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Original Article

A 4-Year Follow-up Study of the Effects of Calcium Supplementation on Bone Density in Elderly Postmenopausal Women

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Abstract. To determine the long-term effect of calcium supplementation on bone density, 84 elderly women (54–74 years) more than 10 years past the menopause were studied for 4 years as part of a follow-up study of a randomized, double-masked, placebo-controlled trial. The placebo group who did not take calcium supplements at all during the 4-year study (control group, n = 21) served as a comparison with the treated group who took calcium supplements for 4 years (calcium supplement group, n = 14). We also studied subjects who were treated for 2 years with calcium supplements and then ceased taking them (non-compliant group, n = 49). The changes in bone density at the lumbar spine, hip and ankle sites, current calcium intake and activity were monitored. Over the 4 years the calcium supplement group (mean calcium intake 1988 ± 90 mg/day) did not lose bone at the hip and ankle site. The control group (mean calcium intake 952 ± 109 mg/day) lost significantly more bone than the calcium supplement group at all sites of the hip and ankle. No overall bone loss was seen at the spine, in either group, over the 4 years of this study. Between years 2 and 4 the non-compliant group (mean calcium intake 981 ± 75 mg/day) lost significantly more bone at all sites of the ankle than the calcium supplement group. Therefore, calcium supplementation produces a sustained reduction in the rate of loss of bone density at the ankle and hip sites in elderly postmenopausal women. Increasing dietary calcium intake in women should be the aim of a public health campaign.

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Introduction

The aetiology of age-related bone loss is unclear, but dietary calcium deficiency has been implicated as a causal factor. Previous randomized studies have shown the effectiveness of 2 years of calcium supplementation in slowing or stopping bone loss in menopausal women [1–5]. In a recent 2-year randomized, placebo-controlled study in women 10 years past the menopause we showed that calcium supplementation as milk powder or as calcium tablets completely prevented bone loss at some areas of the important hip site [6]. To determine whether continuation with a dietary supplement resulted in a continuing positive effect on bone density, the use of a dietary calcium supplement and bone density were monitored after a further 2 years.

Subjects and Methods

Subjects

Subjects were reviewed 4 years after commencing a randomized, double-masked, placebo-controlled study of 2 years' duration to assess the effects of dietary calcium supplementation and exercise on bone density [6]. All 128 subjects who completed the 2-year study were advised to start active treatment of calcium supplementation of 1000 mg/day. At the 4-year follow-up 84 subjects were available to complete a self-administered questionnaire reporting their compliance with supplementation of calcium tablets between years 2 and 4 of the study. The 44 subjects who were not followed declined to continue, were not contactable or were enrolled in a new trial. The placebo group who did not take calcium supplements at all during the 4-year study (control group, $n = 21$) served as a comparison with the treated group who continued to take 1 g of calcium lactate gluconate (Sandoz Basle) at night for 4 years (calcium supplement group, $n = 14$). We also studied subjects who were treated for 2 years with calcium supplements and then ceased taking them (non-compliant group, $n = 49$).

Measurements

Bone density at the lumbar spine (L1–4), distal tibia/fibula (ankle) and the hip sites were assessed using Dual-energy X-ray absorptiometry, on a QDR 1000 machine (Hologic, Waltham, MA). The software was not changed during the study. The quality control data, in the form of 100-day rolling averages from daily spine phantoms over the 5 years, were examined. Bone density was adjusted by a factor of 1.00315 for the fall seen in quality control data at the 12-, 18- and 24-month measurements.

Calcium intake was determined from 4-day weighed diet records at baseline, 1, 2 and 4 years in 71 subjects. A 4-day average intake was calculated for calcium intake at each year. At years 1 and 2 the subjects who were treated with either a calcium tablet or milk powder had a daily amount of 1000 mg or 1087 mg of calcium added to their average daily calcium intake respectively [6]. At year 4 the subjects reported whether or not they were currently taking calcium supplements and, if they were, the daily amount of elemental calcium taken. If subjects reported current calcium supplementation the daily intake was calculated and added to their daily calcium intake. A change in total calcium intake between years 2 and 4 was calculated. Activity was assessed by 7-day activity records in 69 subjects [6]. The study was approved by the Human Rights Committee of the University of Western Australia. Informed consent was obtained from each subject.

Statistical Analysis

The first comparison examined on the basis of *a priori* considerations was that the calcium supplement group had less bone loss than the control group. A regression line for the change in bone density over 4 years was calculated by least squares analysis for each individual completing five or more bone density estimations. This summary statistic was pooled for each group and used to calculate bone loss in mg/cm^2 per year. This 4-year change in bone density (mg/cm^2 per year) for the calcium supplement and control groups was compared with no change in bone density using a single-sample t-test. The 4-year change in bone density (mg/cm^2 per year) between the two groups was also examined by an independent t-test and by ANOVA to allow adjustment for weight and current activity level.

The second comparison examined on the basis of *a priori* considerations was that the non-compliant group lost more bone than the calcium supplement group between years 2 and 4. The change in bone density between years 2 and 4 was calculated by difference. This summary statistic was pooled for each group and used to calculate the bone loss (mg/cm^2 per year). The 2-year difference between the calcium supplement group and the non-compliant group was examined by an independent t-test and by ANOVA to allow adjustment for confounding factors, weight and current activity level.

All results are reported as the mean and SEM unless otherwise indicated. All p values are two-tailed. The statistical package used was SPSS for Windows (SPSS, Chicago).

Results

Four-Year Comparison of Calcium Supplement and Control Groups

The groups were matched for initial bone density at all sites (Table 1). Table 2 shows the characteristics of the two groups measured at year 4. The control group had significantly greater body weight than the calcium supplement group (Table 2). The total calcium intake was significantly higher in the calcium supplement group than the control group (Table 2).

Over 4 years the control group lost significantly more bone than the calcium supplement group at all sites of the hip (Fig. 1) and ankle (Fig. 2) when analysed by an independent t-test (Table 3). These differences persisted at all the hip sites, the ankle and the ultradistal tibial site of the ankle after adjusting for potential confounding variables, weight and current activity. In the control group significant bone loss occurred at all sites of the ankle and the intertrochanter and femoral neck site of the hip. In the calcium supplement group

Table 1. Bone mineral density (mg/cm^2) of the subjects in the control and calcium supplement groups measured at baseline at various skeletal sites

Measurement site	Calcium supplement (n=14)	Control (n=21)	Non-compliant (n=49)
Intertrochanteric	994±52	1009±27	1013±19
Trochanteric	627±23	648±18	655±12
Femoral neck	707±33	711±20	731±13
Total hip	846±38	860±23	868±15
Mid-tibial	664±27	673±17	666±12
Ultradistal tibial	652±34	662±19	650±14
Ankle	680±27	688±16	681±12
Lumbar spine	900±41	911±31	912±19

Values are the mean ± SEM.

Table 2. Characteristics of the subjects in the control and calcium supplement groups measured at year 4

	Calcium supplement (n=14)	Control (n=21)	Non-compliant (n=49)
Age (years)	67.6± 1.1	65.6± 0.9	66.0± 0.7
Years since menopause	18.8± 1.3	18.7± 0.9	19.1± 0.8
Total calcium intake (mg/day)	1988 ±90[a,b] (n=12)	952 ±109[a] (n=15)	981 ±75[b] (n=37)
Change in calcium intake (mg/day) between years 2 and 4	120 ±33[a] (n=12)	279 ±112[b] (n=15)	−731 ±62[a,b] (n=36)
Current activity (METS)	411 ±12 (n=12)	388 ± 15 (n=15)	380 ±10 (n=36)
Body weight (kg)	62.3± 2.6[a]	72.9± 2.3[a,b]	66.2± 1.1[b] (n=48)
Height (cm)	158.3± 1.7	160.9± 1.4	160.9± 0.9 (n=48)

Values are the mean ± SEM.
Sample size was as stated at the top of the column unless otherwise indicated in parentheses.
Values with the same superscripts are significantly different at p<0.05.

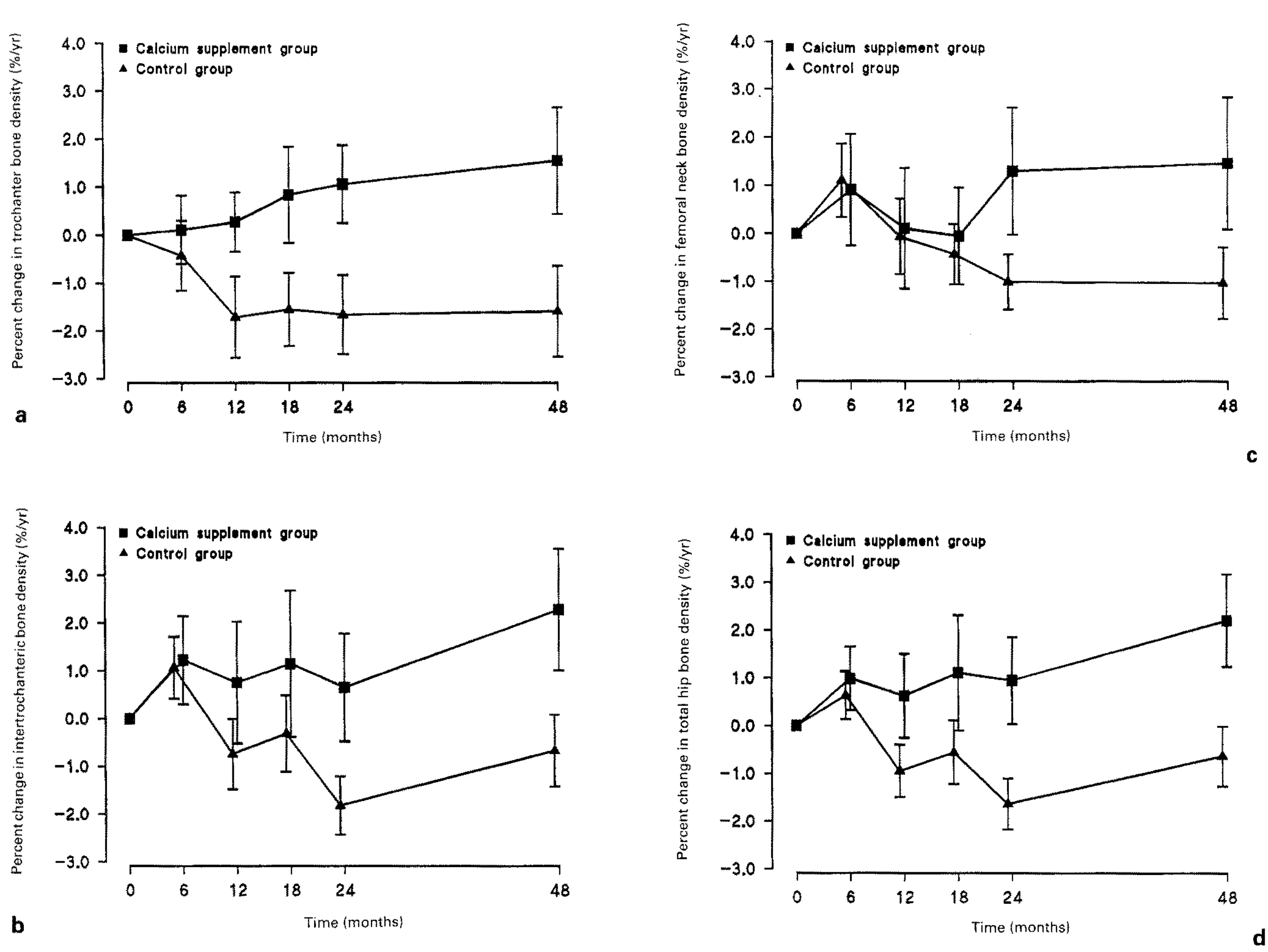

Fig. 1. Percentage change in bone density at **a** trochanter, **b** intertrochanteric, **c** femoral neck and **d** total hip sites. Results are the mean ± SEM. The 4-year change in bone density determined from the slope of the least squares regression analysis was significantly different between the control group (*triangles*; n=21) and calcium supplemented group (*squares*; n=14).

significant bone gain occurred at the total hip site with no significant loss at any site (Table 3). At the lumbar spine there were apparent increases in bone density in both the calcium supplement and control groups which were not significantly different.

Comparison of Non-compliant and Calcium Supplement Groups

At year 4 the average daily total calcium intake was lower in the non-compliant group (981 ± 75 mg) than

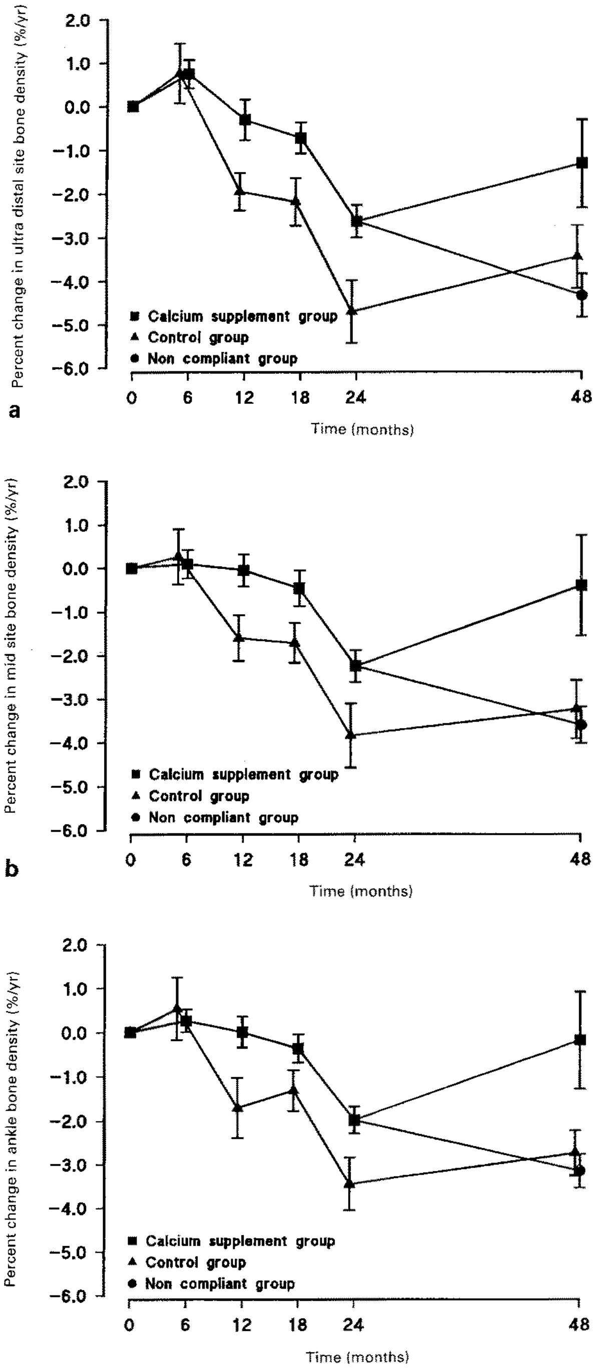

Fig. 2. Percentage change in bone density at **a** ultradistal tibial site of the ankle, **b** mid-tibial site of the ankle and **c** ankle. Results are the mean ± SEM. The 4-year change in bone density determined from the slope of the least squares regression analysis was significantly different between the control group (*triangles*; n=21) and calcium supplemented group (*squares*; n=12). The change between the 2- and 4- year bone density was significantly different between the calcium supplemented group (*squares*; n=12) and those who stopped calcium supplements at 24 months (*circles*; non-compliant group, n=48).

the calcium supplement group (1988 ± 90 mg) (Table 2). The non-compliant group had a fall in calcium intake (−731 ± 62 mg) whereas intake in the calcium supplement group rose slightly (120 ± 33 mg calcium).

Table 3. The 4-year change in bone mineral density at various skeletal sites (expressed as mg/cm^2 per year) for the control and calcium supplement groups

Measurement site	Calcium supplement (n=14)	Control (n=21)
Intertrochanteric	3.49±2.21*	−3.45±1.64†
Trochanteric	2.04±1.54*	−2.57±1.37
Neck	1.73±1.44**	−3.05±0.95††
Total hip	3.34±1.36**†	−2.43±1.26
Mid-tibial	−1.69±1.72* (n=12)	−6.69±1.28†††
Ultradistal tibial	−2.32±1.36* (n=12)	−7.54±1.35†††
Ankle	−0.87±1.72* (n=12)	−5.98±1.09†††
Spine	3.44±1.68	3.21±1.23†

Results are the mean ± SEM.
Sample size was as stated at the top at the column unless otherwise indicated in parentheses.
*p<0.05 compared with control group; **p<0.01 compared with control group; †p<0.05 compared with no change, ††p<0.01 compared with no change; †††p<0.001 compared with no change.

The change in bone density between years 2 and 4 for the non-compliant group was compared with that in the calcium supplement group. The non-compliant group lost more bone at all sites of the ankle than the calcium supplement group (Table 4, Fig. 2); this difference persisted when analysed by ANOVA after adjusting for potential confounding variables, weight and current activity.

In all subjects the 2 year change in bone density was significantly correlated with the change in total calcium intake measured between years 2 and 4 at the mid-tibial (r = 0.38, p<0.005), ultradistal tibial (r = 0.38, p<0.005) and ankle sites (r = 0.41, p<0.005) and the lumbar spine (r = 0.30, p<0.05). From these correlations it was evident that the greater the reduction in calcium intake the greater the reduction in bone density

Table 4. The change between 2-year and 4-year bone mineral density at various skeletal sites (expressed as mg/cm^2 per year) for the calcium supplement and non-compliant groups

Measurement site	Calcium supplement (n=14)	Treated non-compliant (n=48)
Intertrochanteric	7.15±3.48	−0.10±1.86
Trochanteric	0.97±2.06	−1.81±1.36
Neck	0.27±2.78	−2.94±1.76
Total hip	4.45±2.26	0.16±1.34
Mid-tibial	4.31±3.09 (n=12)	−3.35±1.32*
Ultradistal tibial	2.71±3.43 (n=12)	−4.40±1.48*
Ankle	4.54±3.04 (n=12)	−2.96±1.11**
Spine	3.71±3.03	1.28±2.06

Results are the mean ± SEM.
Sample size was as stated at the top at the column unless otherwise indicated in parentheses.
*p<0.05 compared with calcium supplement group; **p<0.01 compared with calcium supplement group.

at the ankle, and the smaller the rise in bone density at the lumbar spine.

Discussion

The main aim of this study was to see whether a high calcium intake which prevented bone loss for 2 years would continue to be effective for a further 2 years. The data showed that the continuous use of a calcium supplement (1000 mg/day) for 4 years completely prevented bone loss at all sites of the hip and ankle in elderly postmenopausal women. The continuing loss of bone at the hip and ankle sites in the control group remained apparent for the entire study. No overall bone loss at the spine site occurred in either group over the 4 years, as previously shown by us in the 2-year data of this group [6] and others [7,8], and may be explained by degenerative joint disease obscuring bone density changes at this site. Previous randomized 2-year studies have shown the effectiveness of calcium supplementation in slowing or stopping bone loss in menopausal women [1,3–5,9]. Our data extend the findings of a recent 4-year study which shows a long-term protective effect of calcium supplementation on bone density in women on average 10 years past the menopause, to an older group on average 15 years past menopause at baseline [10].

The non-compliant group who were treated with a 1000 mg/day calcium supplement for the first 2 years of the study but not the last 2 years showed a large reduction in total calcium intake of 731 mg/day at 4 years and lost significantly more bone at all sites of the ankle compared with those who maintained their intake, even after allowing for differences in body weight and activity. The lack of compliance by the non-compliant group with calcium supplementation is likely to be explained by a reduction in motivation once the randomized clinical trial ceased.

A probable cause of bone loss in the elderly is negative calcium balance, which results from a reduction in intestinal calcium absorption [11] and a rise in parathyroid hormone levels with increasing age [12]. Thus, bone turnover in elderly women is high compared with that in premenopausal women [12]. Studies have shown that calcium supplementation in postmenopausal women restores calcium balance and reduces bone loss and markers of bone formation and bone resorption [1,10]. The prevention of bone loss over 4 years in this study argues that the effect addresses a fundamental long-term causative factor in bone loss rather than merely reflecting a remodelling transient.

The lack of significance of the rates of loss at the hip site between the calcium-supplemented and non-compliant groups may be due to regional differences in bone turnover in different types of bone tissue. Higher rates of bone loss are demonstrated at the ankle site in all groups when compared with the hip and spine sites. In addition the non-compliant group had a reduced calcium intake for only 2 of the 4 years. The shorter duration of the reduced calcium intake may account for the lack of significance at the hip and spine sites when compared with the calcium-supplemented group. One could speculate that if the study were continued for a further 2 years, a difference may be seen between the non-compliant group and the calcium-supplemented group.

In conclusion, these data show that if women more than 10 years past the menopause increase their calcium intake with a daily 1 g calcium supplement (to bring the total intake to approximately 2 g per day) for 4 years, they can stop bone loss at the hip and ankle sites. However, at a lower calcium intake of approximately 900 mg they have continuing bone loss at these sites. Cessation of calcium supplementation after 2 years is associated with a resumption of bone loss. Even though the follow-up study was neither double-masked nor randomized, and the sample size was limited due to the long-term nature of the study, these data are consistent with a growing body of data that suggests calcium intakes of over 1500 mg/day are associated with a slowing or cessation of bone loss and a reduction in fracture rate [10,13–15]. This increasing evidence points to a beneficial effect of increasing calcium intake. This intervention has been associated with beneficial consequences for other organs [16–19] without deleterious effects and should be considered for community-based intervention programmes.

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