

EFFECT OF CALCIUM AND VITAMIN D SUPPLEMENTATION ON BONE DENSITY IN MEN AND WOMEN 65 YEARS OF AGE OR OLDER

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ABSTRACT

Background Inadequate dietary intake of calcium and vitamin D may contribute to the high prevalence of osteoporosis among older persons.

Methods We studied the effects of three years of dietary supplementation with calcium and vitamin D on bone mineral density, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures in 176 men and 213 women 65 years of age or older who were living at home. They received either 500 mg of calcium plus 700 IU of vitamin D₃ (cholecalciferol) per day or placebo. Bone mineral density was measured by dual-energy x-ray absorptiometry, blood and urine were analyzed every six months, and cases of nonvertebral fracture were ascertained by means of interviews and verified with use of hospital records.

Results The mean (\pm SD) changes in bone mineral density in the calcium-vitamin D and placebo groups were as follows: femoral neck, $+0.50 \pm 4.80$ and -0.70 ± 5.03 percent, respectively ($P=0.02$); spine, $+2.12 \pm 4.06$ and $+1.22 \pm 4.25$ percent ($P=0.04$); and total body, $+0.06 \pm 1.83$ and -1.09 ± 1.71 percent ($P<0.001$). The difference between the calcium-vitamin D and placebo groups was significant at all skeletal sites after one year, but it was significant only for total-body bone mineral density in the second and third years. Of 37 subjects who had nonvertebral fractures, 26 were in the placebo group and 11 were in the calcium-vitamin D group ($P=0.02$).

Conclusions In men and women 65 years of age or older who are living in the community, dietary supplementation with calcium and vitamin D moderately reduced bone loss measured in the femoral neck, spine, and total body over the three-year study period and reduced the incidence of nonvertebral fractures. (N Engl J Med 1997;337:670-6.)

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IN ADEQUATE intake of calcium and vitamin D leads to reduced calcium absorption, increased serum parathyroid hormone concentrations, and bone loss. Low bone mass is a strong predictor of fracture.¹ Supplemental calcium reduces bone loss in middle-aged, postmenopausal women²⁻⁸ and lowers rates of vertebral fracture in women with previous vertebral fractures.⁹ Supplementation with vitamin D alone reduced bone loss from the femoral neck in postmenopausal women,^{10,11} but it did not reduce the rate of hip fracture among elderly Dutch men and women.¹² Annual intramuscular injections

of vitamin D did, however, reduce rates of arm fracture among elderly Finnish subjects.¹³

There is a rationale for supplementing the diets of elderly subjects with a combination of calcium and vitamin D. Absorption of calcium¹⁴ and possibly of vitamin D¹⁵ and production of vitamin D¹⁶ by the skin decline with aging. Diets that are deficient in calcium tend also to be deficient in vitamin D because a single food, milk, is the principal dietary source of both these nutrients. Combined calcium and vitamin D supplementation has reduced rates of nonvertebral fracture among elderly women living in retirement homes.¹⁷ In the one available study of men (mean age, 58 years) who lived at home, calcium and vitamin D together did not reduce bone loss.¹⁸ The role of combined supplements in elderly men and women living at home is unknown. We examined the effects of combined calcium and vitamin D supplementation on bone loss, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures in men and women 65 years of age or older who were living in the community.

METHODS**Subjects**

We studied only healthy, ambulatory men and women 65 years of age or older who were recruited through direct mailings and presentations in the community. The criteria for exclusion included current cancer or hyperparathyroidism; a kidney stone in the past five years; renal disease; bilateral hip surgery; therapy with a bisphosphonate, calcitonin, estrogen, tamoxifen, or testosterone in the past six months or fluoride in the past two years; femoral-neck bone mineral density more than 2 SD below the mean for subjects of the same age and sex; dietary calcium intake exceeding 1500 mg per day; and laboratory evidence of kidney or liver disease.

We prescreened 848 subjects by means of a questionnaire and invited 545 for screening. Of these, 51 were found to be ineligible, 49 were potentially eligible but were not enrolled, and 445 (199 men and 246 women) were enrolled. There were 430 whites, 11 blacks, and 4 Asians. The protocol was approved by the Human Investigation Review Committee at Tufts University, and written informed consent was obtained from each subject.

Study Design and Supplements

In this three-year, double-blind, placebo-controlled trial, the subjects were randomly assigned to either the placebo or the calcium-vitamin D group with stratification according to sex, race, and decade of age. At study entry, we performed physical examinations and assessed the subjects' medical history, diet, and phys-

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ical-activity level; analyzed blood and urine; and measured bone mineral density. The subjects were advised to maintain their usual diets and to avoid taking supplemental calcium and vitamin D on their own for two months before and throughout the study. At bedtime, the subjects took separate pills containing 500 mg of elemental calcium in the form of calcium citrate malate¹⁹ and 700 IU of cholecalciferol or separate placebo tablets containing microcrystalline cellulose.

Calcium citrate malate (Procter & Gamble, Cincinnati) was prepared in two batches; assays confirmed that the contents were as expected. The vitamin D tablets used initially contained 707 IU; two years later, the tablets were found to contain 563 IU (80 percent) of the planned dose of 700 IU; a second lot initially containing 768 IU was used during the second half of the study. The tablets were stored in opaque bottles at room temperature.

Status of Subjects and Compliance

During the trial, 127 subjects discontinued treatment; 4 died, 40 stopped for personal reasons (e.g., they lost interest or moved away), 46 withdrew because of illness, 17 started estrogen or glucocorticoid therapy, and 20 withdrew because of problems with the medication. The majority of subjects who discontinued treatment did so in the first year. These subjects were encouraged to return for all subsequent follow-up evaluations. At the last visit, 389 subjects (87 percent of the 445 enrolled) were evaluated and were included in the main intention-to-treat analyses. The 318 subjects who remained in the two study groups (i.e., those who took the supplements throughout the study period) were included in the analyses of subjects who completed the study according to the protocol.

The mean (\pm SD) rate of compliance with treatment, assessed on the basis of pill counts, was 92 ± 10 percent for the calcium or placebo tablets and 93 ± 10 percent for the vitamin D or placebo tablets among the 318 subjects who completed the study.

Measurements

The subjects came to the center every six months for measurements of bone mineral density, biochemical assays, and other measurements. Their calcium and vitamin D intake was estimated on the basis of a food-frequency questionnaire.²⁰ During the study, 44 of the subjects who completed the study treatment (23 in the placebo group and 21 in the calcium-vitamin D group) reported taking products that contained some calcium or vitamin D. They were asked to stop taking these products, and the intake from supplements was added to their dietary intake during the relevant period. Leisure, household, and occupational activity was estimated with use of the Physical Activity Scale for the Elderly questionnaire.²¹ Tobacco use was determined by questionnaire. Height was measured with a stadiometer, and weight with a digital scale.

The subjects were asked to send in a postcard after any fall. When such a postcard was received, a staff member called the subject to verify the circumstances. Subjects reported any additional falls at each follow-up visit. Nonvertebral fractures were identified during interviews at the same visits. The principal investigator, who was unaware of the subjects' study-group assignments, classified the fractures as nonosteoporotic (resulting from severe trauma) or osteoporotic (resulting from moderate-to-minor trauma — i.e., a fall from standing height or less). All but one nonvertebral fracture (a presumed toe fracture that was not treated) were verified by review of x-ray reports or hospital records.

Analytic Methods

Bone mineral density in the hip, spine, and total body was measured by dual-energy x-ray absorptiometry with use of a DPX-L scanner (Lunar Radiation, Madison, Wis.). Scanner software versions 1.2 and 1.3y were used for data acquisition and analysis, respectively. The coefficients of variation for the measurements were 2.0 percent (femoral neck), 1.0 percent (spine), and 0.6 percent (total body). The scans of the hip were performed in duplicate,

with repositioning between scans, and the values were averaged. A phantom consisting of bone ash embedded in a 12-cm block was scanned every other week as a control; the bone mineral density of the phantom was stable throughout the study.

Blood was drawn between 7:00 and 9:30 a.m. after the subjects had fasted for at least eight hours. Urine measurements were made in 24-hour collections. Plasma 25-hydroxyvitamin D was measured by the method of Preece et al.,²² plasma 1,25-dihydroxyvitamin D by a competitive protein-binding method,²³ serum parathyroid hormone by immunometric assay (Nichols Institute, San Juan Capistrano, Calif.), serum osteocalcin by immunoradiometric assay (Nichols Institute), urinary N-telopeptide cross-links by enzyme-linked immunosorbent assay (Ostex International, Seattle), and serum ionized calcium and urinary calcium and creatinine as reported previously.²⁰ The coefficients of variation for these measures ranged from 5.6 percent to 7.7 percent. Analyses were performed as the samples were collected, except for the plasma 1,25-dihydroxyvitamin D and urinary N-telopeptide assays, for which initial and final samples were analyzed at the same time.

Statistical Analysis

Comparisons between the study groups were made with two-sample t-tests and, when adjustments were required, with analysis of covariance. Terms for the interaction of sex and study group in analysis-of-variance models of the change in bone mineral density were statistically significant only at the femoral neck in the subjects in the intention-to-treat analysis; this term did not remain significant after adjustment for the duration of treatment. The relative risks of fracture among the subjects in the calcium-vitamin D and placebo groups were compared by means of the chi-square test. Analyses were conducted with SPSS (SPSS Inc., Chicago) and SAS (SAS Institute, Cary, N.C.) software. All P values are two-sided. Intention-to-treat analyses were conducted according to the principles described by Newell²⁴; selected secondary analyses were restricted to subjects who completed the study.

RESULTS

The base-line characteristics of the 389 subjects are shown in Table 1. As compared with placebo, supplementation with calcium and vitamin D had a significant positive effect on the change over three years in bone mineral density measured at the femoral neck, spine, and total body in all subjects together and in the men (Table 2). The women in the calcium-vitamin D group had significantly less total-body bone loss than those in the placebo group; the differences in the changes at the femoral neck and spine were smaller and not statistically significant. Adjustment for differences between the study groups in base-line bone mineral density and calcium intake did not alter the results.

The time course of the response to treatment was examined in the 318 subjects who completed the study. Their clinical characteristics and bone mineral density at base line did not differ significantly from those of subjects who discontinued the study treatment, except that smoking was more prevalent in the latter group (10 percent, as compared with 4 percent among those who completed the study; $P = 0.02$). During the first year there was significantly less bone loss at the hip, spine, and total body in the calcium-vitamin D group; during the second and third years, however, there was significantly less loss only in the total body (Table 3).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 389 STUDY SUBJECTS.*

CHARACTERISTIC	MEN		WOMEN	
	PLACEBO GROUP (N=90)	CALCIUM-VITAMIN D GROUP (N=86)	PLACEBO GROUP (N=112)	CALCIUM-VITAMIN D GROUP (N=101)
Age (yr)	71±5	70±4	72±5	71±4
Height (cm)	173.8±6.9	174.3±6.2	159.5±6.6	159.2±6.4
Weight (kg)	81.5±12.8	82.4±11.3	68.1±12.4	67.6±12.1
Dietary calcium intake (mg/day)	673±349	748±391	798±366	689±286
Dietary vitamin D intake (IU/day)	197±117	202±104	184±110	174±90
Smoker (%)	4.4	7.0	5.4	5.9
Physical-activity score	127±56 (89)	124±60 (85)	108±54	105±48
Bone mineral density (g/cm ²)				
Femoral neck	0.95±0.12	0.99±0.14	0.81±0.11	0.80±0.11
Spine	1.27±0.20 (89)	1.32±0.21	1.05±0.20 (109)	1.03±0.18 (97)
Total body	1.19±0.09 (89)	1.22±0.09	1.02±0.09	1.02±0.10

*Plus-minus values are means ±SD. When there were missing data, the number of subjects for whom data were available is shown in parentheses.

TABLE 2. CHANGE IN BONE MINERAL DENSITY OVER THREE YEARS IN ALL SUBJECTS AND IN SUBJECTS WHO COMPLETED THE STUDY.*

SUBJECTS AND SITE	ALL SUBJECTS (N=389)			SUBJECTS COMPLETING STUDY (N=318)		
	PLACEBO GROUP (N=202)	CALCIUM-VITAMIN D GROUP (N=187)	P VALUE	PLACEBO GROUP (N=170)	CALCIUM-VITAMIN D GROUP (N=148)	P VALUE
	percent change			percent change		
All subjects						
Femoral neck	-0.70±5.03 (201)	+0.50±4.80 (185)	0.02	-0.45±5.07 (170)	+0.81±4.44 (148)	0.02
Spine (L2-L4)	+1.22±4.25 (197)	+2.12±4.06 (180)	0.04	+1.27±4.31 (166)	+2.56±3.93 (145)	0.006
Total body	-1.09±1.71 (199)	+0.06±1.83 (186)	<0.001	-1.04±1.71 (168)	+0.30±1.58 (148)	<0.001
Men						
Femoral neck	-1.35±4.70 (90)	+0.95±4.07 (85)	<0.001	-0.88±4.59 (77)	+0.91±3.92 (71)	0.01
Spine (L2-L4)	+1.74±3.85 (89)	+2.93±3.42 (84)	0.03	+2.03±3.69 (76)	+3.34±3.33 (70)	0.03
Total body	-0.85±1.53 (88)	+0.34±1.40 (86)	<0.001	-0.67±1.47 (75)	+0.48±1.34 (71)	<0.001
Women						
Femoral neck	-0.17±5.25 (111)	+0.11±5.34 (100)	0.70	-0.09±5.43 (93)	+0.71±4.90 (77)	0.31
Spine (L2-L4)	+0.78±4.54 (108)	+1.41±4.45 (96)	0.32	+0.63±4.71 (90)	+1.85±4.32 (75)	0.09
Total body	-1.29±1.82 (111)	-0.17±2.11 (100)	<0.001	-1.34±1.84 (93)	+0.14±1.76 (77)	<0.001

*Plus-minus values are means ±SD. The number of subjects for whom data were available is shown in parentheses. An interaction of sex with study group was statistically significant only at the femoral neck in all subjects (P=0.05); the P value for this interaction in subjects who completed the study was 0.36.

Among the 318 subjects who completed the study, those treated with calcium and vitamin D had significantly greater changes in a number of biochemical measures of bone metabolism (Table 4). Serum osteocalcin concentrations and urinary excretion of N-telopeptide were significantly lower in the men than in the women throughout the study (P=0.005).

Among the 389 study subjects, 37 (5 men and 32 women) had at least one nonvertebral fracture during the study period. The cumulative incidence of a first fracture at three years was 5.9 percent in the cal-

cium-vitamin D group and 12.9 percent in the placebo group (relative risk, 0.5; 95 percent confidence interval, 0.2 to 0.9; P=0.02) (Table 5 and Fig. 1). Among the women in the placebo group, the incidence of fractures at three years was 19.6 percent. Twenty-eight subjects (76 percent) had fractures classified as osteoporotic; the three-year cumulative incidence of a first osteoporotic fracture in the calcium-vitamin D group was lower than that in the placebo group (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; P=0.01). Only two men, both

TABLE 3. RATES OF CHANGE IN BONE MINERAL DENSITY IN 318 SUBJECTS WHO COMPLETED THE STUDY, ACCORDING TO THE DURATION OF TREATMENT.*

SUBJECTS AND SITE	YEAR 1			YEARS 2 AND 3		
	PLACEBO GROUP	CALCIUM-VITAMIN D GROUP	P VALUE	PLACEBO GROUP	CALCIUM-VITAMIN D GROUP	P VALUE
	percent change/year			percent change/year		
All						
Femoral neck	-0.22±3.65 (168)	+0.64±3.96 (145)	0.05	-0.08±2.42 (168)	+0.18±1.90 (145)	0.30
Spine (L2-L4)	-0.29±2.92 (165)	+1.09±2.59 (145)	<0.001	+0.79±1.90 (166)	+0.73±1.50 (144)	0.75
Total body	-0.76±1.28 (168)	-0.16±1.11 (146)	<0.001	-0.14±0.68 (168)	+0.23±0.70 (146)	<0.001
Men						
Femoral neck	-0.55±3.61 (76)	+0.56±3.36 (69)	0.06	-0.12±2.22 (76)	+0.36±1.72 (69)	0.15
Spine (L2-L4)	+0.31±2.83 (76)	+1.29±1.95 (71)	0.02	+0.87±1.59 (76)	+1.00±1.54 (70)	0.61
Total body	-0.33±1.11 (76)	-0.10±1.14 (70)	0.22	-0.17±0.65 (76)	+0.30±0.59 (70)	<0.001
Women						
Femoral neck	+0.05±3.68 (92)	+0.72±4.46 (76)	0.30	-0.04±2.60 (92)	+0.01±2.04 (76)	0.88
Spine (L2-L4)	-0.80±2.91 (89)	+0.90±3.08 (74)	<0.001	+0.72±2.13 (90)	+0.46±1.43 (74)	0.36
Total body	-1.11±1.30 (92)	-0.22±1.08 (76)	<0.001	-0.11±0.71 (92)	+0.18±0.79 (76)	0.02

*Plus-minus values are means ±SD. The number of subjects for whom data were available is shown in parentheses.

TABLE 4. INITIAL LABORATORY VALUES AND CHANGES AT THREE YEARS IN 313 SUBJECTS WHO COMPLETED THE STUDY, ACCORDING TO STUDY GROUP.*

INDEX AND STUDY GROUP	MEN (N = 146)		WOMEN (N = 167)	
	INITIAL VALUE	CHANGE	INITIAL VALUE	CHANGE
Serum ionized calcium (mg/dl)				
Placebo	5.0±0.2	+0.0±0.1	5.0±0.2	+0.0±0.2
Calcium-vitamin D	5.0±0.2	+0.1±0.2†	5.1±0.2	+0.1±0.1
Plasma 25-hydroxyvitamin D (ng/ml)				
Placebo	33.6±12.7	-2.68±10.2	24.5±10.3	+0.7±8.1
Calcium-vitamin D	33.0±16.3	+11.8±11.6†	28.7±13.3‡	+16.1±14.3†
Plasma 1,25-dihydroxyvitamin D (pg/ml)§				
Placebo	33.3±6.7	-4.8±8.7	37.3±8.0	-6.7±8.7
Calcium-vitamin D	33.6±7.0	-6.3±11.0	36.5±7.3	-5.8±9.5
Serum parathyroid hormone (pg/ml)				
Placebo	34.8±13.6	+6.2±11.2	42.6±18.9	+5.7±15.0
Calcium-vitamin D	38.0±19.1	-7.0±12.9†	37.4±15.3‡	-5.5±13.2†
Serum osteocalcin (ng/ml)				
Placebo	5.7±1.9	+0.2±1.6	7.0±2.4	+0.0±2.1
Calcium-vitamin D	5.3±1.3	-0.5±1.4†	6.9±2.5	-0.9±1.9†
24-hr urinary calcium:creatinine ratio (mg/g)				
Placebo	98±46	-4±44	119±55	+9±62
Calcium-vitamin D	98±50	+35±51†	113±64	+67±64†
24-hr urinary N-telopeptide:creatinine ratio (nmol/mmol)				
Placebo	32±16	+1±10	48±30	-2±32
Calcium-vitamin D	29±9	-2±12	45±17	-2±16

*Plus-minus values are means ±SD. To convert values for calcium to millimoles per liter, multiply by 0.25; to convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50; to convert values for 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.40; to convert values for parathyroid hormone to picomoles per liter, multiply by 0.106; to convert values for osteocalcin to nanomoles per liter, multiply by 0.172; to convert values for the 24-hour urinary calcium:creatinine ratio to millimoles per mole, multiply by 2.82. Initial or final laboratory values were missing for five subjects.

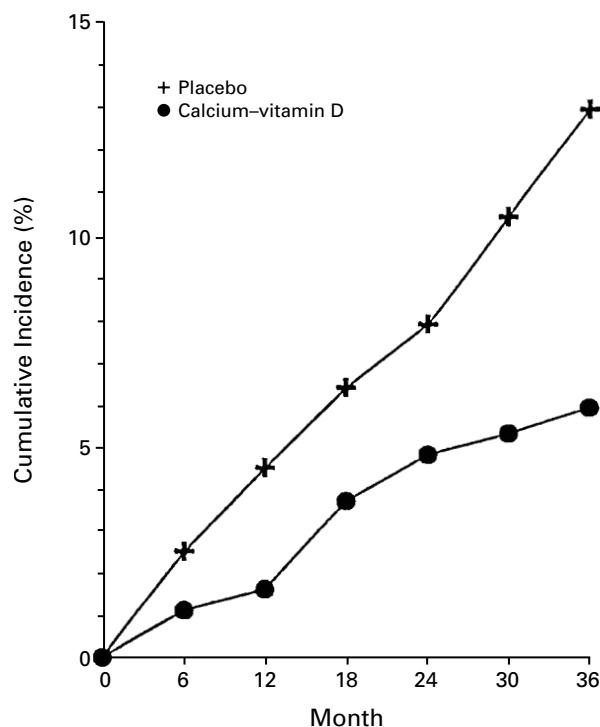
†P<0.005 for the comparison between the study groups.

‡P≤0.05 for the comparison between the study groups.

§Final measurements were made at 18 months.

TABLE 5. NUMBER OF FIRST NONVERTEBRAL FRACTURES AMONG ALL SUBJECTS, ACCORDING TO SKELETAL SITE.

SITE OF FRACTURE	PLACEBO GROUP (N=202)	CALCIUM-VITAMIN D GROUP (N=187)
Face	1	1
Shoulder, humerus, or clavicle	4	3
Radius or ulna	5	1
Hand	1	1
Ribs	2	2
Pelvis	2	0
Hip	1	0
Tibia or fibula	1	1
Ankle or foot	7	2
Multiple sites	2	0
Total	26	11

**Figure 1.** Cumulative Percentage of All 389 Subjects with a First Nonvertebral Fracture, According to Study Group.

By 36 months, 26 of 202 subjects in the placebo group and 11 of 187 subjects in the calcium-vitamin D group had had a fracture ($P=0.02$).

in the placebo group, had osteoporotic fractures, and the best predictor of osteoporotic fracture was female sex ($P<0.001$). Among the 318 subjects who completed the study, the relative risk of any first nonvertebral fracture in the calcium-vitamin D group as compared with the placebo group was 0.4 (95 percent confidence interval, 0.2 to 1.0; $P=0.03$), and that for fractures classified as osteoporotic was 0.4 (95 percent confidence interval, 0.2 to 1.1; $P=0.06$). There was no significant difference between the treatment groups in the percentage of subjects who fell; among women, the number of falls per subject who fell was somewhat higher in the calcium-vitamin D group than in the placebo group (data not shown). Two women (one in each study group) had a second osteoporotic fracture during the study.

The supplements were generally well tolerated, but 11 subjects discontinued treatment because of difficulty swallowing the pills and 9 discontinued because of other side effects (in the placebo group: 2 because of epigastric distress and 1 because of flank pain; in the calcium-vitamin D group: 3 because of constipation, 1 because of epigastric distress, 1 because of sweating, and 1 because of hypercalciuria).

DISCUSSION

In this study, dietary supplementation with calcium and vitamin D reduced bone loss moderately in men and women 65 years of age or older who were living in the community. Among the men, there was a significant effect of treatment at the hip, spine, and total body. In an earlier study by Orwoll et al., a similar regimen of calcium and vitamin D had no effect, perhaps because the men in that study were younger and had a higher mean calcium intake than the men we studied (1160 vs. about 700 mg per day).¹⁸ The reduction in total-body bone loss in women in this study was similar to that in other trials of calcium supplementation alone.^{3,4} The estimated differences in bone mineral density at the femoral neck and spine among the women in the two study groups were similar to those found in other studies,^{2-4,6,10,11,25} although the differences did not reach statistical significance in our study. The effect of supplementation in all subjects was similar to that in the subjects who completed the study, as would be expected, given the high degree of overlap between the two groups. Treatment caused few symptoms or side effects.

In both men and women, calcium-vitamin D supplementation reduced total-body bone loss not only in the first year (an effect that could be ascribed to the closure of bone-remodeling space²⁶), but also in the second and third years, suggesting long-term effectiveness of supplementation in terms of the skeleton as a whole. The initial effects of supplementation at the hip and spine during year 1 were maintained but not increased during the ensuing two years of the

study. Others have reported a cumulative benefit in terms of total-body^{3,4} and femoral-neck³ bone density with the use of higher doses of calcium in younger postmenopausal women. Spinal bone mineral density increased in both study groups, probably because of increases in osteoarthritis and aortic calcification.^{27,28}

After three years of calcium-vitamin D supplementation, serum osteocalcin concentrations were 9 percent lower in the men and 14 percent lower in the women than at base line, indicating that supplementation led to a sustained reduction in the rate of bone remodeling. The lack of change in urinary N-telopeptide excretion may reflect the variability of this measurement. Our study confirms previous observations that the rate of bone turnover, as measured by urinary excretion of pyridinoline cross-links²⁹ and serum osteocalcin concentrations,³⁰ is lower in men than in women.

The reduction in the incidence of nonvertebral fractures in the calcium-vitamin D group should be interpreted with some caution, because of the small number of study subjects. Nonetheless, the magnitude of the reduction in the risk of fracture was similar to that reported in a study of more than 3400 elderly French women treated with 1200 mg of calcium plus 800 IU of vitamin D or placebo each day.¹⁷ In a study of 2600 elderly Dutch men and women, there was no reduction in the incidence of fractures among those given 400 IU of vitamin D daily (without calcium), as compared with those given placebo.¹² Our results differ from those of the Dutch study, possibly by chance (we studied fewer subjects) or because the treatments differed. When comparing the three-year rates of nonvertebral fractures among women assigned to placebo in several recent trials, we found that the 19.6 percent rate in this study was intermediate between the 9 percent reported for women who were, on average, 7 years younger than our subjects³¹ and the 27 percent reported for women who were 13 years older.¹⁷ We do not know the individual contributions of calcium or vitamin D to the results in our study.

The limited effect of calcium and vitamin D on bone mineral density, which was evident primarily in year 1, seems unlikely to account for the constant decline in the rate of nonvertebral fractures during the three-year study. A treatment-induced reduction in the incidence of falls does not appear to account for the reduction in the rate of fractures, since the number of falls was similar in the two groups. The reduction in the rate of bone turnover may have influenced the fracture rate by reducing the potential for trabecular perforation and reducing cortical porosity.

In conclusion, calcium and vitamin D supplementation leads to a moderate reduction in bone loss and may substantially reduce the risk of nonvertebral fractures among men and women 65 years of age or older who live in the community.

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REFERENCES

1. Melton LJ III, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res* 1993;8:1227-33.
2. Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 1990;323:878-83.
3. Aloia JE, Vaswani A, Yeh JK, Ross PL, Flaster E, Dillman FA. Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. *Ann Intern Med* 1994;120:97-103.
4. 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;98:331-5.
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;4:245-52.
6. Elders PJM, Netelenbos JC, Lips P, et al. Calcium supplementation reduces vertebral bone loss in perimenopausal women: a controlled trial in 248 women between 46 and 55 years of age. *J Clin Endocrinol Metab* 1991;73:533-40.
7. Riis B, Thomsen K, Christiansen C. Does calcium supplementation prevent postmenopausal bone loss? A double-blind, controlled clinical study. *N Engl J Med* 1987;316:173-7.
8. 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;10:1068-75.
9. Recker RR, Henders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;11:1961-6.
10. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D. *Am J Clin Nutr* 1995;61:1140-5.
11. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJF, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. *J Clin Endocrinol Metab* 1995;80:1052-8.
12. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;124:400-6.
13. Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992;51:105-10.
14. Bullamore JR, Wilkinson R, Gallagher JC, Nordin BEC, Marshall DH. Effect of age on calcium absorption. *Lancet* 1970;2:535-7.
15. Barragry JM, France MW, Corless D, et al. Intestinal cholecalciferol absorption in the elderly and in younger adults. *Clin Sci Mol Med* 1978;55:213-20.
16. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D₃. *J Clin Invest* 1985;76:1536-8.
17. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D₃ and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637-42.
18. Orwoll ES, Oviatt SK, McClung MR, Deftos LJ, Sexton G. The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann Intern Med* 1990;112:29-34.
19. Smith KT, Heaney RP, Flora L, Henders SM. Calcium absorption from a new calcium delivery system (CCM). *Calcif Tissue Int* 1987;41:351-2.
20. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. *N Engl J Med* 1989;321:1777-83.
21. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993;46:153-62.
22. Preece MA, O'Riordan JL, Lawson DE, Kodicek E. A competitive protein-binding assay for 25-dihydroxycholecalciferol and 25-hydroxyergocalciferol in serum. *Clin Chim Acta* 1974;54:235-42.

23. Reinhardt TA, Horst RL, Orf JW, Hollis BW. A microassay for 1,25-dihydroxyvitamin D not requiring high performance liquid chromatography: application to clinical studies. *J Clin Endocrinol Metab* 1984;58:91-8.
24. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol* 1992;21:837-41.
25. Ensrud KE, Palermo L, Black DM, et al. Hip and calcaneal bone loss increase with advancing age: longitudinal results from the study of osteoporotic fractures. *J Bone Miner Res* 1995;10:1778-87.
26. Remodeling as a determinant of envelope physiology. In: Frost HM. Bone remodeling and its relationship to metabolic bone diseases. Orthopedic lectures. Vol. 3. Springfield, Ill.: Charles C Thomas, 1973:28-53.
27. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. *BMJ* 1994;309:691-5.
28. Greenspan SL, Maitland LA, Myers ER, Krasnow MB, Kido TH. Femoral bone loss progresses with age: a longitudinal study in women over age 65. *J Bone Miner Res* 1994;9:1959-65.
29. Delmas PD, Gineyts E, Bertholin A, Garnero P, Marchand F. Immunoassay of pyridinoline crosslink excretion in normal adults and in Paget's disease. *J Bone Miner Res* 1993;8:643-8.
30. Epstein S, Poser J, McClintock R, Johnston CC Jr, Bryce G, Hui S. Differences in serum bone GLA protein with age and sex. *Lancet* 1984;1:307-10.
31. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333:1437-43.