral fracture.

Subjects kept a diary of falls. Grip strength was measured in triplicate in the dominant hand. Height was measured using a Harpenden stadiometer. Serum 25-hydroxyvitamin D concentrations were measured at baseline by radioimmunoassay (Diasorin, Stillwater, MN). Serum total alkaline phosphatase activity, iron, iron-binding capacity, ferritin, and magnesium were measured on a Roche Modular autoanalyzer (Roche, Stockholm, Sweden). The Roche Elecsys 2010 platform was used for serum osteocalcin, serum β-C-terminal telopeptide of type I collagen (β-Crosslaps, Roche Diagnostics, Mannheim, Germany), and serum procollagen type-I N-terminal propeptide (PINP). Adverse events were recorded at each visit, but specific symptoms were not.

The study was approved by the local ethics committee, and each subject gave written informed consent. The study was registered with the Australian Clinical Trials Registry, ACTRN 012605000242628.

Statistics

The primary end point of the study was the time to first clinical fracture at any site. Secondary end points were bone density and the following fracture subgroups: total vertebral fractures, hip fractures, distal forearm fractures, and osteoporotic fractures (comprising all fractures except those of the head, hands, feet, and ankles, and resulting from major trauma). Pathologic fractures (eg, resulting from local malignancy) were excluded from all analyses. Intention-to-treat and per protocol analyses were carried out. Because of the likelihood that other anti-osteoporotic therapies would have much greater effects on bone density and fracture than calcium, the per-protocol analysis was prespecified as primary.

The study was powered (80%, with $\alpha = 0.05$) to detect a 40% decrease in fracture rate, because previous studies had suggested an effect of this magnitude.[5-7] The time to first fracture was modeled using a Cox proportional hazards approach with adjustment for the stratification variables (age and thiazide use). The proportional hazards assumption was verified, and a log-rank statistic was estimated. Comparisons between treatment and placebo arms were made using the Fisher exact test for categoric data and the Student unpaired t test for normally distributed continuous variables. For adverse events with indistinct individual start and stop dates (eg, constipation) the number of individuals experiencing at least one episode was compared between groups (Fisher exact test). Events per woman-year also were accumulated and presented as rate (95% confidence interval [CI]). All analyses were conducted using the programs of SAS v9.2 (SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant, and all tests were

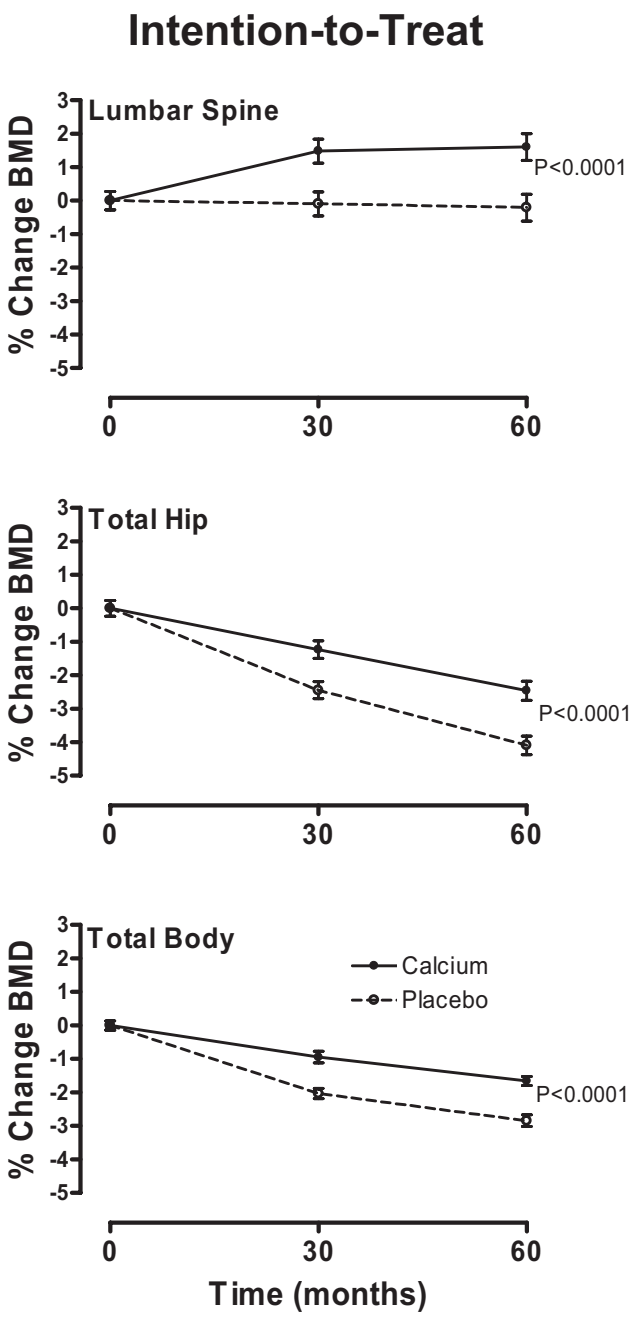

Figure 2 Effects of calcium supplementation on changes in bone mineral density over 5 years. Data are mean ± standard error of mean (SEM), and based on the intention-to-treat cohort. Treatment effects were significant at each site ($P < .0001$).

2-tailed. Results are from the intention-to-treat cohort, unless stated otherwise.

RESULTS

Subject Disposition and Adherence

Subject disposition is shown in Figure 1. Of the women entering the study, noncompletion was attributable to death in 63, illness in 103, and personal reasons in 50. Among those still taking trial medication at 5 years, tablet compliance was approximately 85% in both treatment groups in each 6-month period. When subjects who discontinued trial medication are included, compliance over the entire study was 58% in the placebo group and 55% in the calcium group ($P = .13$).

Bone Mineral Density

In the intention-to-treat analyses, calcium supplementation had a beneficial effect on densities throughout the skeleton (Figure 2). In the spine, there was no loss in the placebo group, but an increase of 1.5% in the calcium group at 30 months. This was maintained until the trial's end, at which time the between-groups difference was 1.8%. The patterns of loss were more linear in both the total hip and total body, with between-groups differences at 5 years of 1.6% and 1.2%, respectively. The calcium effect on density was most evident in the first half of the study. When changes between 30 and 60 months alone were analyzed, there was no significant treatment effect in the spine and total body, although there was in the total hip ($P = .04$).

To determine whether the effect of calcium on density was influenced by dietary calcium intake, a series of breakpoints from 400 to 1000 mg/day were considered. Only when the cohort was divided at 800 mg/day, did those with lower intakes have larger increases in total hip density in response to calcium supplementation ($P = .007$). A similar analysis of the influence of age showed no interaction of age with treatment effect.

Analysis of data from the per-protocol population with compliance greater than 60% showed a similar pattern of density changes (Figure 3). Between-groups differences at 5 years were 2.3% in the spine, 2.8% in the hip, and 1.8% in the total body. This represents a 64% reduction in bone loss at the hip and 59% reduction in total body loss in the calcium group. In this analysis, the waning of the effect in the second half of the study was much less evident, and the between-groups differences increased significantly during this time at the hip ($P = .0002$) and total body ($P = .0009$), suggesting that decreasing compliance contributed to the waning effect in the intention-to-treat analysis.

Fractures

A total of 425 fractures (204 in the calcium group, 221 in the placebo group) occurred in 281 women (134 in the calcium group, 147 in the placebo group) during the study. The cumulative proportion of all first clinical fractures in the intention-to-treat population is shown in Figure 4, and the hazard ratios for various fracture categories are shown in Table 2. For total clinical fractures and osteoporotic fractures, there was little evidence of a difference between groups, although hip fractures were more common in those allocated to calcium, and forearm fractures seemed to be less common in this group.

Because of the likelihood that any therapeutic effect of calcium would be overshadowed by the effects on bone of other medications and illnesses, a per-protocol analysis also

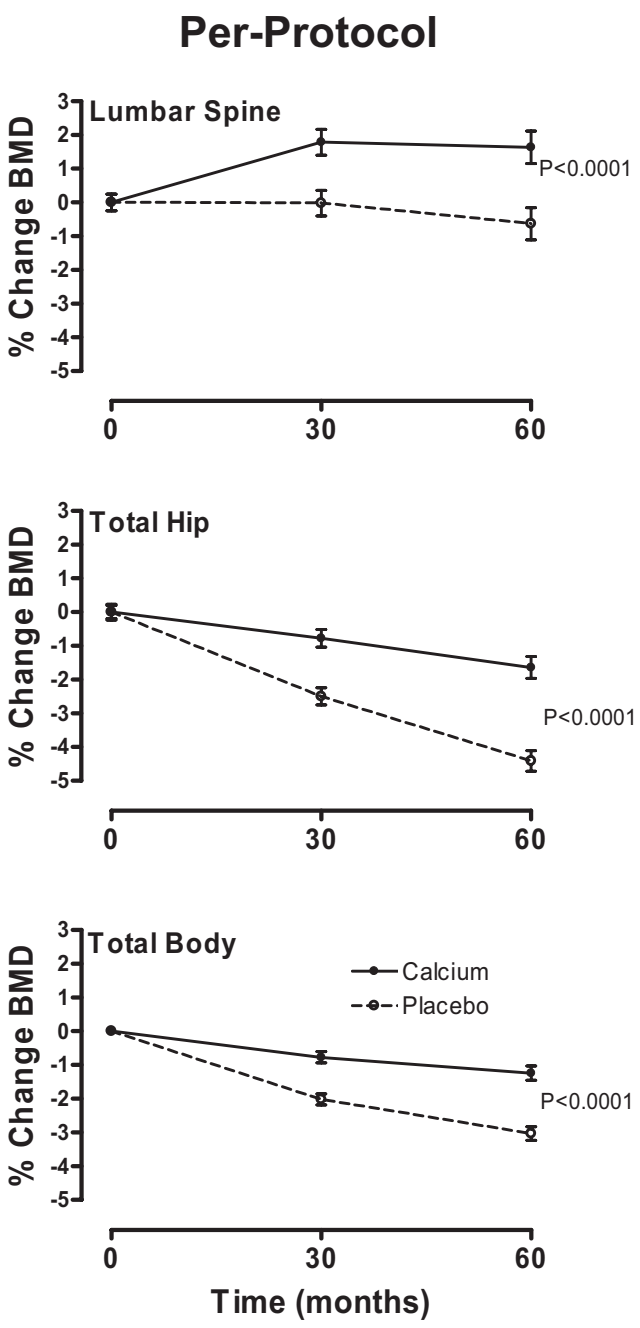

Figure 3 Effects of calcium supplementation on changes in bone mineral density over 5 years. Data are mean ± SEM, and based on the per-protocol cohort. Treatment effects were significant at each site ($P < .0001$).

was performed in which subjects were excluded from the time they started on a bone-active medication (eg, bisphosphonates, estrogen, glucocorticoids) or from the time when they were diagnosed with malignancy (Table 2, middle panel). This produced results similar to those of the intention-to-treat analysis, except that a significant increase in hip fractures was no longer found, and the trends elsewhere toward benefit with calcium were slightly greater. A further analysis then excluded subjects during periods in which their tablet compliance was less than 60%. These results are shown in the lower part of Table 2 and Figure 5, and suggest that calcium reduces fractures, although this was only significant for forearm fractures. In the placebo group, 229 subjects had at least one 6-month period in which compliance was less than 60%, similar to that of the 240 subjects in the calcium group.

Height loss, a surrogate for vertebral fracture, was linear in both groups. At 5 years in the intention-to-treat analysis, mean (± standard error) loss was 10.3 ± 0.2 mm in both groups ($P = .46$). The per-protocol population with compliance greater than 60% showed height losses of 9.9 ± 0.3 mm in the placebo group and 9.0 ± 0.3 mm in the calcium group ($P = .03$), consistent with the trend to fewer vertebral fractures.

Bone Turnover Markers

Serum alkaline phosphatase activity was measured in all subjects at baseline and 5 years (Figure 6). Values decreased more in the calcium group than in the placebo group during the study (11% vs 6%, $P < 0.001$. Other markers were measured at 5 years only in 80 subjects who were still taking study medication (40 chosen randomly from each group). PINP levels were 22% lower in the calcium group ($P = .03$). Serum osteocalcin and β-C-terminal telopeptide of type I collagen concentrations were also slightly lower in the calcium group than in the placebo group (16% and 15%, respectively), but neither of these differences was significant.

Other Measures

To assess the possibility that calcium might impact on muscle function and the frequency of falls, grip strength was assessed at each visit. Baseline mean values were comparable (placebo, 18.4 kg; calcium, 18.6 kg, $P = .33$). Over the study period, grip strength declined by 0.51 ± 0.14 kg in the placebo group and by 1.2 ± 0.15 kg in the calcium group (least squares means ± standard error, $P = .04$). The incidence of falls was 595 per 1000 woman-years (95% CI, 566-626) for calcium, and 585 per 1000 woman-years (95% CI, 556-615) for placebo ($P = .81$).

In the 80 subjects who had serum assessments at 5 years, the calcium and placebo groups showed comparable levels of iron (18 ± 6, 18 ± 4 μmol/L), iron-binding capacity (56 ± 7, 55 ± 9 μmol/L), ferritin (156 ± 117, 134 ± 111 μg/L), and magnesium (0.84 ± 0.08, 0.85 ± 0.06 mmol/L) (mean ± standard deviation, all P values $> .4$).

Loss of at least one tooth occurred in 25.6% (95% CI, 21.5-30.2) of women in the placebo group, compared with 28.8% (95% CI, 24.4-33.6) in those randomized to calcium ($P = .33$).

Adverse Events

Constipation was reported by 132 women (18%) in the calcium group and by 82 women (11%) allocated to placebo ($P = .0002$). Two subjects in the calcium group had urinary calculi as did four allocated to placebo. Discontinuation of

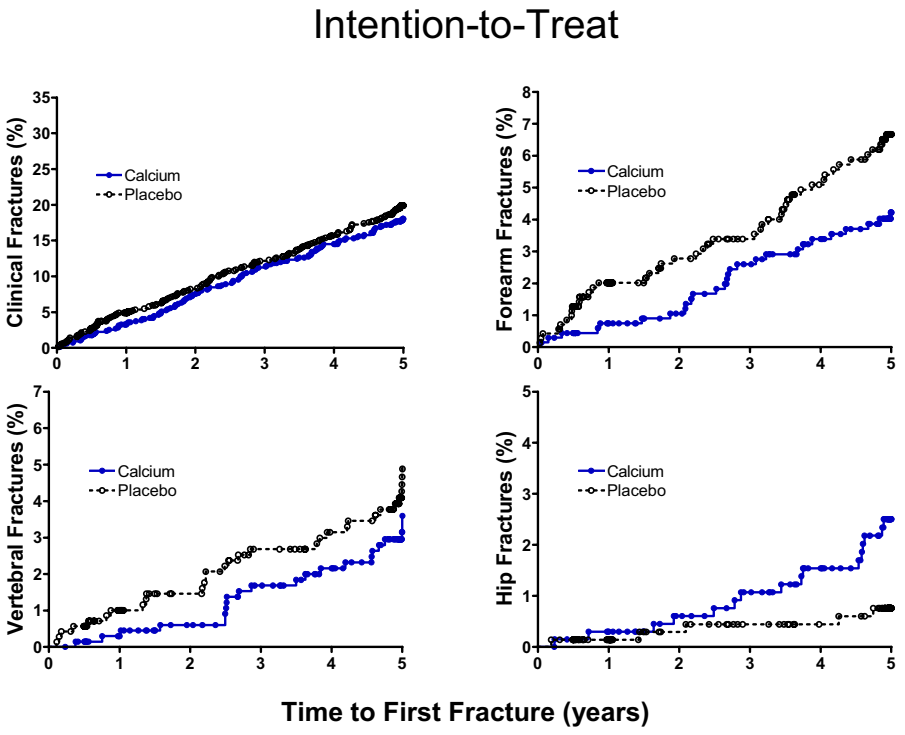

Figure 4 Cumulative fracture incidence over time (Kaplan-Meier plots) in the intention-to-treat population. Significance of effects is shown in Table 2.

Table 2 Effect of Calcium Supplementation on Fracture Risk[1]

	Placebo	Calcium	Hazards Ratio (95% CI)	P
Intention to treat analysis				
Symptomatic fracture	132	119	0.91 (0.71, 1.17)	.46
Osteoporotic fracture	120	104	0.87 (0.67, 1.14)	.31
Vertebral	38	27	0.72 (0.44, 1.18)	.19
Hip	5	17	3.55 (1.31, 9.63)	**.013**
Distal forearm	44	28	0.64 (0.40, 1.03)	.066
Years of follow-up	4.5	4.4		.64
Per protocol analysis[2]				
Symptomatic fracture	120	102	0.87 (0.67, 1.14)	.31
Osteoporotic fracture	106	86	0.83 (0.62, 1.10)	.19
Vertebral	29	17	0.61 (0.33, 1.11)	.10
Hip	5	10	2.12 (0.72, 6.19)	.17
Distal forearm	39	20	0.53 (0.31, 0.91)	**.021**
Years of follow-up	4.1	4.0		.19
Per protocol compliers analysis[3]				
Symptomatic fracture	91	76	0.86 (0.64, 1.17)	.35
Osteoporotic fracture	78	61	0.81 (0.58, 1.13)	.22
Vertebral	26	15	0.62 (0.33, 1.16)	.14
Hip	2	6	3.24 (0.65, 16.1)	.15
Distal forearm	29	12	0.43 (0.22, 0.85)	**.015**
Years of follow-up	3.2	3.1		.33

[1]Data are hazards ratios, based on time to first fracture from the beginning of the study. Years of follow-up are means.

[2]Censoring those who became ineligible because of cancer, or use of bone active medication. Data were censored from the time they developed these exclusions.

[3]Censoring those who became ineligible because of compliance $< 60\%$, cancer, or use of bone active medication, from the time they developed these exclusions.

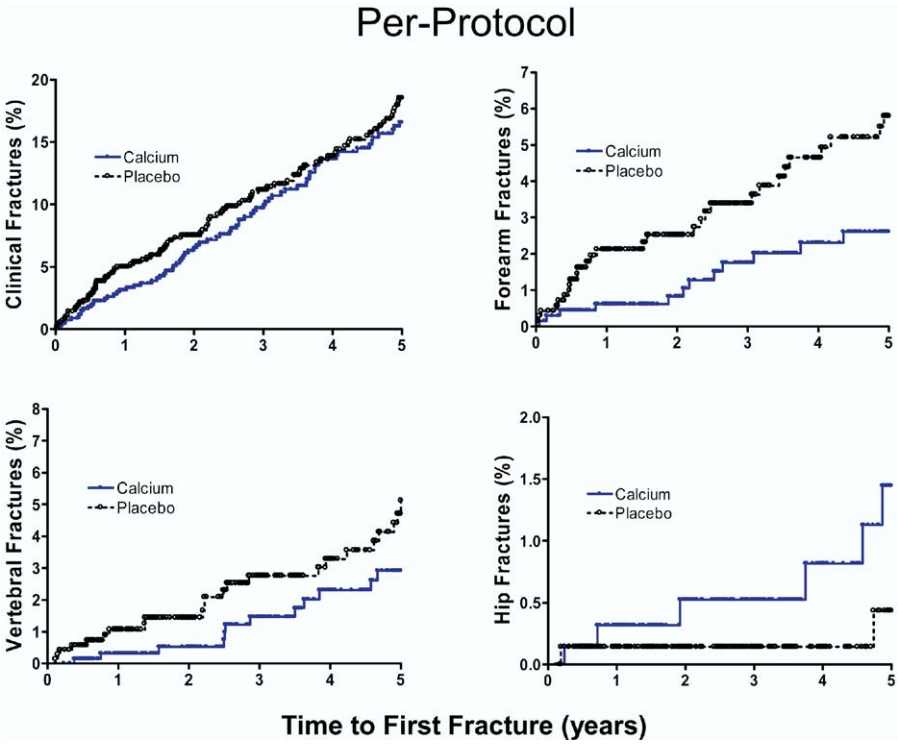

Figure 5 Cumulative fracture incidence over time (Kaplan-Meier plots) in the per-protocol population with medication compliance greater than 60%. Significance of effects is shown in Table 2.

trial tablets was more common in those allocated to calcium (336, compared with 296, $P = .02$). Health reasons were more often cited as the reason for tablet discontinuation in the calcium group (133, compared with 105 for placebo group, $P = .04$). This difference seemed to be fully accounted for by the increased incidence of constipation in the calcium group.

DISCUSSION

This study confirms the beneficial effects of calcium supplementation on bone density in healthy older women. It shows that these benefits are present throughout the skeleton, that they are independent of age, and that they are present in individuals with both high and low dietary calcium intakes. These results provide confirmation of similar findings in a number of smaller studies, but the size of the present trial allows these conclusions to be reached with much greater certainty. In particular, the beneficial effects of calcium supplementation on bone density are clearly statistically significant when analyzed with a rigorous intention-to-treat approach; most previous studies of calcium supplementation have only published data from subjects who were protocol- and medication-compliant. The present study has the further advantage that its duration is greater than that of almost all such studies in the past. This allows the time course of the effect of calcium on bone density to be assessed more adequately. Although most of the beneficial effect of calcium on bone density in the spine and total body scans occurs in the first 30 months in the intention-to-treat analysis, there are cumulative benefits evident in the proximal femur. The per-protocol analysis, however, shows a cumulative benefit over time in both the proximal femur and the total body, suggesting that decreasing compliance is a major contributor to the apparent plateauing of effect. This implies that use of calcium supplementation over longer periods is likely to result in even greater effects on bone density.

The bone density findings are reinforced by the bone marker data, which indicate that even after 5 years, a reduction in bone turnover is still present in subjects taking calcium. The 3 bone-specific markers assessed show similar degrees of suppression; the fact that this was only statistically significant for PINP is probably a reflection of the lesser variability of this measure. Thus, the present study establishes more clearly than previously that calcium supplementation provides a significant and sustained reduction in bone turnover, which results in modest positive effects on density.

The positive findings with density in this study contrast with the lack of a clear-cut effect of calcium on fracture rates. The intention-to-treat analysis would be consistent with a small beneficial effect on total numbers of symptomatic fractures. When subjects are censored from the time that they developed major protocol violations or became noncompliant with study medication, the trends to fracture reduction become more marked, but are still not conclusive. Thus, the present study leaves the important question of the anti-fracture efficacy of calcium unresolved but does rule

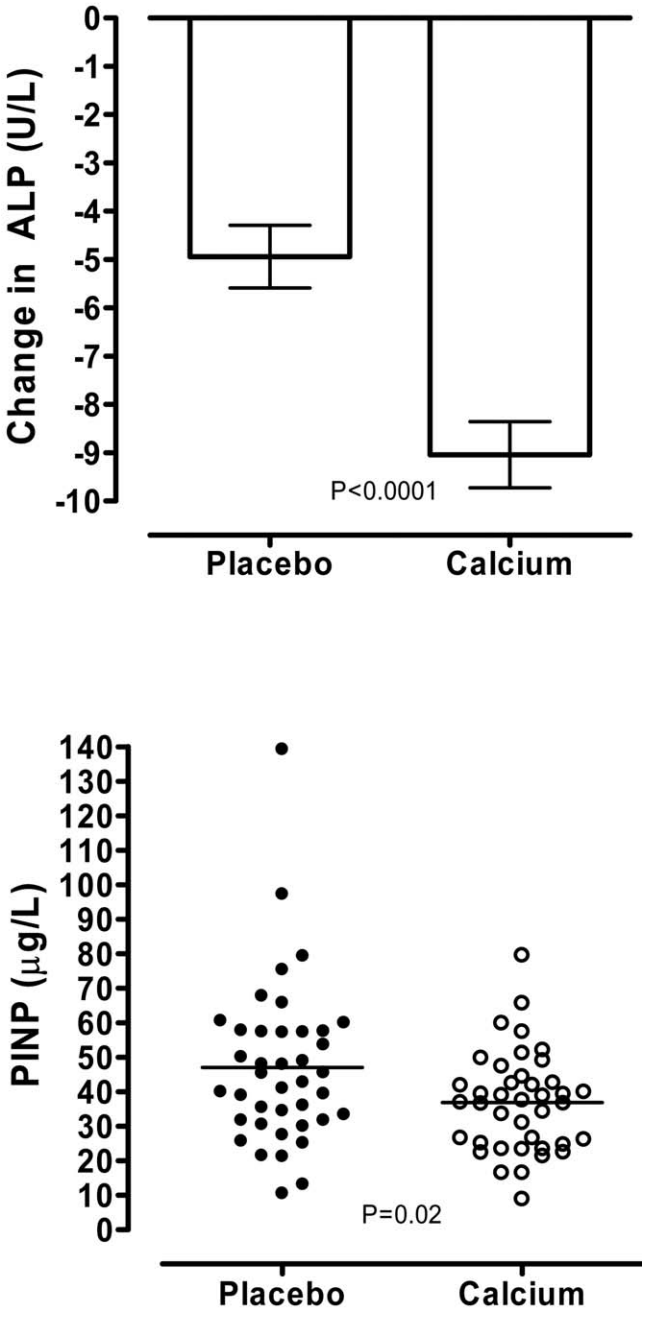

Figure 6 Effects of calcium supplementation on changes in serum alkaline phosphatase (ALP) activity from baseline to 5 years (*upper*). Values were comparable in the groups at baseline (85 ± 20 in each group) but decreased more in the calcium group ($P < .0001$). Data are mean ± SEM. Procollagen type-I N-terminal propeptide (PINP) levels at 5 years in 40 subjects from each group (*lower*). Values are significantly lower in the calcium group.

out suggestions from the very limited data available to date that total fracture numbers might be reduced by as much as 50%.[7] However, the 10% to 20% reduction in total fracture rate suggested by this study would be of value in the large osteopenic population that sustains the majority of postmenopausal fractures.[14] The present data provide a substantial increase in the quantity of fracture data available for future meta-analysis, because it comprises more women-years than the total in the Shea review.[4]

The apparent increase in hip fracture incidence in the present study is surprising, particularly in light of the beneficial effects of calcium supplementation on density at the total hip and femoral neck. This trend in hip fractures is contrary to that seen elsewhere in the skeleton. In light of this, and the clear evidence in the literature that calcium combined with vitamin D *prevents* hip fractures,[15] it is likely that the present result is a chance finding arising from the small numbers of this particular fracture.

The importance of the issue of the anti-fracture efficacy of calcium is attested to by the recent presentation of several large studies. The RECORD study[12] recruited subjects aged more than 70 years with a history of fracture. Median follow-up was 45 months. For the calcium intervention, the hazard ratio was 0.94 (95% CI, 0.81-1.09). Compliance was approximately 50%, and there was significant contamination from other therapies. This result is similar to that of the present study. A study of the same size and duration as the present one has recently been presented.[16] The intention-to-treat analysis showed a relative risk of fracture of 0.85, which reduced to 0.66 in the protocol-compliant cohort. Both studies are suggestive but not conclusive of a weak anti-fracture effect.

The present study highlights the difficulties inherent in the use of calcium supplementation, both in the context of a clinical trial and in clinical practice. These doses of calcium are bulky, usually requiring multiple tablets each day. This results in considerable problems with subject adherence, complicating trial interpretation and clinical utility. The increased incidence of constipation is confirmed in the present study and is likely to limit adherence. However, this study is reassuring in regard to calcium's effects on iron and magnesium levels, although it finds no benefit on muscle strength, falls, or tooth loss.

The present study is larger and longer than any study of calcium monotherapy yet published. As such, it is able to establish the beneficial effects of calcium supplementation on bone density with greater certainty than has been possible thus far. It also shows that calcium effects on bone turnover are sustained over time. Although contributing these important findings, the study did not resolve the critical question of whether calcium is able to reduce fracture incidence. It is probably only through meta-analysis that this question will be addressed, and the present study makes an important contribution to the quantity of data available for such future analyses. In the meantime, the role of calcium in fracture prevention remains uncertain.

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References

1. Dawson-Hughes B, Dallal GE, Krall EA, et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med.* 1990;323:878-883.
2. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. *N Engl J Med.* 1991;325: 1189-1195.
3. Reid IR, Ames RW, Evans MC, et al. Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med.* 1993; 328:460-464.
4. Shea B, Wells G, Cranney A, et al. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocrine Rev.* 2002;23:552-559.
5. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int.* 1994;4:245-252.
6. Reid IR, Ames RW, Evans MC, et al. 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. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Mineral Res.* 1996;11:1961-1966.
8. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med.* 1992;327: 1637-1642.
9. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D-3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporos Int.* 2002;13:257-264.
10. 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.
11. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Mineral Res.* 2004;19:370-378.
12. Grant AM, Anderson FH, Avenell A, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* 2005;365:1621-1628.
13. Reid IR, Horne A, Mason B, et al. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. *J Clin Endocrinol Metab.* 2005;90:3824-3829.
14. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Int Med.* 2004;164:1108-1112.
15. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin-D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med.* 1992;327:1637-1642.
16. Prince RL, Devine A, Dhaliwal SS, Dick IM. Results of a 5 year double blind, placebo controlled trial of calcium supplementation: clinical fracture outcomes. *J Bone Mineral Res.* 2004;19(suppl 1):S3.