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Effect of Vitamin D_3 and Calcium on Fracture Risk in 65- to 71-Year-Old Women: A Population-Based 3-Year Randomized, Controlled Trial—The OSTPRE-FPS

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ABSTRACT

Antifracture efficacy of high-dose vitamin D (800 IU) and calcium (1000 mg) remains controversial. To determine whether daily 800 IU of vitamin D and 1000 mg of calcium supplementation prevents fractures, we randomized 3432 women of the population-based Osteoporosis Risk Factor and Prevention (OSTPRE) Study cohort (ages 65 to 71 years) living in the region of northern Savonia, Finland (latitude 62° to 64°N) for 3 years to receive 800 IU of cholecalciferol and 1000 mg of calcium as calcium carbonate or to a control group that did not receive placebo. The main outcome measure was incident fractures. Fracture data were collected in telephone interviews and validated. Data on 3195 women, 1586 in the intervention group and 1609 in the control group, were available for analysis. In adjusted Cox proportional hazards models, the risk of any fracture decreased in the vitamin D and calcium group by 17% [adjusted hazard ratio (aHR) = 0.83; 95% confidence interval (CI) 0.61–1.12], and the risk of any nonvertebral fracture decreased by 13% (aHR = 0.87; 95% CI 0.63–1.19). The risk of distal forearm fractures decreased by 30% (aHR = 0.70; 95% CI 0.41–1.20), and the risk of any upper extremity fractures decreased by 25% (aHR = 0.75; 95% CI 0.49–1.16), whereas the risk of lower extremity fractures remained essentially equal (aHR = 1.02; 95% CI 0.58–1.80). None of these effects reached statistical significance. In conclusion, this study did not produce statistically significant evidence that vitamin D and calcium supplementation prevents fractures in a 65- to 71-year-old general population of postmenopausal women. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: CLINICAL TRIALS; VITAMIN D; CALCIUM; FRACTURES; POPULATION STUDIES

Introduction

Postmenopausal osteoporosis, bone fragility, and low-energy fractures constitute a major health economic problem in elderly women. Vitamin D and calcium are recognized to play an important role in bone health. While calcium serves as one of the main constituents of bone matrix, vitamin D enhances calcium absorption. Further, vitamin D is also known to have an effect on muscle strength[1] and on postural and dynamic balance.[2] Deficiency of calcium or vitamin D regulates the production of parathyroid hormone (PTH).[3] High PTH levels activate bone turnover and degradation.[4,5] Normal levels of vitamin D and calcium protect the bone matrix by preventing secondary hyperparathyroidism.[4,6] Further, normalization of low vitamin D status helps to maintain normal muscle function and balance, decreasing the risks of falling and fracture.[7–10]

In most cases, dietary sources of vitamin D are not sufficient, and people get most of their vitamin D from sunlight. People living in high latitudes have less exposure to sunlight and thus lower production of vitamin D.[11] The problem is particularly common in the elderly.[12,13]

Postmenopausal osteoporosis constitutes the highest fracture risk in the elderly female population. Several strategies for fracture prevention in this population have been suggested, and the

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fracture-preventing effect of vitamin D has been shown in some trials.[14–19] Results of other trials, however, have been conflicting.[20–27] Meta-analyses suggest that high doses of vitamin D (≥600 IU) do prevent fractures and that this effect is stronger when combined with calcium.[8–10] However, many of the trials focused on high-risk subjects and have been conducted in institutionalized subjects. Moreover, many different exclusion criteria have been used. Therefore, when vitamin D and calcium supplementation is considered as a preventive strategy, generalizing the results of trials in the general elderly female population is compromised. To minimize the selection bias of the target population and to determine whether a prevention program in postmenopausal women would be useful, there is a need for a population-based randomized, controlled trial.

Our hypothesis was that 800 IU of cholecalciferol and 1000 mg of calcium daily offered as a free supplementation would reduce fracture risk. The objective of this population-based randomized, controlled, open-label trial was to determine the efficacy of vitamin D and calcium supplementation as a population-level fracture-prevention strategy in 65- to 71-year-old women.

Materials and Methods

Study subjects and design

The Osteoporosis Risk Factor and Prevention (OSTPRE) Study was launched in 1989 in Kuopio, (eastern) Finland. A population-based sample of all women living in the region of northern Savonia, previous Kuopio Province (latitude 62° to 64°N), born between 1932 and 1941 ($n = 14{,}220$) was recruited to this observational cohort study.[28] A baseline questionnaire in May 1989 was returned by 13,100 women. The cohort received three postal follow-up questionnaires at 5 (1994), 10 (1999), and 15 years (2004). Subjects for the present OSTPRE Fracture Prevention Study (OSTPRE-FPS) were selected from the original cohort in November 2002. The inclusion criteria were age 65 years or older, still living in the region of northern Savonia, willing to participate, and had not participated in any trials or bone mineral density (BMD) measurements of the OSTPRE Study. There were no exclusion criteria. The new baseline postal questionnaire of OSTPRE-FPS with questions related to health and fracture risk was sent to 5407 women of the original sample. A total of 4706 enquiries were returned, 3744 of which were adequately filled out, 3432 by women willing to participate and still living in the region of northern Savonia. These 3432 women were finally enrolled. The subjects were recruited from August to December 2002, and the trial was conducted between February 2003 and June 2007. This study was carried out in the Bone and Cartilage Research Unit (BCRU) of the Clinical Research Centre of the University of Kuopio, Kuopio, Finland. The trial was conducted in accordance with the Declaration of Helsinki, and the study plan of OSTPRE-FPS was accepted by the Ethics Committee of the University Hospital of Kuopio. All subjects gave written informed consent.

Objectives

The primary aim of this study was to determine the efficacy of calcium and vitamin D supplementation in fracture prevention in 65- to 71-year-old women as a population-level intervention. A secondary aim was to determine the effect of the intervention on serum vitamin D levels during follow-up.

Randomization and intervention

The 3432 enrolled subjects were randomized into intervention ($n = 1718$) and control ($n = 1714$) groups by an independent statistician based on simple randomization. Randomization was performed with SPSS for Windows 11.0 (SPSS, Chicago, IL, USA) statistical software without any blocking or stratification. OSTPRE-FPS was an open-label study. The intervention group received tablets containing 400 IU of cholecalciferol and 500 mg of elemental calcium as calcium carbonate twice daily (Calcichew D3 Forte, Leiras Nycomed, Ltd.). Subjects were advised to take the doses separately with meals. Participants in the control group did not receive any intervention or placebo. They were free to use supplements, but they were asked not to change their use of supplemented or dietary vitamin D or calcium. A subsample of 750 women, 375 from both study groups, was randomly selected and invited to the BCRU for clinical testing. The subjects were informed by letter to which group they were randomized. The letter contained information concerning the trial and the prescription for the intervention. Subjects in the subsample visited the BCRU at the beginning of the follow-up and received their information and prescription there. Supplementation was distributed and recorded by the local pharmacies, free of charge. Distribution of the regimen was documented by the pharmacists, and compliance was calculated as the percentage of delivered tablets of the calculated consumption of follow-up period. Continuation or discontinuation of the supplementation with possible reasons (adverse effects or other reasons) was registered in telephone interviews together with the primary outcome data (see below).

Outcome measures

The primary outcome measure was a fracture. Data on fractures were collected by telephone interviews once a year. In the subsample, telephone interviews were performed every 4 months. All self-reported fractures were validated using medical records or radiologic reports. Only fractures with radiologic confirmation were regarded as valid fractures, with the exception of rib fractures, for which a physician's clinical diagnosis was regarded as valid. All fractures, regardless of the trauma energy, were included. Thoracic and lumbar vertebral fractures were analyzed as clinical vertebral fractures. Fractures other than cervical, thoracic, or lumbar vertebral fractures were defined and analyzed as nonvertebral fractures. We also separately analyzed fractures distal from the glenohumeral joint as upper extremity fractures and those distal from the hip joint as lower extremity fractures. All clinical vertebral fractures and fractures of the distal forearm, proximal humerus, and hip were analyzed as osteoporotic fractures regardless of mechanism of injury. The secondary outcome measure was the effect of the intervention on the level of 25-hydroxyvitamin D [25(OH)D] during the follow-up period in the subsample.

Measurements in the subsample [25(OH)D and BMD]

Subjects in the subsample were invited to the BCRU at the beginning and end of the follow-up period. To avoid seasonal variations, nonfasting serum samples for 25(OH)D measurement were collected at baseline and at the end of the follow-up in the same month between February and May. Frozen serum samples were analyzed after trial closure by radioimmunoassay using a 25(OH)D RIA kit from DiaSorin (Stillwater, MN, USA), with a coefficient of variation (CV) from 8.2% to 11.0%, according to the manufacturer.

Subjects also underwent BMD measurements of the lumbar spine (L_2 to L_4) and left proximal femur with dual-energy X-ray-absorptiometry (DXA) using a Lunar Prodigy device (General Electric, Madison, WI, USA). Quality control determinations of the DXA instruments were run daily. The long-term reproducibility (CV) for the total femur region was 1.0%. The technical quality of each DXA measurement was checked carefully, and measurements with errors were not included in the statistical analyses.

Questionnaire

The baseline questionnaire contained questions about anthropometric measures (height in centimeters and weight in kilograms), age at menopause (years), use (no/yes) and duration (years) of hormone therapy (HT), gynecologic history, use of alcohol (doses per week), smoking (no/yes), physical ability, previous fractures (no/yes), parental fractures (no/yes), health disorders, and medications. Time (years) since menopause was calculated using the self-reported beginning of amenorrhea and the date of baseline. Total baseline calcium intake was calculated as milligrams per day from a 7-day food frequency questionnaire about milk products (120 mg/dL of other milk products, 87 mg/slice of cheese[28]) and self-reported use of supplements. Secondary osteoporosis was considered present if subjects reported type 1 diabetes, hyperthyroidism, early menopause (age < 45 years), chronic malnutrition (body mass index < 18.5), chronic malabsorption, or chronic liver disease.[29]

Statistical analysis

Power calculations to determine sample size were carried out with the expected fracture rate of 30 per 1000 subjects per year[30] and an estimated 20% loss during follow-up. The adequate sample size to show a 30% reduction in fracture rate with 90% power was calculated to be 1130 per group.

The main analyses of these data were performed on a modified intention-to-treat (ITT) basis, where all subjects assigned to treatment were included. Subjects who did not provide any follow-up data on the primary endpoint variable could not be included in time-dependent Cox survival analysis. Thus these 237 subjects (Fig. 1) were excluded from the analyses. All other subjects were analyzed according to the group allocation, including those lost to follow-up and those who discontinued the intervention. In the ITT analysis, 3195 subjects, 1586 from the intervention group and 1609 from the control group, were included.

For baseline characteristics, group differences of continuous normally distributed variables were analyzed with the independent-samples *t* test and non–normally distributed variables with the nonparametric Mann-Whitney test. Class variables were tested with the Pearson chi-square test. The effect of intervention on fracture risk was calculated as hazard ratios (HRs) using the Cox proportional hazards model, where subjects were followed from the start of the trial until the end of follow-up, until their first incident fracture, or until their loss to follow-up. The effect size was calculated for different fracture types separately as a univariate model and adjusted for age, body mass index (BMI), smoking, use of alcohol, previous fracture, parental hip fracture, glucocorticoid use, and diagnosed rheumatoid arthritis and secondary osteoporosis, all well-known and well-validated confounders of fracture risk estimation.[29] Missing data on the continuous variable BMI (3.9%) were replaced by the mean; class variables smoking (10.9%) and use of alcohol (16.4%) with an extra category; and previous fracture (4.8%), parental hip fracture (1.8%), glucocorticoid use (6.7%), diagnosed rheumatoid arthritis (0.8%), and secondary osteoporosis (0.8%) were coded as negative. The proportionality and linearity assumptions of hazards were explored with cumulative hazards and log-minus-log blots and confirmed by Schoenfeld and Martingale residuals, respectively. We also used a Kaplan-Meier survival model for the plotting of fracture-free survival curves with the corresponding log rank test. Change in mean 25(OH)D levels within groups over time was compared with paired-samples *t* test. Change in the use of prescribed vitamin D in the control group during the follow-up was analyzed with the McNemar test. All statistical analyses were performed with SPSS for Windows 14.0 statistical software.

Results

Subjects

Initially, 3432 women were considered eligible and were enrolled and randomized. After randomization, 237 women were excluded from the analyses, 132 from the intervention group and 105 from the control group (Fig. 1). In the intervention group, all exclusions were due to consent withdrawals. In the control group, 83 women were excluded owing to consent withdrawal, 15 owing to death before onset of the trial, and 7 owing to loss of contact before the first telephone interview. A total of 1586 women in the intervention group and 1609 women in the control group were assigned to treatment. During follow-up, 20 women in the intervention group and 36 women in the control group were lost from the study. Of the 375 subjects randomly selected from each group, 290 in the intervention group and 313 in the control group were assigned to treatment. The mean time of follow-up was 3.01 (SD 0.22) years.

Baseline characteristics

The baseline characteristics of the study groups are summarized in Table 1. A history of previous fracture was more frequent and parental history of hip fracture was less frequent in the intervention group than in the control group (37.3% versus 33.4%, $p = .02$, and 11.9% versua 14.3%, $p = .05$, respectively). There were no other differences between the intervention and control groups. We compared all baseline characteristics of the 237 women who were excluded from analyses in the intervention and control groups, and there were no statistically

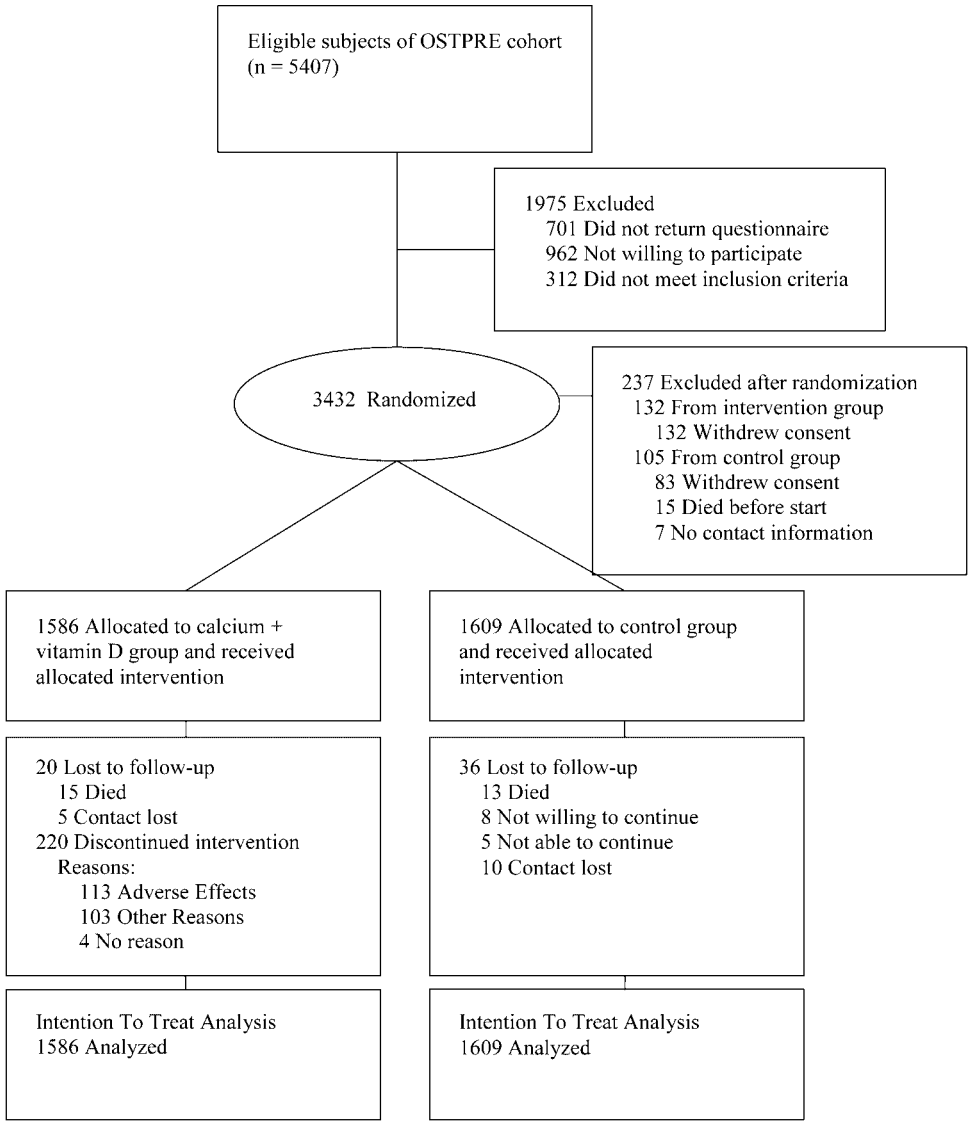

Fig. 1. Flowchart of the OSTPRE-FPS Study.

significant differences between the groups. Further, the baseline characteristics of the excluded subjects were compared with those of the subjects who remained in the study. This analysis showed a typical exclusion effect: The excluded subjects had statistically significantly higher body weight (72.8 versus 70.7 kg, $p = .03$) and BMI (28.5 versus 27.7, $p = .04$) and lower self-assessed physical ability (restricted walking 21.9% versus 9.5%, $p < .0001$). Further, there were fewer hormone therapy (HT) users (40.0% versus 52.3%, $p < .0001$), and the duration of HT among users was shorter (8.6 versus 10.5 years, $p = .03$) among excluded subjects. Similarly, the proportions of smokers (9.1% versus 5.2%, $p = .02$), subjects with a history of previous fractures (42.6% versus 35.3%, $p = .02$), and subjects not using any alcohol (60.8% versus 49.3%, $p = .01$) were higher.

Adverse effects and compliance

In the intervention group, 1566 women completed the follow-up, and 220 of these discontinued the intervention, 113 owing to adverse effects of the treatment, 103 owing to other reported reasons, and 4 reporting no reason. The most common adverse effects causing discontinuation were gastrointestinal symptoms (64 of 220), nausea (12 of 220), and skin reactions (9 of 220). Compliance data were available for 1508 of 1586 subjects (95.1%) in the intervention group who were assigned to treatment. Mean compliance in the intervention group was 78%. At the same time, in control group, intake of prescribed vitamin D was elevated from 3.8% to 16.1% ($p < .001$) during follow-up.Fractures

During follow-up, a total of 189 fractures occurred in 172 subjects. The most common type of fracture was a distal forearm fracture ($n = 60$). The number of hip ($n = 6$) and proximal humeral ($n = 12$) fractures was very low, and risk assessment for these fracture types cannot be considered adequate. The distribution of different fracture types by groups is displayed in Table 2.

Risk of fracture

In ITT analyses, the hazard ratio (HR) for any fracture in the intervention group compared with the control group was 0.85

Table 1. Group Comparison: Baseline Characteristics by Study Groups Displayed as Mean (SD) for Continuous Variables and Distribution in Percentages for Categorical Variables

Baseline characteristics	Intervention group ($n = 1586$)	Control group ($n = 1609$)	p
Age (years)	67.4 (1.9)	67.3 (1.8)	.16
Weight (kg)	70.7 (12.4)	70.8 (11.6)	.82
Height (cm)	160 (5.3)	160 (5.3)	.28
BMI	27.7 (4.6)	27.7 (4.4)	.98
Age at menopause (years)	49.3 (4.7)	49.6 (4.5)	.15
Years since menopause	18.2 (5.0)	17.8 (4.9)	.09
History of HT use (%)			
Never-users	47.7%	47.7%	.98
Users	52.3%	52.3%	
Duration of HT use (years)	10.5 (6.9)	10.4 (7.4)	.72
Use of calcium supplement	16.3%	18.0%	.19
Calcium/milk products (mg/d)	895 (475)	895 (475)	.81
Calcium supplements (mg/d)	323 (190)	311 (188)	.48
Calcium total (mg/d)	955 (490)	959 (481)	.87
Prescribed medications	2.7 (2.6)	2.6 (2.6)	.30
Alcohol, doses/week (%)			
No alcohol	48.8%	49.9%	.98
$<$1 dose/week	23.5%	22.9%	
1–4.9 doses/week	25.0%	24 5%	
5–9.9 doses/week	2.3%	2.4%	
$\geq$10 doses/eek	0.5%	0.4%	
Smoking status (%)			
Current smoker	4.9%	5.6%	.38
Nonsmoker	95.1%	94.4%	
Self-assessed physical ability			
Capable of running	48.0%	50.8%	.16
Capable of walking	42.8%	39.5%	
Walking max. 1000 m	6.5%	7.4%	
Walking max. 100 m	2.7%	2.2%	
Rheumatoid arthritis (%)	4.5%	4.4%	.93
Glucocorticoid use (%)	2.0%	1.6%	.47
Previous fracture (%)	37.3%	33.4%	.02
Parental hip fracture (%)	11.9%	14.3%	.05
Chronic kidney disease	0.9%	1.3%	.25
Secondary osteoporosis	21.5%	20.0%	.28
Type 1 diabetes	2.5%	2.2%	.59
Hyperthyroidism	2.6%	3.4%	.20
Early menopause (age $<$ 45 years)	15.5%	13.5%	.12
Chronic malnutrition (BMI $<$ 18.5)	0.4%	0.2%	.35
Chronic malabsorption	1.4%	1.4%	.92
Chronic liver disease	0.4%	0.5%	.82
Bone mineral density	($n = 278$)	($n = 309$)	
Femur neck (g/cm2)	0.866 (0.132)	0.866 (0.120)	.98
	($n = 231$)	($n = 261$)	
L_2 to L_4 (g/cm^2)	1.082 (0.189)	1.096 (0.190)	.42
25(OH) D levels	($n = 279$)	($n = 295$)	
Baseline	50.0 (18.7)	49.1 (17.7)	
3 years	74.6 (21.9)	55.9 (21.9)	
Change (%)	49%	14%	
p (change over time)[a]	$<$.001	$<$.001	

(*Continued*)

Table 1. (*Continued*)

Baseline characteristics	Intervention group ($n = 1586$)	Control group ($n = 1609$)	p
Use of prescribed vitamin D ± calcium			
Baseline	—	3.8%	
3 years	—	16.1%	
p (change over time)[b]		<.001	

Changes in vitamin D levels in groups and use of prescribed vitamin D in the control group over time.
[a]Paired-samples t test.
[b]McNemar test.

(95% CI 0.63–1.15), and the respective aHR was 0.83 (95% CI 0.61–1.12). For any nonvertebral fracture, the HR was 0.89 (95% CI 0.65–1.22), and the respective aHR was 0.87 (95% CI 0.63–1.19). For osteoporotic fractures, the HR was 0.83 (95% CI 0.55–1.25), and the aHR was 0.81 (95% CI 0.54–1.22). For distal forearm fractures, the HR was 0.74 (95% CI 0.43–1.27), and the aHR was 0.70 (95% CI 0.41–1.20). And for clinical vertebral fractures, the HR 0.71 (95% CI 0.3–1.66), and the aHR was 0.67 (95% CI 0.29–1.58). The HR for upper extremity fractures was 0.77 (95% CI 0.51–1.19), and the aHR was 0.75 (95% CI 0.49–1.16), whereas the HR for lower extremity fractures was 1.04 (95% CI 0.59–1.82), and the aHR was 1.02 (95% CI 0.58–1.80; Table 3 and Fig. 2). The intervention showed no statistically significant effect on fracture risk in any of these fractures. The fracture-free survival curves for any fracture and upper extremity fractures are shown in Fig. 3.

Table 2. Incident Fractures by Groups During the Trial Displayed as Number of Fractured Subjects With the Number of Fractures in Brackets if Different

Type of fracture	Intervention group: Number of subjects (fractures)	Control group: Number of subjects (fractures)
Any fracture	78 (86)	94 (103)
Any nonvertebral fracture	71 (77)	82 (89)
Osteoporotic fracture	42 (44)	52 (56)
Distal forearm	23 (25)	32 (35)
Proximal humerus	6	6
Vertebral	9	13
Hip	4	2
Upper extremity		
Clavicula	1	1
Scapula	3	0
Proximal humerus	6	6
Diaphyseal humerus	0	3
Elbow	0	3
Antebrachium	0	1
Distal forearm	23 (25)	32 (35)
Hand	8	4
Lower extremity		
Hip	4	2
Crus	0	1
Ankle	11	12
Foot	7	5
Other		
Face and scull	4	2 (3)
Thorax	5	7
Cervical spine	0	1
Thoracal spine	3	2
Lumbal spine	6	11
Pelvis	1	2

Subgroup analyses of risk of fracture

We also analyzed antifracture efficacy of the supplementation in seven different subgroups (age $\geq$ 70 years, age $\geq$ 68 years, calcium intake $\leq$ 700 mg/d, treatment received at any compliance, treatment received with 90% or greater compliance, and prescribed vitamin D (users in the control group excluded, subjects with secondary osteoporosis in both groups excluded). None of these subgroups provided a statistically significant ($p < .05$) effect in favor of the intervention (data not shown).

Serum 25(OH)D levels

In the intervention group, the mean baseline 25(OH)D level of 50.0 nmol/L (SD 18.7 nmol/L) was elevated by 49% to 74.6 (21.9) nmol/L ($p < .001$) during follow-up. In the control group, the change by 14% from a baseline of 49.1 (17.7) nmol/L to 55.9 (21.9) nmol/L was remarkably smaller but statistically significant ($p < .001$).

Discussion

Supplemented cholecalciferol 800 IU/day and calcium 1000 mg/day caused a clear increase in serum 25(OH)D levels of 49%, indicating a compliant use of the supplementation. In the control group, a smaller but significant increase of 14% was measured. 25(OH)D levels of 75 nmol/L or higher have been considered sufficient for antifracture efficacy.[31] In the intervention group, the mean vitamin D concentration (74.6 nmol/L) reached this level. Further, this intervention showed a trend toward decreasing the risk of any fracture by 17%, any nonvertebral fracture by 13%, distal forearm fractures by 30%, and any osteoporotic fracture by 19%. Further, the supplementation decreased upper extremity fractures by 25% in contrast to those of the lower extremity, where no effect was seen. However, none of these risk reductions reached statistical significance. We also have shown a lower risk of recurrent falling in the same vitamin

Table 3. Hazard Ratios (HRs) With Corresponding 95% Confidence Intervals (95% CI)

Type of fracture	Unadjusted HR ($n = 3195$)	Adjusted HR[a] ($n = 3195$)
Any type of fracture	0.85 (0.63–1.15)	0.83 (0.61–1.12)
Any nonvertebral fracture	0.89 (0.65–1.22)	0.87 (0.63–1.19)
Osteoporotic fracture	0.83 (0.55–1.25)	0.81 (0.54–1.22)
Distal forearm fracture	0.74 (0.43–1.27)	0.70 (0.41–1.20)
Proximal humerus fracture	1.02 (0.33–3.15)	1.01 (0.32–3.14)
Hip fracture	2.19 (0.40–12.00)	2.23 (0.41–12.29)
Vertebral fracture	0.71 (0.30–1.66)	0.67 (0.29–1.58)
Upper extremity fracture	0.77 (0.51–1.19)	0.75 (0.49–1.16)
Lower extremity fracture	1.04 (0.59–1.82)	1.02 (0.58–1.80)

[a]Adjusted for age, BMI, background fracture, parental hip fracture, smoking, use of alcohol, glucocorticoid use, and diagnosed rheumatoid arthritis and secondary osteoporosis.

D–supplemented group.[32] This is in concordance with our findings—fractures are often a consequence of falling.

Previous data on the antifracture efficacy of low-dose vitamin D (≤400 IU) are somewhat controversial. Randomized trials in Dutch ($n = 2578$) and Norwegian ($n = 1144$) populations[20,21] have not shown a fracture-protective effect. However, a Danish study of 9605 subjects[18] showed a 16% reduction in fracture incidence rate in a nonrandomized setting. Further, Jackson and colleagues reported a 29% risk reduction in hip fractures with low-dose (400 IU) vitamin D in women with high (≥80%) adherence to treatment[33] in the randomized Women's Health Initiative (WHI) study ($n = 36{,}282$). Several trials with a higher vitamin D dose (700 to 800 IU) showed a clear antifracture effect,[14,16,17] whereas some with an even higher dosage (800 to 1000 IU) remained negative.[22–27] According to several metaanalyses, in selected subjects, vitamin D in sufficient dose (>600 IU/d) clearly reduces the incident nonvertebral and hip fractures,[8–10] and a dose-response effect exists.[34] Further, calcium supplementation additionally decreases fracture risk.[9,10] A trend toward upper extremity fracture risk reduction, as suggested by this study, was not reported in any of these trials. However, this same finding has been reported by Heikinheimo and colleagues[19] in a Finnish population with annual intramuscular injections of 150,000 to 300,000 IU of ergocalciferol. While this has been reported only in these two Finnish trials, it is possible that the preventive effect, that is, the improvement in balance, has a clearer effect on falling in high northern latitudes, where snow-related slips/falls are more frequent.

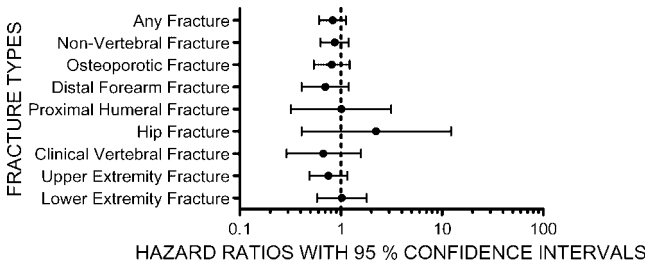

Fig. 2. Adjusted[a] hazard ratios (•) of different fracture types with 95% confidence intervals (*bars*). [a]Adjusted for age, BMI, background fracture, parental hip fracture, smoking, use of alcohol, glucocorticoid use, and diagnosed rheumatoid arthritis and secondary osteoporosis.

The result of the decreasing trend of fracture incidence with supplementation seems to be consistent with previous literature. Some factors cause limitations that may have reduced the effect of the intervention in this study. First, the population in this study was relatively young and healthy, and therefore, fracture incidence was lower than expected. Further, the effect size of the intervention was lower than expected. This study was powered

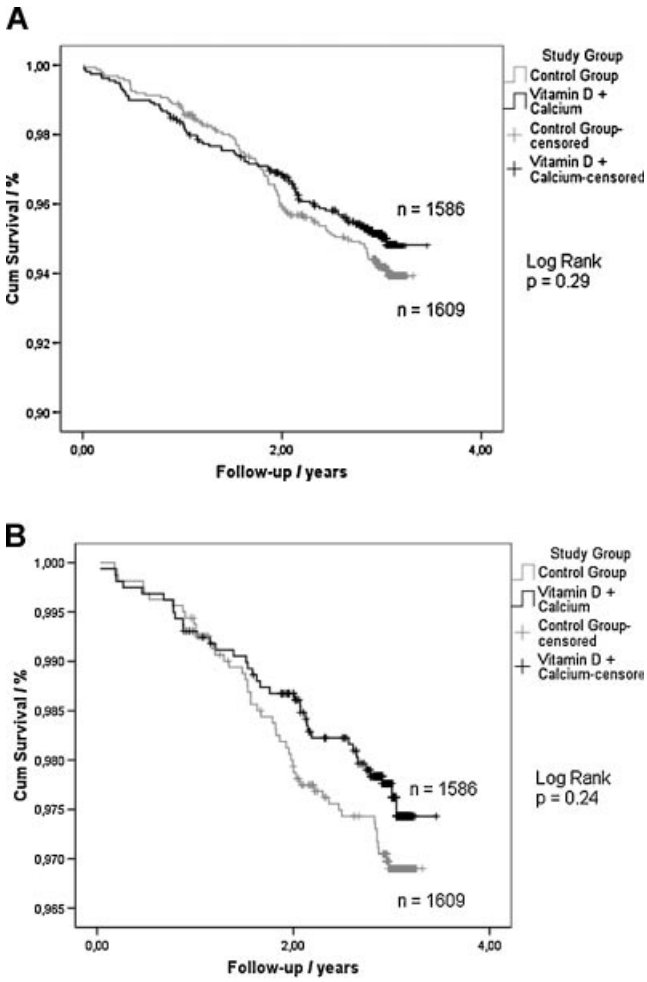

Fig. 3. Kaplan-Meier survival curves for (*A*) any fracture and (*B*) upper extremity fracture with corresponding log rank tests.

to detect a 30% decrease in fracture rate with an expected incidence of 30 per 1000 per year, an estimate based on a Swedish study.[30] The supplementation seemed to decrease the fracture risk by only 17%. The detected incidence of first fracture also was smaller: 18 per 1000 per year. Thus this study did not have enough power to show statistical significance for the treatment effect in this population. Second, owing to considerable vitamin D deficiency in the Finnish population, milk products (ie, milk, sour milk, and yoghurt) and fat products (ie, butter and margarine) have been fortified with cholecalciferol at 0.5 μg/100 mL and 10 μg/100 g, respectively, since 2003, that is, over the whole duration of this trial.[5] Regardless of supplement use in control ssujects, milk and fat products thus form a source of moderate basal intake of vitamin D in the control group. Further, baseline levels of vitamin D were quite high in both groups (50.0 and 49.1 nmol/L) and were not too far from the fracture-protecting threshold of 75 nmol/L. Third, the additive role of calcium supplementation in fracture prevention has been recognized.[9,10,35] In the present population, the mean nutritional calcium intake was relatively high, 895 mg/day in both groups, reflecting the exceptionally high use of milk products in Finland. High nutritional calcium intake may mask part of the additional positive effect of supplementation in this trial. Fourth, only 3432 of 5407 women were enrolled in this study, which may limit the benefit of low selection bias of a population-based trial. Further, the exclusion of the 237 dropouts may cause exclusion bias in the study. Typically, subjects who have low adherence are older and have more health disorders and medications, so they also may have a higher risk of fracture. Fifth, an open-label design with a free control group has the disadvantage that awareness of the health benefits of the intervention may increase the use of supplementation in the control group and dilute the effect. In fact, at the end of follow-up, the use of prescribed vitamin D was almost fourfold compared with baseline. The mild increase in the mean 25(OH)D level (14%) in the control group may reflect this change. An open-label design also may have caused biased reporting of endpoint data. In this study, this effect is probably not present because a fracture is an easily recalled "hard" surrogate outcome measure. The fracture-confirmation process has been validated in the OSTPRE Study.[36] In our opinion, fracture in this study remains a very reliable outcome. Sixth, when analyzed on an ITT basis, the presence of nonadherent subjects in the intervention group dilutes the actual effect of the treatment. Finally, the fact that intervention elevates 25(OH)D to an acceptable level, 74.6 nmol/L, still means that half the sample remains below 75 nmol/L, the threshold for antifracture efficacy. In this manner, this trial also describes the in vivo efficacy of uncontrolled intake of the tested intervention on 25(OH)D levels at the population level.

The strength of this study lies in its population-based strategy for testing the antifracture efficacy of vitamin D and calcium. Considering our primary aim, testing the efficacy of a population-level intervention, this setting offers better external validity for the result than in many other studies concentrating on high-risk subjects. Further, this population is not limited to institutionalized women but consists of a more complete variety of subjects with different housing status, functional capacity, and health status. The mean compliance of this study, 78%, was sufficient to adequately show the achievable effect of the intervention.

In conclusion, supplementation of 800 IU of cholecalciferol and 1000 mg of calcium daily as a population-level preventive strategy failed to produce a statistically significant reduction in fracture risk. A population of relatively young age and in good health combined with a good basal intake of vitamin D and calcium does not achieve the benefit in fracture prevention. For this purpose, the supplementation needs to be targeted more effectively.

Disclosures

None of the funding sources had any role in the design and conduct of this study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Trial registration: OSTPRE-FPS is registered at clinicaltrials.gov as identifier NCT00592917.

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References

1. Moreira-Pfrimer LD, Pedrosa MA, Teixeira L, Lazaretti-Castro M. Treatment of vitamin D deficiency increases lower limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial. Ann Nutr Metab. 2009;54:291–300.
2. Bischoff-Ferrari HA, Conzelmann M, Stahelin HB, et al. Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? Osteoporos Int. 2006;17:656–663.
3. Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. Vitamin D and bone health in the elderly. Am J Clin Nutr. 1982;36:1014–1031.
4. Lips P, Wiersinga A, van Ginkel FC, et al. The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. J Clin Endocrinol Metab. 1988;67:644–650.
5. Lamberg-Allardt C, Kärkkäinen M, Outila T, Natri A-M. Suomalaisten D-vitamiinitilanteen kohentaminen – auringosta, ruoasta vai purkista? Suom Lääkäril. 2003;58:1055–1056.
6. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22:477–501.
7. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004;291:1999–2006.

8. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257–2264.
9. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007;92:1415–1423.
10. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;370:657–666.
11. Lamberg-Allardt CJ, Outila TA, Karkkainen MU, Rita HJ, Valsta LM. Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? J Bone Miner Res. 2001;16:2066–2073.
12. Gloth FM 3rd, Gundberg CM, Hollis BW, Haddad JG Jr, Tobin JD. Vitamin D deficiency in homebound elderly persons. JAMA. 1995;274:1683–1686.
13. Margiloff L, Harris SS, Lee S, Lechan R, Dawson-Hughes B. Vitamin D status of an outpatient clinic population. Calcif Tissue Int. 2001;69:263–267.
14. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ. 1994;308:1081–1082.
15. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, Garnero P, Meunier PJ. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int. 2002;13:257–264.
16. 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.
17. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326:469.
18. 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 Miner Res. 2004;19:370–378.
19. Heikinheimo RJ, Inkovaara JA, Harju EJ, Haavisto MV, Kaarela RH, Kataja JM, Kokko AM, Kolho LA, Rajala SA. Annual injection of vitamin D and fractures of aged bones. Calcif Tissue Int. 1992;51:105–110.
20. 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;124:400–406.
21. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002;17:709–715.
22. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, Baverstock M, Birks Y, Dumville J, Francis R, Iglesias C, Puffer S, Sutcliffe A, Watt I, Torgerson DJ. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005;330:1003.
23. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, Anderson FH, Cooper C, Francis RM, Donaldson C, Gillespie WJ, Robinson CM, Torgerson DJ, Wallace WA. RECORD Trial Group. 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.
24. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000;15:1113–1118.
25. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20:315–322.
26. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, Thomas J, Lowndes C, Hopper JL, Wark JD. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc. 2005;53:1881–1888.
27. Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B, Evans R, Wareham K, Stone MD. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int. 2007;18:811–818.
28. Tuppurainen M, Honkanen R, Kroger H, Saarikoski S, Alhava E. Osteoporosis risk factors, gynaecological history and fractures in perimenopausal women--the results of the baseline postal enquiry of the Kuopio Osteoporosis Risk Factor and Prevention Study. Maturitas. 1993;17:89–100.
29. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19:385–397.
30. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12:417–427.
31. Bischoff-Ferrari HA. How to select the doses of vitamin D in the management of osteoporosis. Osteoporos Int. 2007;18:401–407.
32. Kärkkäinen M, Tuppurainen M, Rikkonen T, Salovaara K, Sandini L, Rikkonen T, Sirola J, Honkanen R, Arokoski J, Alhava E, Kröger H. Vitamin-D 800IU/Day+Calcium 1000mg Supplementation Decreases the Risk of Falling Among Postmenopausal Ambulatory Women – A Population-based, Randomized 3-Year Study (OSTPRE-FPS). J Bone Miner Res. 2007;22(S1): S117.
33. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D. Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669–683.
34. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169:551–561.
35. Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA. Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. Am J Clin Nutr. 2008;87:1945–1951.
36. Honkanen K, Honkanen R, Heikkinen L, Kroger H, Saarikoski S. Validity of self-reports of fractures in perimenopausal women. Am J Epidemiol. 1999;150:511–516.