VITAMIN D_3 AND CALCIUM TO PREVENT HIP FRACTURES IN ELDERLY WOMEN

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Abstract *Background.* Hypovitaminosis D and a low calcium intake contribute to increased parathyroid function in elderly persons. Calcium and vitamin D supplements reduce this secondary hyperparathyroidism, but whether such supplements reduce the risk of hip fractures among elderly people is not known.

Methods. We studied the effects of supplementation with vitamin D_3 (cholecalciferol) and calcium on the frequency of hip fractures and other nonvertebral fractures, identified radiologically, in 3270 healthy ambulatory women (mean [±SD] age, 84±6 years). Each day for 18 months, 1634 women received tricalcium phosphate (containing 1.2 g of elemental calcium) and 20 μg (800 IU) of vitamin D_3, and 1636 women received a double placebo. We measured serial serum parathyroid hormone and 25-hydroxyvitamin D (25(OH)D) concentrations in 142 women and determined the femoral bone mineral density at base line and after 18 months in 56 women.

Results. Among the women who completed the 18-month study, the number of hip fractures was 43 percent lower ($P = 0.043$) and the total number of nonvertebral fractures was 32 percent lower ($P = 0.015$) among the women treated with vitamin D_3 and calcium than among those who received placebo. The results of analyses according to active treatment and according to intention to treat were similar. In the vitamin D_3–calcium group, the mean serum parathyroid hormone concentration had decreased by 44 percent from the base-line value at 18 months ($P<0.001$) and the serum 25(OH)D concentration had increased by 162 percent over the base-line value ($P<0.001$). The bone density of the proximal femur increased 2.7 percent in the vitamin D_3–calcium group and decreased 4.6 percent in the placebo group ($P<0.001$).

Conclusions. Supplementation with vitamin D_3 and calcium reduces the risk of hip fractures and other nonvertebral fractures among elderly women. (N Engl J Med 1992;327:1637-42.)

THE risk of hip fractures and other nonvertebral fractures increases in the elderly, reaching near-epidemic levels in many developed countries. Although many factors contribute to such fractures, the most important causes are a reduction in bone mass and an increased frequency of falls. Bone density progressively decreases with age.[1,2] The decrease can be explained, at least in part, by increased parathyroid hormone secretion[3-5] resulting from vitamin D deficiency and low calcium intake that are not compensated for by an increase in 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production.[6] Whether vitamin D or calcium supplements, or both, retard bone loss and reduce the rate of fractures among elderly people (those more than 70 years of age) is not known. In a previous study, we found that six months of supplementation with calcium (1 g per day) and vitamin D_2 (ergocalciferol; 800 IU per day) reduced the biochemical indexes of secondary hyperparathyroidism in elderly persons.[7] The present study was undertaken to determine whether vitamin D_3 (cholecalciferol) and calcium supplements decrease the frequency of nonvertebral fractures, particularly fractures of the femoral neck, among ambulatory elderly women living in nursing homes.

METHODS

Subjects

We studied 3270 women, 69 to 106 years of age (mean [±SD], 84±6), who were living in 180 nursing homes or apartment houses for elderly people. To be eligible for the study the women had to be ambulatory (with activity levels ranging from going outdoors easily to walking indoors with a cane or a walker), to have no serious medical conditions, and to have a life expectancy of at least 18 months. Women who had received drugs known to alter bone metabolism, such as corticosteroids, thyroxine, or anticonvulsant drugs, within the past year were excluded, as were women who had been treated with fluoride salts for more than three months or with vitamin D or calcium during the previous six months or for more than one year within the past five years. Women who had had fractures in the past and women who had taken or were taking estrogen or a thiazide diuretic agent were not excluded. Less than 1 percent of these women had received estrogen-replacement therapy after menopause. Other medications were continued during the study.

The study was approved by the local ethics committee, and informed consent was obtained from all study subjects.

Study Design and Supplements

In order to minimize social, nutritional, and lifestyle differences between the treatment groups, the women were randomly assigned to the vitamin D_3–calcium group or the placebo group in groups of four at each nursing home. The planned study period was 18 months. Each day the 1634 women in the treatment group received 1.2 g of elemental calcium in the form of tricalcium phosphate powder in an aqueous suspension and 800 IU (20 μg) of vitamin D_3 given as two pills of 400 IU each. The 1636 women in the placebo group received two pills containing lactose and a suspension of lactose, kaolin, and starch each day. The supplements were taken at lunchtime in the presence of a nurse to ensure compliance.

At base line, the women's clinical status was assessed and their dietary calcium intake was estimated with use of food records. The frequency of falls from a lying, sitting, or standing position was estimated on the basis of interviews with the nurses, and women who had fallen at least once in the three months before recruitment were defined as "fallers." The women were assessed at 6, 12, and 18 months, at which times their clinical status was assessed, they were asked about side effects, and fractures were recorded. Nonvertebral fractures were identified on the basis of clinical symptoms confirmed by x-ray films. No attempt was made to alter the women's diet or activity level during the study period. Serum samples were obtained after an overnight fast at base line and every six months in a subgroup of 142 women (69 women in the placebo group and 73 women from the vitamin D_3–calcium group) who lived near the

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study center. In addition, femoral bone mineral density was measured at base line and after 18 months in 56 women (27 in the vitamin D_3–calcium group and 29 in the placebo group).

Measurements

Serum calcium, phosphate, creatinine, total protein, and alkaline phosphatase concentrations were measured by standard laboratory methods. Serum intact parathyroid hormone was measured by immunochemoluminometric assay (Ciba–Corning Diagnostic) (normal range for adults 40 to 70 years of age, 11 to 55 pg per milliliter [1.2 to 5.8 pmol per liter]). Serum 25-hydroxyvitamin D (25(OH)D) and $1,25(OH)_2D$ were measured by competitive-binding protein assay after extraction and purification. The ranges for these forms of the vitamin in normal adults were as follows: 25(OH)D, 15 to 50 ng per milliliter (37 to 125 nmol per liter), and $1,25(OH)_2D$, 23 to 45 pg per milliliter (57 to 112 pmol per liter). Serum osteocalcin was measured by radioimmunoassay with use of a polyclonal rabbit antiserum against purified bovine osteocalcin (normal range in adults, 7 to 12 μg per liter [1.2 to 2.0 nmol per liter]). The intraassay and interassay coefficients of variation for these assays ranged from 4.5 percent to 12.5 percent. The samples for the parathyroid hormone, 25(OH)D, $1,25(OH)_2D$, and osteocalcin assays were kept frozen and were analyzed at the same time every 6 months, except for $1,25(OH)_2D$, which was measured only at base line and at 18 months in 40 women (19 in the vitamin D_3–calcium group and 21 in the placebo group).

The bone mineral density of the proximal femur was measured by dual-energy x-ray absorptiometry with use of a Hologic QDR 1000 machine at four sites on the nondominant hip: the femoral neck, the trochanter, the intertrochanteric area, and the total proximal femur. The coefficient of variation of these four measurements, determined by three measurements on one hip in eight elderly women,[1] was 1.1 percent, 2.7 percent, 1.7 percent, and 1.4 percent, respectively. X-ray films of the spine and measurements of lumbar bone mineral density were not performed.

Statistical Analysis

The sample size for this study was chosen so that a reduction of 30 percent in the annual hip-fracture rate, which was estimated at 3.5 percent on the basis of the mean age of the women, could be detected.[8] The principal aim of the analysis was to compare the number of fractures in the placebo group with the number in the treatment group. Hip fractures and other nonvertebral fractures were analyzed separately in three different ways. Among women treated and followed for the full 18-month period, the number of fractures was analyzed with chi-square tests. Among women who had received treatment for varying lengths of time when they had a fracture, dropped out, or died (active-treatment analysis) and among women who ceased to receive treatment for any reason but were subsequently followed (intention-to-treat analysis), the results were analyzed by log-rank tests. In the intention-to-treat analysis only death and loss to follow-up resulted in the censoring of data. The actuarial method was used for graphic comparison of the results.

Biochemical and bone-density data at base line were assessed by unpaired t-tests. Analysis of variance was used for other comparisons. All P values were two-tailed.

Results

The characteristics of the women at base line are shown in Table 1. There were no significant differences in age or weight between the groups. The dietary intake of calcium was low in both groups. The mean vitamin D intake was not determined, but it was considered to be similar to that measured in a similar group of 104 elderly women in a previous study[7] (mean [±SD], 123±45 IU per day).

Of the 3270 women enrolled in the study, 1765 (54 percent) were treated and followed for the full 18 months. The dropout rates during the study were similar in the two groups (deaths, 16 percent in the vitamin D_3–calcium group and 17 percent in the placebo group; withdrawal for other reasons, 30 percent in the vitamin D_3–calcium group and 29 percent in the placebo group) (Table 2). Among the deaths, 43 were due to hip fracture (24 percent of 176 hip fractures).

Table 1. Base-Line Characteristics of the Elderly Women Assigned to Receive Vitamin D_3 and Calcium or to Receive Placebo.*

Characteristic	Vitamin D_3–Calcium (N = 1634)	Placebo (N = 1636)	P Value
Age (yr)	84±6	84±6	NS
Weight (kg)	56±12	56±12	NS
Height (cm)	153±7	154±8	0.003
Dietary calcium intake (mg/day)	511±172	514±158	NS
Fallers (%)†	12	14	NS

*Plus–minus values are means ±SD. NS denotes not significant.

†Women who had at least one fall during the three-month period before the beginning of the study.

Rate of Fracture

The results for the 1765 women who completed the study are shown in Table 3. There were 32 percent fewer nonvertebral fractures (66 vs. 97, P = 0.015) and 43 percent fewer hip fractures (21 vs. 37, P = 0.043) in the vitamin D_3–calcium group than in the placebo group.

The results of the active-treatment analysis were similar (Table 3). During the 18 months of follow-up, there were 151 nonvertebral fractures in the vitamin D_3–calcium group (73 hip fractures and 78 other nonvertebral fractures) and 204 in the placebo group (103 hip fractures and 101 other nonvertebral fractures; P = 0.02 and P = 0.04, respectively). Only nine patients had more than one fracture (five in the vitamin D_3–calcium group and four in the placebo group). Figure 1 shows the curves for the probability of hip and other fractures, based on the active-treatment analysis and estimated by the life-table method. There was a decreased probability of both hip fractures (P = 0.040) and other fractures (P = 0.015) in the vitamin D_3–calcium group as compared with the placebo group. The curves for the two groups began to diverge at 10 months for hip fractures and at 2 months for the other fractures. Ninety-nine percent of the fractures resulted from a fall, and 1 percent of the fractures were spontaneous or resulted from other trauma.

The results of the intention-to-treat analysis were similar (Table 3). There were 160 nonvertebral fractures in the vitamin D_3–calcium group and 215 in the placebo group (P<0.001); the numbers of hip fractures were 80 and 110, respectively (P = 0.004). In this analysis, there were 26 percent fewer other nonvertebral fractures in the vitamin D_3–calcium group than in the placebo group (P<0.001).

The most frequent sites of other nonvertebral frac-

Table 2. Reasons for the Exclusion of Elderly Women Assigned to Receive Vitamin D_3 and Calcium or to Receive Placebo from the Active-Treatment Analysis.

Reason	Vitamin D_3–Calcium (N = 1634)	Placebo (N = 1636)
	no. (%)	
Death	258 (16)	274 (17)
Noncompliance*	279 (17)	255 (16)
Inability to walk during the study	89 (5)	70 (4)
Loss to follow-up	44 (3)	63 (4)
Intercurrent illness	47 (3)	58 (4)
Adverse effects	40 (2)	28 (2)
Total	757 (46)	748 (46)

*Denotes a rate of compliance below 70 percent (estimated on the basis of the number of bags of calcium and pills of vitamin D_3 remaining at each visit).

tures were as follows: wrist and forearm, 22 in the vitamin D_3–calcium group and 34 in the placebo group; humerus, 13 and 19, respectively; and pelvis, 12 and 13. The odds ratio for hip fractures among women in the placebo group as compared with those in the vitamin D_3–calcium group was 1.7 (95 percent confidence interval, 1.0 to 2.8), and that for other nonvertebral fractures was 1.4 (95 percent confidence interval, 1.4 to 2.1).

In the placebo group, there was a marked increase in the incidence of hip fracture over time, whereas the incidence in the vitamin D_3–calcium group was stable. Thus, treatment reduced the age-related risk of fracture at 18 months ($P = 0.007$ for hip fractures and $P = 0.009$ for all nonvertebral fractures) (Table 4).

Biochemical Changes

At base line, the women in both groups had normal serum calcium concentrations, high normal serum concentrations of intact parathyroid hormone, low normal serum concentrations of 25(OH)D, and normal serum $1,25(OH)_2D$ (Table 5). The mean serum creatinine, phosphorus, osteocalcin, and total protein concentrations did not change in either group after 6, 12, or 18 months. The serum calcium concentration did not change in the vitamin D_3–calcium group, but it decreased significantly from base line in the placebo group ($P<0.01$) and was significantly lower in the placebo group than in the vitamin D_3–calcium group after 12 months ($P<0.001$) and 18 months ($P = 0.005$). In the vitamin D_3–calcium group, the mean serum parathyroid hormone concentration was significantly lower than the base-line value at 6, 12, and 18 months; the value at 18 months was 44 percent below the base-line value ($P<0.001$). In the placebo group, in contrast, the serum parathyroid hormone concentration had increased significantly from base line at 12 months (by 20 percent, $P = 0.006$) and at 18 months (by 12 percent, $P = 0.009$).

The mean serum 25(OH)D concentration increased significantly in the vitamin D_3–calcium group at 6, 12, and 18 months (by 162 percent at 12 and 18 months, $P<0.001$) but remained low in the placebo group. The serum $1,25(OH)_2D$ concentration, measured only at base line and at 18 months, did not change significantly in either group. The serum alkaline phosphatase concentration had decreased significantly from the base-line value in the vitamin D_3–calcium group at 6 months and was significantly lower than that in the placebo group at 6, 12, and 18 months ($P = 0.025$).

Femoral Bone Density

There was no difference between the groups at base line in bone density at any site (Table 6). After 18 months of treatment the bone density of the total proximal femoral region had increased 2.7 percent in the vitamin D_3–calcium group and decreased 4.6 percent in the placebo group ($P<0.001$). The density of the femoral neck also increased more in the vitamin D_3–calcium group than in the placebo group, and the density of the trochanteric region decreased less in the vitamin D_3–calcium group than in the placebo group.

Side Effects

A total of 68 women had gastrointestinal symptoms (nausea, diarrhea, or epigastric pain) — 40 in the vitamin D_3–calcium group and 28 in the placebo group — that led to the discontinuation of treatment ($P>0.05$) (Table 2). Among them was one woman in the vitamin D_3–calcium group in whom mild hypercalcemia developed (11.2 mg per deciliter [2.8 mmol per liter]) that proved to be due to primary hyperparathyroidism. No other woman had hypercalcemia at any time, and none had renal calculi.

Discussion

The results of this study indicate that vitamin D_3 and calcium supplements reduce the risk of hip fracture and other nonvertebral fractures, decrease parathyroid hormone secretion, increase the mineral densi-

Table 3. Effects of Vitamin D_3 and Calcium Supplementation on the Number of Fractures in Elderly Women Treated with Vitamin D_3 and Calcium or with Placebo.

Variable	Vitamin D_3–Calcium	Placebo	P Value
Women treated and followed for 18 mo			
No. of women	877	888	—
All nonvertebral fractures	66	97	0.015*
Hip fractures	21	37	0.043*
Active-treatment analysis			
No. of women†	1208	1168	—
All nonvertebral fractures	151	204	0.020‡
Hip fractures	73	103	0.040‡
Intention-to-treat analysis			
No. of women	1387	1403	—
All nonvertebral fractures	160	215	<0.001‡
Hip fractures	80	110	0.004‡

*By the chi-square test.

†The number of women at risk in the middle of the study period.

‡By the log-rank test.

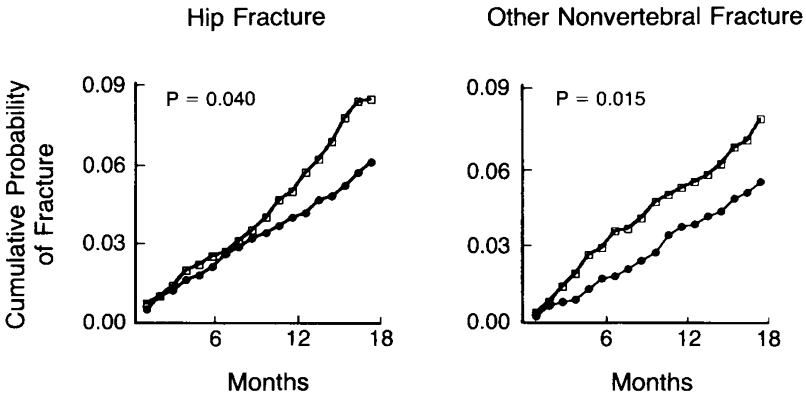

Figure 1. Cumulative Probability of Hip Fracture and Other Nonvertebral Fracture in the Placebo Group (□—□) and the Group Treated with Vitamin D_3 and Calcium (●—●), Estimated by the Life-Table Method and Based on the Length of Time to the First Fracture.

ty of the proximal femur in elderly women, and are safe. Although women living in nursing homes or residences for the elderly, such as those we studied, may not be representative of all elderly women, they are probably the women at highest risk for vitamin D deficiency and nonvertebral fractures. The rate of vertebral fractures was not determined in this study, because many vertebral fractures are asymptomatic among elderly women, because the interpretation of spinal x-ray films may be complicated by osteoarthritis or scoliosis, and because of the large size of the study.

Among the mechanisms involved in bone loss in elderly women, particularly many years after menopause, low calcium intake, decreased calcium absorption, and vitamin D deficiency are probably the most important.[9] Low calcium intake is particularly common in non-Scandinavian European countries. Vitamin D insufficiency, especially in institutionalized subjects,[3] is due mainly to a lack of exposure to sunshine that is not compensated for by increased dietary vitamin D intake; this is particularly true in France, where dairy products are not fortified with vitamin D. The response to a deficit in calcium and vitamin D intake is a negative calcium balance that stimulates the secretion of parathyroid hormone. This secondary hyperparathyroidism may lead to an increase in bone turnover, bone loss, and the risk of hip fracture. Since up to 60 percent of patients with hip fractures may have vitamin D deficiency,[10] the potential effect of calcium or vitamin D deficiency on bone mass and on the risk of hip fracture has been investigated in several studies.[11-14]

In a recent prospective study in California, the rate of hip fracture was 60 percent lower among men and women with a calcium intake of more than 765 mg per day than among those with an intake below 470 mg per day.[11] In another study, in contrast, a low dietary calcium intake was not found to be a risk factor for hip fracture.[12] Several controlled trials have shown that increasing dietary calcium reduces bone loss in elderly persons.[13,14]

Vitamin D supplementation, at doses ranging from 400 to 2400 IU per day, can restore normal serum 25(OH)D concentrations and lower serum parathyroid hormone concentrations in elderly persons.[15-18] In an elderly population with serum 25(OH)D concentrations within the normal range, six weeks of supplementation with 2000 IU of vitamin D_3 per day induced a 100 percent increase in the serum 25(OH)D concentration but not in the serum $1,25(OH)_2D$ concentration[19]; this is similar to findings in our previous study[7] and in this study. The lack of increase in the serum $1,25(OH)_2D$ concentration can be explained by the decrease in renal 1-hydroxylase activity that follows increases in serum calcium concentrations and decreases in serum parathyroid hormone concentrations.

Combined calcium and vitamin D_2 supplementation increases cortical bone density.[14-21] Recently, Tilyard et al. reported that treatment with calcium (1 g per day) and $1,25(OH)_2D$ (calcitriol, 0.50 μg per day) for three years prevented an increase in the rate of new vertebral fractures in women with osteoporosis.[22] We found in our intention-to-treat analysis that 18 months of daily supplementation with calcium and vitamin D_3 prevented 55 nonvertebral fractures — 30 hip fractures and 25 other fractures. As has been reported in several other studies,[23-27] the annual incidence of hip fracture increased exponentially with age in the placebo group, reaching more than 40 per thousand among women more than 85 years of age and 50 per thousand among those more than 90 years of age. The calcium and vitamin D_3 supplements successfully prevented this increased age-related risk not only for hip fracture but also for other nonvertebral fractures. Although femoral bone density was measured in only a few women, supplementation also prevented further bone loss at several sites in the femur.

We chose to use vitamin D_3 in this study instead of vitamin D_2 because in the same doses vitamin D_3 sup-

Table 4. Incidence of Fractures among Elderly Women Treated with Vitamin D_3 and Calcium or with Placebo, According to Length of Follow-up.

Type of Fracture and Group	Follow-up		
	0–6 mo	6–12 mo	12–18 mo
	no./1000/yr		
All nonvertebral fractures			
Vitamin D_3–calcium	70	79	81*
Placebo	96	95	116*
Hip fracture			
Vitamin D_3–calcium	38	37	39†
Placebo	45	47	66†

*P = 0.009 for the comparison between the vitamin D_3–calcium group and the placebo group at 12 to 18 months.

†P = 0.007 for the comparison between the vitamin D_3–calcium group and the placebo group at 12 to 18 months.

Table 5. Serum Biochemical Values in the Vitamin D_3–Calcium and Placebo Groups at Base Line and after 6, 12, and 18 Months of Follow-up.*

Serum Index and Group†	Base Line	Follow-up		
		6 mo	12 mo	18 mo
Calcium (mg/dl)†				
Vitamin D_3–calcium	9.17±0.36	9.28±0.35	9.20±0.33	9.21±0.39
Placebo	9.15±0.40	9.15±0.36	9.00±0.39‡	9.00±0.35‡
PTH (pg/ml)§				
Vitamin D_3–calcium	54±37	35±21¶	33±23¶	30±14¶
Placebo	50±24	50±23	60±30‡	56±29‡
25(OH)D (ng/ml)‖				
Vitamin D_3–calcium	16±11	40±11¶	42±9¶	42±9¶
Placebo	13±9	13±9	10±8‡	11±7
$1,25(OH)_2D$ (pg/ml)**				
Vitamin D_3–calcium	26±10	ND	ND	27±9
Placebo	29±10	ND	ND	26±9
Alkaline phosphatase (U/liter)				
Vitamin D_3–calcium	69±25	60±22¶	62±20‡	67±22
Placebo	72±22	72±27	79±32††	89±27‡
Osteocalcin (μg/liter)‡‡				
Vitamin D_3–calcium	8±3	8±3	7±3	7±2
Placebo	8±3	9±3	7±3	8±3

*Plus–minus values are means ±SD. Normal ranges for adults 40 to 70 years of age: calcium, 9.2 to 10.2 mg per deciliter; parathyroid hormone (PTH), 11 to 55 pg per milliliter; 25(OH)D, 15 to 50 ng per milliliter; $1,25(OH)_2D$, 23 to 45 pg per milliliter; and osteocalcin, 7 to 12 μg per liter. ND denotes not determined. Values are for 73 women in the vitamin D_3–calcium group and 69 in the placebo group, except for $1,25(OH)_2D$ (19 in the vitamin D_3–calcium group and 21 in the placebo group).

†To convert serum values to millimoles per liter, multiply by 0.25.

‡$P<0.01$ for the comparison with the base-line value.

§To convert values to picomoles per liter, multiply by 0.11.

¶$P<0.001$ for the comparison with the base-line value.

‖To convert values to nanomoles per liter, multiply by 2.5.

**To convert values to picomoles per liter, multiply by 2.5.

††$P<0.05$ for the comparison with the base-line value.

‡‡To convert values to nanomoles per liter, multiply by 0.17.

plementation raises serum 25(OH)D concentrations more than does vitamin D_2.[28,29] In the presence of low gastric acid secretion, which is common among elderly persons, calcium phosphate may be poorly soluble and may therefore precipitate in the stomach.[30] In order to maximize calcium absorption, calcium phosphate was given with a meal. According to Heaney,[31] a mean of 25 percent of the calcium in tricalcium phosphate is absorbed, providing about 300 mg of elemental calcium for each 3.3-g dose of tricalcium phosphate. In addition to calcium, the supplements provided 600 mg of phosphorus. Because of the favorable ratio of calcium to phosphorus, it is possible that phosphate supplementation itself might have had a positive effect on calcium absorption.

Table 6. Changes in Femoral Bone Mineral Density after 18 Months in Elderly Women Treated with Vitamin D_3 and Calcium or with Placebo.*

Site	Vitamin D_3–Calcium (N = 27)	Placebo (N = 29)	P Value
	% change from base line		
Femoral neck	+2.9±6.4	+1.8±9.4	0.036
Total proximal femoral region	+2.7±5.5	−4.6±9.2	<0.001
Trochanter	−1.0±6.9	−6.4±12.3	0.044
Intertrochanteric region	+1.1±4.7	+3.2±20.1	NS

*Plus–minus values are means ±SD. NS denotes not significant.

In conclusion, 18 months of daily supplementation with 1.2 g of elemental calcium and 800 IU of vitamin D_3 was safe and decreased the incidence of hip fractures and other nonvertebral fractures among elderly women. As these results demonstrate, it may never be too late to prevent hip fracture.

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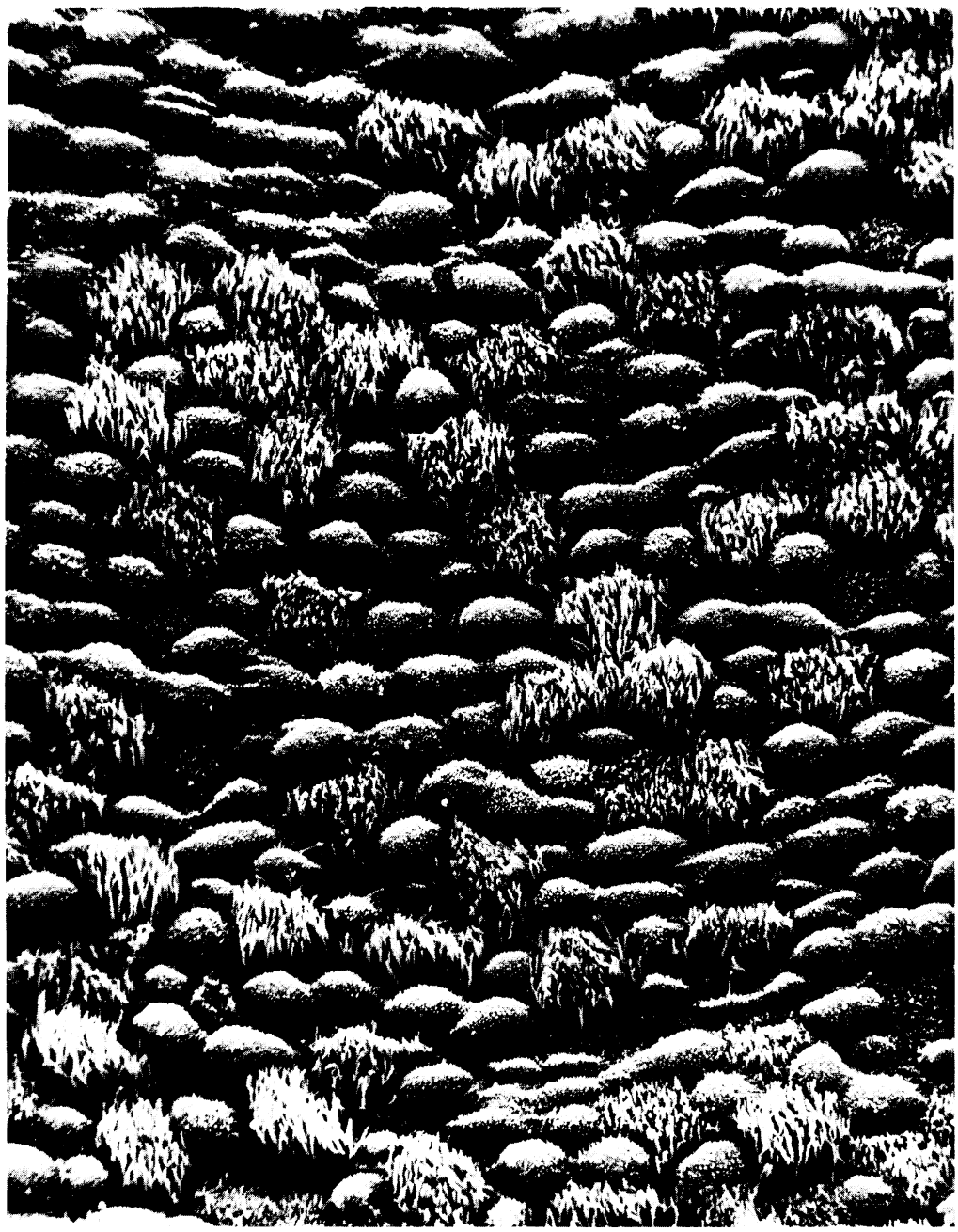

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DAVID M. PHILLIPS, PH.D.