VITAMIN D₃ 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 D₃ (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 D₃, and 1636 women received a double placebo. We measured serum parathyroid hormone and 25-hydroxyvitamin D (25(OH)D) concentrations in 142 women in the control group and in 140 women in the 25(OH)D group 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 D₃ 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 D₃-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 by 2.7 percent in the vitamin D₃-calcium group and decreased 4.6 percent in the placebo group (P < 0.001).


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 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.⁴ 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 D₃ (ergocalciferol; 800 IU per day) reduced the biochemical indexes of secondary hyperparathyroidism in elderly persons.⁵ The present study was undertaken to determine whether vitamin D₃ (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 from the Institut National de la Santé et de la Recherche Médicale (INSERM), Unité 234, Pavillon F, Hôpital Edouard Herriot, 69437 Lyon, France, where reprint requests should be addressed to Dr. Chapuy.

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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 D3–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 pg 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 D3–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, 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. 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 (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 D3–calcium group and 17 percent in the placebo group; withdrawal for other reasons, 30 percent in the vitamin D3–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).

**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 D3–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 D3–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 D3–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 D3–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 D3–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 D3–calcium group than in the placebo group (P<0.001).

The most frequent sites of other nonvertebral frac-
tured 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 baseline, 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)$_2$D (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 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)$_2$D 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-
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In conclusion, 18 months of daily supplementation with 1.2 g of elemental calcium and 800 IU of vitamin D₃ 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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