Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women[1–4]

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ABSTRACT

Background: Supplementation with calcium and vitamin D reduces bone loss and prevents fractures in elderly people, but it is not known whether any lasting benefit remains if the supplements are discontinued.

Objective: The objective was to determine whether gains in bone mineral density (BMD) induced by calcium and vitamin D supplementation persist after supplement withdrawal.

Design: Two-hundred ninety-five healthy, elderly men and women (aged ≥68 y) who had completed a 3-y randomized, placebo-controlled trial of calcium and vitamin D supplementation were followed for an additional 2 y during which no study supplements were given. BMD was measured by dual-energy X-ray absorptiometry, and biochemical variables related to calcium metabolism and bone turnover were measured.

Results: In the 128 men, supplement-induced increases in spinal and femoral neck BMD were lost within 2 y of supplement discontinuation, but small benefits in total-body BMD remained. In the 167 women, there were no lasting benefits in total-body BMD or at any bone site. Consistent with the observations on BMD, the bone turnover rates in both men and women (as measured by serum osteocalcin concentrations) returned to their original higher concentrations within the same 2-y period.

Conclusion: Discontinued calcium and vitamin D supplementation has limited cumulative effect on bone mass in men and women aged ≥68 y. *Am J Clin Nutr* 2000;72:745–50.

KEY WORDS Calcium, vitamin D, supplement withdrawal, bone mineral density, bone mineral content, bone turnover, fractures, osteoporosis, elderly

INTRODUCTION

Osteoporosis will remain a serious global health problem for the foreseeable future, but improved diagnostic methods and the availability of a broader range of bone- active agents now make it possible for physicians and their elderly patients to take a more active role in the prevention and management of this disease. It is now widely accepted that prescribing appropriate calcium and vitamin D intakes is an important clinical strategy, whether or not medications are also recommended. For many reasons, individuals may not continue a particular medication or supplement routine for as long as might be desirable. In such situations, individuals may receive some continued or permanent benefit from having followed the regimen in the past. It was shown in postmenopausal women that bone loss resumed after estrogen use was discontinued (1, 2), but some protection against hip fracture remained for ≈2 y (3).

The continued effects of alendronate may last longer: studies lasting up to 2 y showed that much of the benefit derived during active treatment remained after withdrawal from the drug (4). To our knowledge, no information is available about the effect of withdrawal from calcium and vitamin D supplementation in elderly adults. There is some evidence that calcium-induced gains in bone mass are not maintained in growing children (5–8), but the effects under the different metabolic conditions of aging may be different.

The completion of a 3-y randomized, controlled trial of calcium and vitamin D supplementation in 295 elderly men and women (9) provided an opportunity to observe changes in bone mineral density (BMD) and bone turnover that occur when the study supplements are discontinued. This 3-y trial showed that supplementation with calcium and vitamin D reduced bone loss from the femoral neck, spine, and total body, and also reduced the incidence of nonvertebral fractures.

SUBJECTS AND METHODS

Subjects and study design

During a previous intervention study of the effects of calcium and vitamin D supplementation on BMD (9), one-half of the subjects were randomly assigned to receive 500 mg Ca/d as calcium citrate malate and 17.5 μg (700 IU) vitamin D/d (supplemented group) and the other half a placebo (placebo group). The intervention study enrolled only healthy, ambulatory men and women who had no disease and did not use any medications known to

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TABLE 1
Characteristics of the subjects at the beginning of the follow-up study (month 36), by prior treatment group in the intervention study (9)[1]

	Men		Women	
	Placebo (n = 65)	Supplemented (n = 63)	Placebo (n = 83)	Supplemented (n = 84)
Age (y)	74 ± 5[2]	73 ± 4	74 ± 5	73 ± 4
Height (m)	1.73 ± 0.07	1.74 ± 0.06	1.58 ± 0.07	1.58 ± 0.07
Weight (kg)	81.3 ± 12.5	82.0 ± 12.7	68.4 ± 13.4	66.9 ± 12.5
Dietary calcium (mg/d)	688 ± 331	769 ± 443	821 ± 478	686 ± 293[3]
Dietary vitamin D				
(μg/d)	5.0 ± 3.4	5.1 ± 2.9	4.7 ± 3.8	4.4 ± 2.3
(IU/d)	198 ± 134	202 ± 116	187 ± 152	177 ± 91
Smokers (%)	4.6	4.8	4.8	3.6
Physical activity score	118 ± 56	117 ± 51	113 ± 59	105 ± 47

[1] The supplemented group received 500 mg Ca plus 17.5 μg (700 IU) vitamin D daily for 3 y.
[2] $\bar{x}$ ± SD.
[3] Significantly different from placebo, P = 0.029.

affect calcium or bone metabolism. Measurements of BMD and other variables (*see* below) were made every 6 mo from 0 (baseline) to 36 (end of the study) mo.

The 389 subjects who completed the 36-mo intervention were invited to participate in the present follow-up study. Three-hundred twenty-five men and women aged ≥68 y were enrolled and 295 (91%) were followed annually for the full 2 y (through 60 mo). During the 2-y follow-up study, subjects were not given supplements; however, for ethical reasons, subjects were not asked to avoid taking supplements and their use of supplements was recorded as described below. At 48 mo (the middle of the follow-up study), each subject was informed of the results of the intervention study and of their treatment assignment in that study. Both the intervention and follow-up studies were approved by the Human Investigation Review Committee at Tufts University, and written, informed consent was obtained from each subject.

Measurements

At each study visit, subjects provided a medical history that included a description of the medications they used in the past year that are known to affect bone metabolism; calcium, vitamin D, and other supplements used in the past week; and the number of cigarettes smoked in the past year. The questionnaires used in the follow-up study were the same as those used in the intervention study. Dietary calcium and vitamin D intakes were assessed with a food-frequency questionnaire. Leisure, household, and occupational activities were estimated with the Physical Activity Scale for the Elderly questionnaire (10). Weight was measured with a digital scale and height with a Harpenden stadiometer (British Indicators Ltd, London). Nonvertebral fractures were identified during interviews at each visit. All nonvertebral fractures were verified by review of X-ray reports or medical records. At each study visit, subjects had BMD scans. Laboratory measurements were made at the initial and final visits (36 and 60 mo, respectively).

Analytic methods

BMDs of the femoral neck, spine (L2–L4 vertebrae), and total body were measured as described previously (9) with a DPX-L scanner (Lunar Radiation, Madison, WI); software versions 1.2 and 1.3 y were used for acquisition and analysis, respectively. CVs were 2.0% (femoral neck), 1.0% (spine), and 0.6% (total body) (11). Total-body bone mineral content (BMC) was measured with the same scanner and had a CV of 1.2%. The hip scans were performed in duplicate, with repositioning between scans, and the values were averaged. A phantom consisting of bone ash embedded in a 12.0-cm block was scanned bimonthly and the measurements were stable throughout the study.

Blood was drawn between 0700 and 0930 after the subjects had fasted for ≥8 h. Serum osteocalcin was measured by immunoradiometric assay (INCSTAR Corp, Stillwater, MN), as was serum intact parathyroid hormone (PTH) (Nichols Institute, San Juan Capistrano, CA). The interassay variation of these 2 measures was 4–5%. For each analysis, baseline (36 mo) and final (30 mo) samples were analyzed at the same time.

Statistical analysis

Comparisons between the study groups were made with two-sample t tests and with analysis of covariance when adjustments were required. Within-group changes in selected variables between the beginning and end of the study were examined with paired t tests. Potential interactions of selected variables with BMC were examined in multiple regression analyses. Dietary intake, physical activity, and biochemical data were missing in as many as 2 subjects per group; bone data were missing in as many as 5 subjects per group. Statistical tests were conducted at the two-tailed 0.05 level. SPSS for WINDOWS (release 8.0; SPSS Inc, Chicago) was used for the analyses.

RESULTS

The characteristics of the 295 subjects at the beginning of the follow-up study (36 mo) are shown in **Table 1**. In the women, dietary calcium intake was lower in those treated previously with calcium and vitamin D than with placebo. The difference was smaller and not significant by the end of the follow-up study. There was no significant change in dietary calcium or vitamin D intake in either treatment group during the 3-y intervention period. During the follow-up period, however, mean daily dietary calcium and vitamin D intakes rose significantly (P < 0.01) by a mean (±SD) of 87 ± 343 mg and 0.9 ± 3.2 μg (36 ± 128 IU), respectively. The magnitude of these increases did not differ significantly between the 2 treatment groups. Physical activity scores did not differ significantly by prior treatment during the follow-up study.

TABLE 2
Selected medication and supplement use during the follow-up study, by prior treatment group in the intervention study (9)[1]

	Men		Women	
	Placebo (n = 65)	Supplemented (n = 63)	Placebo (n = 83)	Supplemented (n = 84)
Glucocorticoids (%)	4.6	6.3	6.0	2.4
Estrogen (%)	0	0	6.0	8.3
Other medication (%)[2]	0	0	3.6	7.1
Calcium supplement use (%)[3]				
0 mg/d	54.7	54.8	35.4	28.0
1–250 mg/d	23.4	30.6	24.4	22.0
251–500 mg/d	9.4	4.8	13.4	13.4
>500 mg/d	12.5	9.7	26.8	36.6
Vitamin D supplement use (%)[3]				
0 μg/d	60.9	64.5	43.9	35.4
0–10.0 μg/d (1–400 IU/d)	30.0	30.6	42.7	46.3
10.0–17.5 μg/d (401–700 IU/d)	7.8	4.8	11.0	9.8
>17.5 μg/d (>700 IU/d)	1.6	0.0	2.4	8.5

[1] The supplemented group received 500 mg Ca plus 17.5 μg (700 IU) vitamin D daily for 3 y.
[2] Includes bone-active drugs such as alendronate and etidronate.
[3] Amount determined in the previous week (mean of 2 annual assessments).

The number of subjects using medications known to affect BMD was also fairly evenly distributed (**Table 2**). The mean BMD values of the 295 subjects at the start of the intervention study (0 mo) were used as the reference point for subsequent changes in BMD (**Table 3**). At 0 mo, mean femoral neck and spinal BMD were higher in men assigned to calcium and vitamin D than to placebo. Mean BMD changes during the follow-up study in the 295 subjects, by prior treatment assignment, are shown in **Figure 1**. For comparison, changes in BMD in the 295 subjects during the intervention study are shown in the shaded areas of the figure. In the men, significant treatment-by-group differences at the femoral neck and spine, observed at 36 mo, diminished gradually and were gone by the end of the 2-y follow-up (60 mo). In contrast, a significant treatment effect persisted in the total body, apparently in part because of a persistent effect on bone mass of the legs (data not shown). In the women, treatment effects at the spine and femoral neck during the intervention study were similar to those of the men, but were not significant.

By the end of the follow-up study, the BMD of the supplemented and placebo groups had become nearly identical. Similarly, the significant treatment effect on the total body at 36 mo disappeared within 1 y. Adjustment for differences in BMD between treatment group at 0 mo did not substantially alter the net changes in femoral neck or spine BMD through the end of the follow-up study (60 mo) in the men. Similarly, exclusion of the subjects who reported taking the medications shown in Table 2 did not significantly alter the results.

The changes in total-body BMC paralleled the changes in BMD (Figure 1). In the men, mean (±SEM) changes from baseline in total-body BMC in the supplemented and placebo groups were 1.18 ± 0.33 and –0.15 ± 0.34 g, respectively (P = 0.005), at 36 mo and 1.08 ± 0.38 and –0.51 ± 0.40 g, respectively (P = 0.005), at 60 mo. In the women, comparable values were 1.00 ± 0.44 and –0.80 ± 0.33 g, respectively (P = 0.001), at 36 mo and 0.52 ± 0.47 and 0.66 ± 0.50 g, respectively (P = 0.836), at 60 mo. Initial mean values did not differ significantly by treatment group in the men or the women (Table 3).

The percentage of subjects who chose to use calcium and vitamin D supplements during the follow-up study is shown in Table 2. More women than men reported use of calcium (P < 0.001) and vitamin D (P = 0.025) supplements, but within each sex group, the distribution of supplement use did not differ significantly by treatment group. There was no significant interaction between supplement use during the follow-up study and prior treatment assignment in multiple regression analyses of changes in BMD and BMC. Similarly, we were unable to detect a significant effect of supplement use during the follow-up study on the net change in BMD in either group.

TABLE 3
Bone mineral density and content of the subjects at enrollment into the prior intervention study (month 0) by treatment group (9)[1]

	Men		Women	
	Placebo (n = 65)	Supplemented (n = 63)	Placebo (n = 83)	Supplemented (n = 84)
Bone mineral density (g/cm^2)				
Femoral neck	0.94 ± 0.12	0.99 ± 0.14[2]	0.82 ± 0.11	0.81 ± 0.12
Spine	1.26 ± 0.18	1.33 ± 0.20[2]	1.05 ± 0.21	1.04 ± 0.18
Total body	1.19 ± 0.08	1.22 ± 0.09	1.03 ± 0.09	1.02 ± 0.10
Total-body bone mineral content (g)	2901 ± 410	3002 ± 350	1946 ± 338	1915 ± 312

[1] $\bar{x}$ ± SD. The supplemented group received 500 mg Ca plus 17.5 μg (700 IU) vitamin D daily for 3 y.
[2] Significantly different from placebo, P < 0.05.

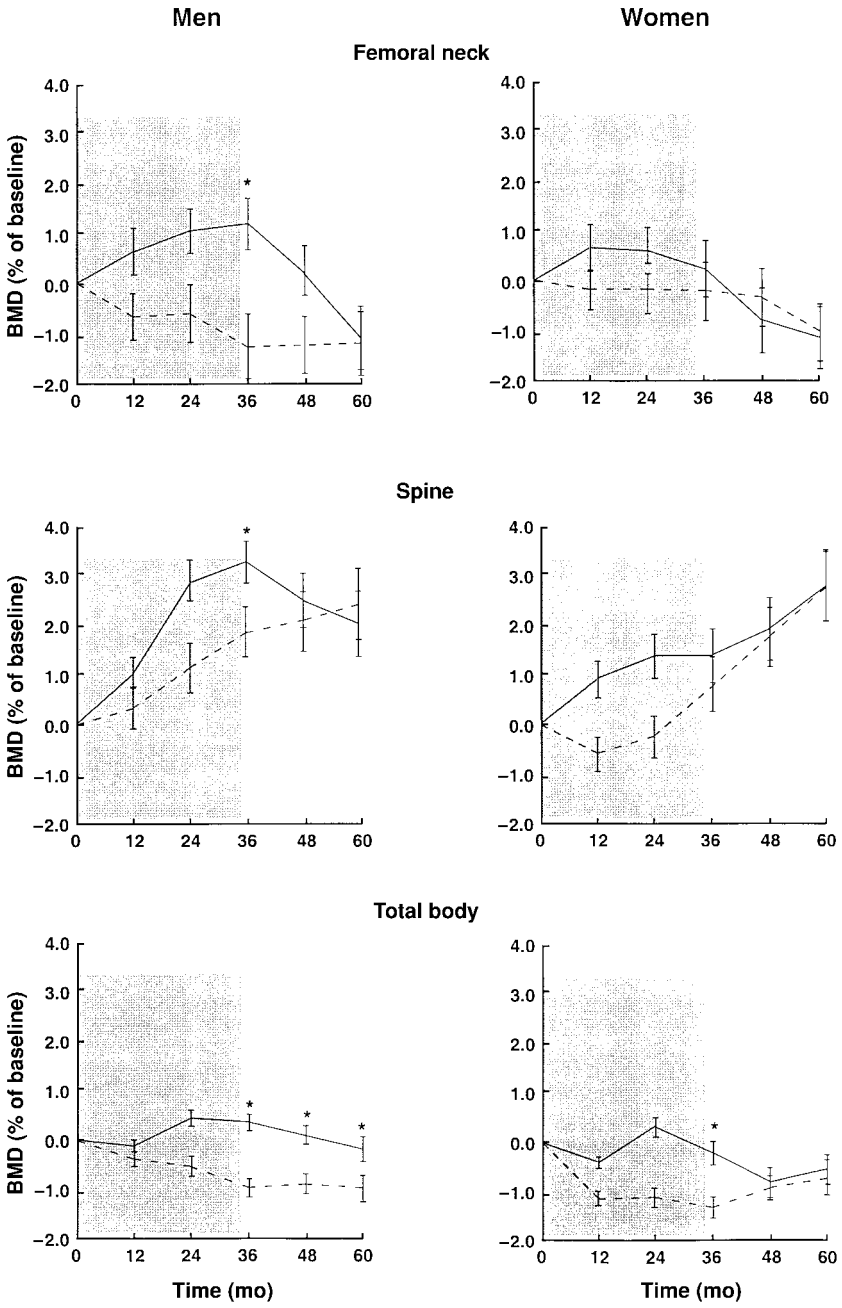

FIGURE 1. Mean (±SEM) changes in bone mineral density (BMD) in 295 men and women treated with placebo (- - -) or calcium and vitamin D (—) for 3 y (shaded areas) and then followed-up for 2 y with no supplementation. *Significantly different from the placebo group, $P < 0.05$.

Mean biochemical measures are shown in **Table 4**. In the men who used calcium and vitamin D supplements previously, the treatment-induced decline in serum PTH at 36 mo had reversed by 60 mo. In the women, there was a significant group difference in PTH at 36 and 60 mo. Serum PTH concentrations gradually increased in the men and women in the placebo group over the 5-y period. In the men, there was a significant treatment-by-group difference in serum osteocalcin at 36 mo but not at 60 mo. In the women, a similar pattern was observed but the difference at 36 mo was not significant.

Fourteen subjects (13 women and 1 man) had nonvertebral fractures during the follow-up study: 9 in the placebo group and 5 in the supplemented group [relative risk (RR): 0.6; 95% CI: 0.2, 1.6]. The fracture sites were ribs (n = 2), forearm (n = 2), knee (n = 1), ankle (n = 2), and foot (n = 2) in the placebo group and arm (n = 1), hand (n = 1), hip (n = 1), and ankle (n = 2) in the supplemented group.

DISCUSSION

Fewer than 1 in 10 American men and women aged >65 y meet the US National Academy of Sciences (12) recommendations for calcium (1200 mg/d) and vitamin D (400–600 IU/d) intakes (13); intakes in many other countries are also low

TABLE 4
Parathyroid hormone and osteocalcin concentrations of the subjects at 0, 36, and 60 mo by prior treatment group in the intervention study (9)[1]

	Men		Women	
	Placebo	Supplemented	Placebo	Supplemented
Parathyroid hormone (pmol/L)				
0 mo	3.70 ± 1.23[2]	3.90 ± 1.76	4.17 ± 1.58	3.89 ± 1.22
36 mo	3.81 ± 1.73	3.14 ± 1.42[3]	4.25 ± 2.17	3.07 ± 1.51[4]
60 mo	4.27 ± 1.79	4.13 ± 1.67	4.90 ± 2.34	4.06 ± 1.66[5]
Change from 36 to 60 mo	0.42 ± 1.33	1.03 ± 1.17[6]	0.62 ± 1.70	0.97 ± 1.43
Osteocalcin (nmol/L)				
0 mo	0.55 ± 0.18	0.51 ± 0.14	0.66 ± 0.22	0.65 ± 0.22
36 mo	0.60 ± 0.22	0.50 ± 0.17[6]	0.69 ± 0.25	0.62 ± 0.24
60 mo	0.56 ± 0.20	0.51 ± 0.19	0.62 ± 0.25	0.61 ± 0.22
Change from 36 to 60 mo	−0.04 ± 0.16	0.02 ± 0.15[7]	−0.08 ± 0.21	−0.01 ± 0.02

[1] The supplemented group received 500 mg Ca plus 17.5 μg (700 IU) vitamin D daily for 3 y.
[2] $\bar{x}$ ± SD.
[3–7] Significantly different from placebo: [3] $P = 0.02$, [4] $P < 0.001$, [5] $P = 0.009$, [6] $P = 0.007$, [7] $P = 0.036$.

(14–16). Although dietary supplements contribute significantly to total calcium and vitamin D intakes (17), use of these supplements is known to be sporadic (18).

This study showed that the improvements in BMD observed in subjects who were supplemented to recommended intakes of calcium and vitamin D were largely lost when supplementation was discontinued. A modest benefit to total-body BMD remained after 2 y in men, but there was no remaining benefit in men or in women at 2 clinically important skeletal sites: the lumbar vertebrae and the femoral neck. For both the men and women, the reduction in the bone remodeling rate that occurred with treatment was also lost. The increase in serum PTH that occurred after supplement withdrawal probably stimulated the reopening of remodeling space. The smaller increases in serum PTH in the placebo group than in the supplemented group are consistent with the changes that occur with aging.

Calcium and vitamin D supplement use during the follow-up study had no discernible effect on the results, perhaps because the amounts taken by users were less than half of those taken during the intervention study and perhaps because of irregular use. The increase in dietary calcium and vitamin D intakes after, but not during, the intervention study may have resulted because of discontinued supplement use as well as other factors. The modest but remaining effect of supplementation on total-body BMD in men but not in women is of interest. It is unlikely that this effect was the result of an incomplete "remodeling transient" (19), because both the changes in bone at other sites and in the biochemical marker of bone turnover (ie, serum osteocalcin) had completely reversed over the 2-y follow-up study. It is possible that endogenous estrogen concentrations, known to be higher in men than in women at this age (20), may have enhanced the utilization of dietary calcium (21, 22) in the men. This study did not have the power to examine possible lasting effects of discontinued supplementation on fracture risk.

In conclusion, there were no remaining supplement-related benefits to spine or femoral neck BMD or to bone turnover in male and female subjects 2 y after supplementation with calcium and vitamin D ended, although some benefit to total-body BMD remained in men only. Because intermittent use of calcium and vitamin D supplements provides limited long-term skeletal benefit in men aged >68 y but no identifiable cumulative benefit in women of this age, we recommend that men and women aged >68 y meet current calcium and vitamin D intake requirements continuously.

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