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Effects of 1α-Hydroxyvitamin D_3 on Lumbar Bone Mineral Density and Vertebral Fractures in Patients with Postmenopausal Osteoporosis

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Abstract. The effects of 1α-hydroxyvitamin D_3 [1α(OH)D_3] on bone mineral density, fracture incidence, and bone metabolism were evaluated by a double-blind, placebo-controlled study. Eighty postmenopausal osteoporotic Japanese women (71.9 ± 7.3 years, mean ± SD) were randomly assigned to 1 μg of 1α(OH)D_3 daily or inactive placebo for 1 year. All patients were given supplemental calcium (300 mg of elemental calcium daily). Lumbar (L2-L4) bone mineral density (BMD) determined by dual energy X-ray absorptiometry increased 0.65% with 1α(OH)D_3 treatment and decreased 1.14% with placebo ($P = 0.037$). BMD in both the femoral neck and Ward's triangle did not yield any significant differences between the two groups, whereas trochanter BMD in the 1α(OH)D_3-treated group increased 4.20% and decreased 2.37% with placebo ($P = 0.055$). X-ray analysis demonstrated that new vertebral fractures occurred in two patients with 1α(OH)D_3 and in seven patients with placebo. The vertebral fracture rate in the treated group was significantly less (75/1000 patient years) than in the control group (277/1000 patient years; $P = 0.029$). Hypercalcemia (12.1 mg/100 ml) occurred in one patient receiving 1α(OH)D_3; however, the serum calcium level in this patient promptly decreased to the reference range after cessation of the treatment. There were no significant changes in serum creatinine level in either group. A significant increase in urinary excretion of calcium was found but there was no significant change in urinary excretion of hydroxyproline in the treated group. The serum level of bone-derived alkaline phosphatase activity significantly decreased by −26 ± 26 (mU/ml) after the treatment ($P = 0.003$). These results indicate that 1α(OH)D_3 treatment is effective for maintaining trabecular bone mass and prevents further vertebral fractures without any serious adverse effects in postmenopausal osteoporosis.

Key words: Osteoporosis — 1α-Hydroxyvitamin D_3 — Bone mineral density — Fracture rate.

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Osteoporosis is an involutional disease that mainly affects senescent women and disturbs elderly people in their daily life because of the presence of bone pain and deformity subsequent to fractures. As 80% of fractures can be explained by a decrease in bone mass, restoring bone mass is extremely important to prevent bone fractures.

Vitamin D preparations such as 1α-hydroxyvitamin D_3 [1α(OH)D_3], 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], or 25-hydroxyvitamin D_3 [25(OH)D_3] are considered to be a possible mode of therapy for osteoporosis. However, there has been some criticism of the effects of active vitamin D_3 preparations. Nordin and Morris [1] have reported that restoration to a positive calcium balance due to a correction of calcium malabsorption by 1,25$(OH)_2D_3$ leads to the prevention of bone loss. Aloia et al. [2] and Gallagher and Goldgar [3] have also reported that 1,25$(OH)_2D_3$ prevented bone loss in both the axial skeleton and total body calcium. Reduction in the occurrence of vertebral fracture by treatment with 1,25$(OH)_2D_3$ has also recently been reported by Tilyard et al. [4] and Gallagher et al. [5]. On the other hand, Christiansen et al. [6], Jensen et al. [7], and Falch et al. [8] have reported no effects with 1,25$(OH)_2D_3$.

1α(OH)D_3 is a pro-drug of 1,25$(OH)_2D_3$ which has been reported to be effective for increasing mineral density in radial bone and decreasing the fracture rate in senile osteoporosis [9–11]. However, these studies were retrospective studies and were not double-blind, placebo-controlled trials. Furthermore, there has been no evidence for the effect of 1α(OH)D_3 on vertebral bone mineral density in osteoporosis.

Therefore, we conducted a 1-year randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of 1α(OH)D_3 in postmenopausal osteoporosis at trabecular bone sites.

Materials and Methods

Patients and Study Design

Eighty-five postmenopausal patients with established osteoporosis in five medical institutions were recruited. The selection criteria

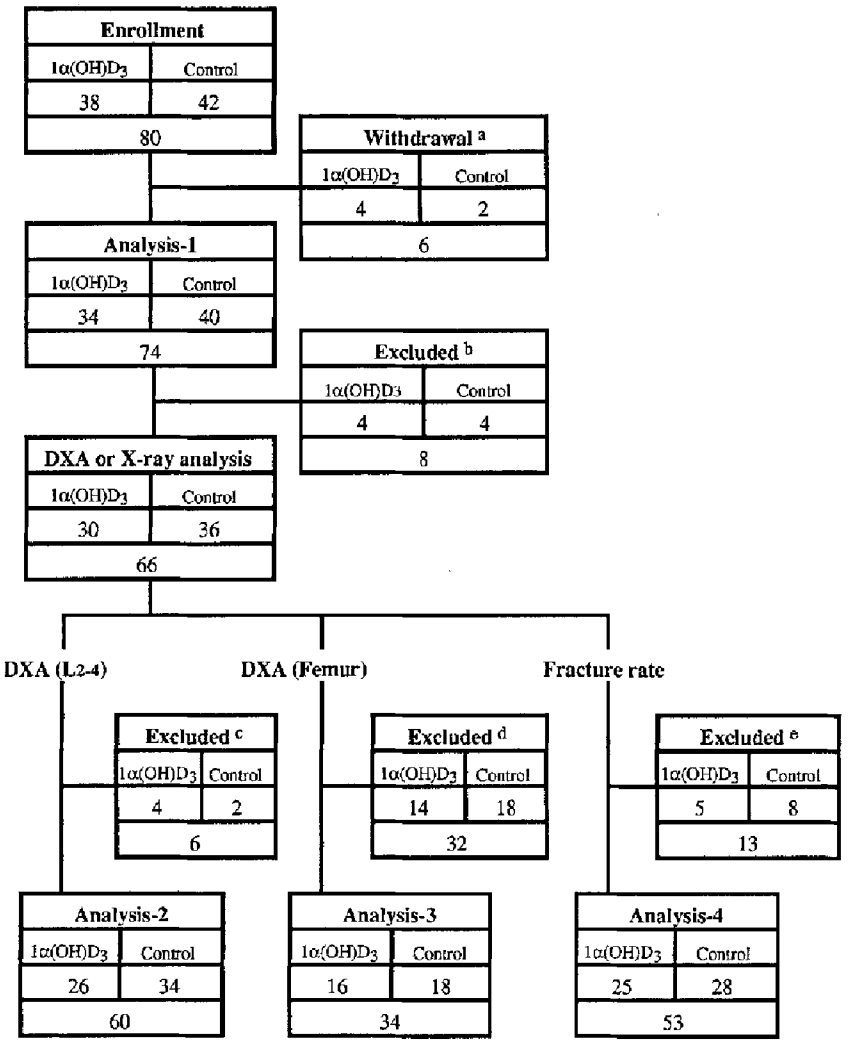

Fig. 1. Breakdown of cases. Analysis-1 (serum and urine chemistry), Analysis-2 (DXA(L2-L4), Analysis-3 (DXA (femur)), and Analysis-4 (fracture rate). [a]Reason for withdrawal (6 cases); dropout (1α(OH)D$_3$: 3, Control:2), side effect (1α(OH)D$_3$:1, Control:0). [b]Reason for exclusion (8 cases); DXA and X-ray film were not done at the end of study (1α(OH)D$_3$:4, Control:4). [c]Reason for exclusion (6 cases); air value mingled (1α(OH)D$_3$:1, Control:1), absence of data (1α(OH)D$_3$:3, Control 1). [d]Reason for exclusion (32 cases); inadequate data by air or insufficient rotation (1α(OH)D$_3$:4, Control:7), absence of data (1α(OH)D$_3$:10, Control:11). [e]Reason for exclusion (13 cases); inadequate X-ray film for Th4-L4 (1α(OH)D$_3$:2, Control:4), absence of X-ray film (1α(OH)D$_3$:3, Control:4).

were as follows: (1) decreased bone mass; (2) presence of fractures (spine, femur neck, radius); (3) 65 years old or older; (4) normal levels of serum calcium, phosphate, and alkaline phosphatase. Exclusion criteria included chronic diseases such as hypercalcemia, osteomalacia, primary/secondary hyperparathyroidism, rheumatoid arthritis, bone metastases of malignant tumors, multiple myeloma, trauma, and secondary osteoporosis such as bilateral oophorectomy. Patients who had previously been immobilized for a prolonged period, or who had taken the following drugs in the previous 2 months were also excluded: anti-osteoporotic agents such as estrogen, progesterone, androgen, calcitonin, bisphosphonate, vitamin D metabolites or analogs, ipriflavone, vitamin K$_2$, corticosteroids, or anticonvulsants. All women were Japanese. The study protocol was approved by the Institutional Review Board at each hospital.

Eighty women who met the above criteria were enrolled and informed consent was obtained from all. The study was a randomized, double-blind, controlled trial. Assignments to the treatment or control group were made from a list of randomly generated treatment codes previously prepared by a controller (N. Ogawa, M.D.). When these patients entered the study, they started taking identical-in-appearance capsules of either 1α(OH)D$_3$, at a dose of 1 μg, or placebo once a day. 1α(OH)D$_3$ (ALFAROL®: 1.0 μg capsule) and placebo were supplied by Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan). Capsules were formally counted to assess compliance. All women were taking supplemental calcium as calcium lactate (300 mg of elemental calcium). The women were given neither specific instructions regarding dietary calcium intake nor a program of exercise. The patients took analgesic drugs if pain was severe, but use of other drugs affecting calcium metabolism was prohibited during the study.

Serum and urine chemical measurements were made every 3 months. Bone mineral density was measured every 3 months. Radiographs of lateral spine were examined at the beginning and end of the study.

Bone Mineral Measurements

Bone mineral density (BMD) of the lumbar spine (L2-L4) and the proximal femur were measured by dual energy X-ray absorptiometry (DXA) every 3 months. The DXA equipment used in this study was either a model DPX (Lunar Radiation, Madison, WI) at four institutions or a model QDR-1000 (Hologic Inc., Waltham, MA) at one institution. As this trial was done in multiple centers, when the last measurement was made, all the measurements were collected and these data were reviewed by one physician (M. Shiraki, M.D.) who was unaware of the treatment received by the patients. If the scan area was incorrect, he ordered reanalysis to adjust scan area. Then the patients' variations of serial scan areas were adjusted to within the range of 5%. The precision of measurement in terms of coefficient of variation (CV) in the patient population (n = 33) was 2.5% for L2-L4 and 3.0% for the femoral neck. The CVs among machines were also evaluated in five healthy male volunteers who visited all the institutions and were measured for their L2-L4 BMD and femoral neck BMD. The CVs for L2-L4 BMD and femoral neck BMD in volunteers were 0.5% and 1.5%, respectively.

Table 1. Baseline characteristics of analyses

	Analysis-1 (74)		Analysis-2 (60)	
	1α(OH)D_3	Control	1α(OH)D_3	Control
Age (years)	70.9 ± 7.0 (34)	72.0 ± 7.3 (40)	69.8 ± 7.3 (26)	71.4 ± 7.5 (34)
Weight (kg)	47.4 ± 7.1 (34)	48.9 ± 9.0 (40)	49.2 ± 5.9 (26)	49.6 ± 9.4 (34)
Height (cm)	148.2 ± 5.7 (34)	147.8 ± 6.9 (40)	148.7 ± 6.0 (26)	147.9 ± 7.0 (34)
Body mass index (kg/m^2)	21.6 ± 3.0 (34)	22.7 ± 4.2 (40)	22.2 ± 2.8 (26)	23.0 ± 4.4 (34)
Age at menopause (years)	48.0 ± 3.9 (34)	47.4 ± 5.2 (40)	48.0 ± 3.8 (26)	48.2 ± 4.5 (34)
Years since menopause	22.5 ± 8.9 (34)	24.0 ± 9.2 (40)	21.5 ± 9.3 (26)	22.6 ± 8.5 (34)
No. of children	2.8 ± 1.8 (34)	3.3 ± 1.7 (40)	2.9 ± 1.8 (26)	3.3 ± 1.8 (34)
No. of vertebral fractures	1.24 ± 2.19 (34)	1.61 ± 2.21 (38)	1.00 ± 1.70 (26)	1.44 ± 2.20 (32)
25(OH)D (ng/ml)	23.2 ± 9.0 (26)	20.1 ± 6.5 (30)	24.2 ± 9.3 (21)	20.2 ± 6.8 (26)
1,25$(OH)_2$D (pg/ml)	49.5 ± 16.6 (26)	43.7 ± 18.0 (31)	49.1 ± 16.6[a] (21)	40.5 ± 13.4 (27)
DPX (BMD (g/cm^2))				
L2–L4	0.820 ± 0.189 (24)	0.803 ± 0.146 (33)	0.835 ± 0.179 (23)	0.816 ± 0.141 (30)
Femoral neck	0.661 ± 0.095 (14)	0.675 ± 0.108 (16)	0.661 ± 0.095 (14)	0.679 ± 0.110 (15)
Trochanter	0.591 ± 0.106 (14)	0.588 ± 0.119 (16)	0.591 ± 0.106 (14)	0.593 ± 0.121 (15)
Ward's Triangle	0.514 ± 0.109 (14)	0.521 ± 0.095 (16)	0.514 ± 0.109 (14)	0.525 ± 0.097 (15)
QDR-100 (BMD (g/cm^2))				
L2–L4	0.739 ± 0.136 (4)	0.705 ± 0.138 (6)	0.800 ± 0.073 (3)	0.742 ± 0.159 (4)
Femoral neck	0.563 ± 0.088 (4)	0.619 ± 0.115 (6)	0.593 ± 0.078 (3)	0.653 ± 0.124 (4)
Trochanter	0.472 ± 0.066 (4)	0.487 ± 0.113 (6)	0.483 ± 0.075 (3)	0.501 ± 0.135 (4)
Ward's Triangle	0.343 ± 0.108 (4)	0.404 ± 0.075 (6)	0.376 ± 0.104 (3)	0.426 ± 0.075 (4)

Data are mean ± SD, with the number of subjects in parentheses
[a] $P < 0.1$, by unpaired t-test against the control group

Radiography

Lateral X-rays of the thoracic and lumbar spine were taken before and after the 1-year period of the trial. The anterior, central, and posterior heights of each of the 13 vertebral bodies from Th4 to L4 were measured using an electronic caliper. These measurements were performed by one observer (Y. Hayashi, M.D.) who was blinded to the treatment assignment. He also interpreted radiographs to determine eligibility for inclusion in the analysis. The precision of this measurement with CV was 2–3%. An initial fracture was considered present if at least one of three height measurements taken from along the length of the same vertebrae had decreased by more than 20% as compared with the height of the nearest uncompressed vertebral body. The vertebral fracture rate was calculated from changes in vertebral shape and expressed as the number of vertebral fractures per 1000 patient years. A new fracture was counted if either the anterior or central height was 20% less than the posterior height. None of the patients developed new compressions at the posterior site of the vertebrae of greater than 15%.

Serum and Urine Chemistry

Serum levels of osteocalcin [12], parathyroid hormone [13], calcitonin [14], tartrate-resistant acid phosphatase (TRAP) [15], alkaline phosphatase, and alkaline phosphatase isoenzyme III [16] were measured serially at 3-month intervals. Also, urinary hydroxyproline [17], creatinine, calcium, phosphate, and sodium were determined serially. Serum concentrations of 1,25$(OH)_2$D [18] and 25(OH)D [19] were assayed before treatment. All the above measurements were made at one laboratory (Mitsubishi Yuka Biochemical Laboratories, Tokyo, Japan) before breaking the treatment code. Serum and urine biochemical measurements such as serum calcium, phosphate, creatinine, BUN, GOT, and GPT were also carried out to monitor toxicity at 3-month intervals during the 1 year of the trial.

Statistical Analysis

The data were recorded and analyzed using the SAS statistical analysis package (SAS Institute, Cary, NC). For BMD measurement, individual values were computed and expressed as the percentage change from baseline. Then the significance of changes within groups was determined by the Wilcoxon test. The two groups were compared using the Wilcoxon rank sum test. Fracture rates were calculated for a given interval from the total number of fractures occurring in the interval divided by the sum of the time intervals (×1000). Analysis of significance of change in fracture rates between the two groups was calculated using a Poisson model according to the methods of Gallagher et al. [5]. For biochemical data, the values within each group were tested using a paired t-test from baseline. The two groups were compared using an unpaired t-test. Data are shown as mean ± standard deviation (SD).

Results

Subjects

Eighty patients were enrolled in the study (38 received 1α(OH)D_3, 42 controls) and 74 completed 1 year. Of the 74 patients, four in either group who had neither DXA nor X-ray films at the end of the study were excluded. The data from 66 (30 received 1α(OH)D_3, 36 controls) were then entered into either DXA or X-ray analysis. Breakdown of cases is shown in Figure 1. The following shows how the analyses were used: Analysis-1 (serum and urine chemistry), Analysis-2 (L2-L4 BMD), Analysis-3 (femoral neck), Analysis-4 (fracture rate).

Four women in the 1α(OH)D_3 group withdrew from the study within 22 weeks. Three patients did not come to the

Table 1. *Continued*

Analysis-3 (34)		Analysis-4 (53)	
1α(OH)D_3	Control	1α(OH)D_3	Control
70.6 ± 8.4 (16)	71.4 ± 8.7 (18)	70.7 ± 7.2 (25)	71.7 ± 7.6 (28)
48.7 ± 6.1 (16)	50.3 ± 7.5 (18)	47.4 ± 7.1 (25)	50.0 ± 9.4 (28)
148.8 ± 7.3 (16)	146.8 ± 5.1 (18)	147.9 ± 6.5 (25)	148.6 ± 7.1 (28)
22.1 ± 2.9 (16)	23.9 ± 4.0 (18)	21.7 ± 3.0 (25)	23.1 ± 4.6 (28)
47.3 ± 3.4 (16)	49.0 ± 4.1 (18)	47.9 ± 4.1 (25)	47.9 ± 4.5 (28)
23.3 ± 10.3 (16)	21.4 ± 8.8 (18)	22.6 ± 9.2 (25)	23.7 ± 9.3 (28)
3.0 ± 2.0 (16)	3.6 ± 2.0 (18)	2.8 ± 1.7 (25)	3.4 ± 1.8 (28)
1.31 ± 2.02 (16)	1.06 ± 2.02 (17)	1.24 ± 2.39 (25)	1.89 ± 2.46 (28)
25.1 ± 10.1[a] (16)	19.2 ± 7.9 (15)	23.6 ± 9.8 (20)	20.8 ± 6.8 (22)
48.7 ± 17.5[a] (16)	38.3 ± 14.0 (16)	47.7 ± 15.4 (20)	40.6 ± 15.4 (23)
0.833 ± 0.213 (13)	0.842 ± 0.118 (14)	0.823 ± 0.201 (21)	0.819 ± 0.157 (25)
0.656 ± 0.097 (13)	0.670 ± 0.109 (14)	0.670 ± 0.092 (13)	0.702 ± 0.113 (10)
0.587 ± 0.109 (13)	0.597 ± 0.125 (14)	0.597 ± 0.107 (13)	0.609 ± 0.122 (10)
0.508 ± 0.111 (13)	0.523 ± 0.101 (14)	0.525 ± 0.105 (13)	0.542 ± 0.096 (10)
0.800 ± 0.073 (3)	0.742 ± 0.159 (4)	0.643 ± 0.124 (2)	0.879 ± 0.018 (2)
0.593 ± 0.078 (3)	0.653 ± 0.124 (4)	0.528 ± 0.080 (2)	0.738 ± 0.097 (2)
0.483 ± 0.075 (3)	0.501 ± 0.135 (4)	0.474 ± 0.053 (2)	0.605 ± 0.108 (2)
0.376 ± 0.104 (3)	0.426 ± 0.075 (4)	0.299 ± 0.079 (2)	0.477 ± 0.070 (2)

hospital at weeks 13, 14, and 22, although the reason for the dropouts was not complications of treatment as far as could be determined. One patient (88 years old, weight 40 kg) developed hypercalcemia at 15 weeks. Her serum calcium increased 12.1 mg/100 ml. Although she also developed weariness and nausea, her symptoms disappeared with an administration of intravenous infusion of saline, furosemide, and intramuscular calcitonin injection. Two patients of the control group dropped out. One patient refused treatment at week 12 and another patient did not come for personal reasons at week 27.

Of the 74 patients that completed 1 year, compliance was satisfactory, i.e., 97.3% in the 1α(OH)D_3 group and 97.5% in the control group followed the regimen. Their baseline characteristics are shown in Table 1 (Analysis-1). The clinical characteristics did not differ between the two groups at the start of the study. The mean body height in either group decreased significantly at the end of the trial. Reduction in the control group (−1.1 cm, $P = 0.009$) was greater than that in the 1α(OH)D_3 group (−0.8 cm, $P = 0.015$), but not significantly. There were no significant changes in body weight or body mass index in either group. Thirty patients (45%) had no fracture at baseline. Distribution of these fracture-free patients in the two groups did not differ significantly ($P = 0.252$). The serum levels of 25(OH)D were in the normal range (reference range in Japanese women: 9–33.9 pg/ml); no patient who showed overt vitamin D deficiency was included in this study. Baseline characteristics of Analysis-2, 3, and 4 are also shown in Table 1.

Bone Density Measurements

The data from six (four receiving 1α(OH)D_3, two controls) of 66 patients were not used because these four cases were collected outside of the study period and two cases had inadequate scans. The L2-L4 BMD values from 60 patients were used for analysis. The baseline values in L2-L4 BMD were not significantly different between the two groups by either DPX or QDR-1000 (Table 1, Analysis-2). The mean value of L2-L4 BMD was 0.824 ± 0.157 g/cm^2 and 0.767 ± 0.157 g/cm^2 by the measurement of DPX and QDR-1000 at the beginning of the study. These values were −3.64 and −3.45 SD below the mean of the peak bone mass in normal Japanese women (DPX 1.159 ± 0.092 g/cm^2, QDR 1.043 ± 0.080 g/cm^2), respectively, so these patients had very low bone mass.

The measurement of femoral neck was determined in 45 cases. However, 11 (four 1α(OH)D_3, seven controls) cases were judged as having had an inadequate scan because of insufficient rotation of the femoral neck and/or insufficient tissue mass around the trochanter. Finally, 34 patients' data on the femoral neck were used to analyze the effects of 1α(OH)D_3 (Table 1, Analysis-3).

Table 2 shows the mean percentage changes in BMD after 1 year of treatment for the two groups. Treatment effects were significant for spine density ($P = 0.037$). Figure 2 shows the percentage changes of spinal L2-L4 BMD for each subject who completed 1 year. Although changes in trochanter BMD in the 1α(OH)D_3 group were greater than that in the control group, the difference between the two groups was not significant ($P = 0.056$).

Fracture Incidence

X-ray analysis was carried out on 53 patients (25 receiving 1α(OH)D_3, 28 controls). The number of fractures was less in the 1α(OH)D_3 group than in the control group at the beginning but not statistically different (Table 1, Analysis-4).

Table 2. Percentage changes in BMD values at 1 year

Variable	Group	% Change at 1 year n	mean ± SD	Difference[a] P value
Spine (g/cm²)	1α(OH)D3	26	0.65 ± 5.17	0.037
	Control	34	−1.14 ± 5.21	
Femoral Neck (g/cm²)	1α(OH)D3	16	2.15 ± 12.70	0.769
	Control	18	−0.31 ± 17.17	
Trochanter (g/cm²)	1α(OH)D3	16	4.20 ± 7.99	0.056
	Control	18	−2.37 ± 28.78	
Ward's Triangle (g/cm²)	1α(OH)D3	16	3.26 ± 20.02	0.343
	Control	18	−0.01 ± 29.44	

[a] By the Wilcoxon rank sum test

Twenty-four patients (45%) had no fracture at baseline. Distribution of these fracture-free patients in the two groups did not differ significantly ($P = 0.139$).

The number of vertebral fractures per 1000 patient years are shown in Table 3. Two new fractures occurred in two 1α(OH)D3-treated patients and eight new fractures in seven placebo-treated patients, giving a fracture rate of 75 and 277 for the 1α(OH)D3 and the control group, respectively. The fracture rate was significantly less ($P = 0.029$) in the 1α(OH)D3 group than in the control group. Neither hip fractures nor nonvertebral other fractures occurred in either group during the study period.

Biochemical Measurements

Changes in serum and urine chemistry which occurred in the 74 patients (34 receiving 1α(OH)D3, 40 controls) listed in Figure 1, "Analysis-1" are shown in Table 4. TRAP was higher in the 1α(OH)D3 group at baseline but the other parameters were not significantly different. Although the changes in serum Ca were within the normal range except for one case receiving 1α(OH)D3, serum Ca increased slightly, but it was not statistically different. Alkaline phosphatase in the 1α(OH)D3 group was significantly decreased at 6 and 12 months compared with the value of the baseline. There was statistical difference between the two groups at 6 months. Also alkaline phosphatase type III isoenzyme was significantly decreased only in the 1α(OH)D3 group at 12 months. Serum parathyroid hormone (PTH) levels were slightly higher (reference range in Japanese 230–560 pg/ml) at baseline and they decreased in both groups at 6 and 12 months, but statistical difference was seen only in the control group at 12 months. On the other hand, no significant changes were observed in serum phosphate, creatinine, BUN, TRAP, or osteocalcin. Although increases in the urinary Ca/creatinine ratio in the 1α(OH)D3 group were significantly different not only against the baseline value but also against the changes in the control group, these values in the 1α(OH)D3 group were in the normal range. Urinary P/creatinine ratio, Na/creatinine ratio, and hydroxyproline/creatinine ratio did not show any significant change in either group.

Table 3. Effects of 1α(OH)D3 or placebo on the vertebral fracture rate/1000 patient years

Group	No. of cases	No of fractures at baseline[a]	No. of new fractures (no. of patients)	Fracture rate/ 1000 patient years
1α(OH)D3	25	1.24 ± 2.39	2 (2)	75[b]
Control	28	1.89 ± 2.46	8 (7)	277

[a] Data are mean ± SD
[b] Denotes statistical significance between groups ($P = 0.029$) by a Poisson model

Discussion

Although many reports have shown a significant increase in

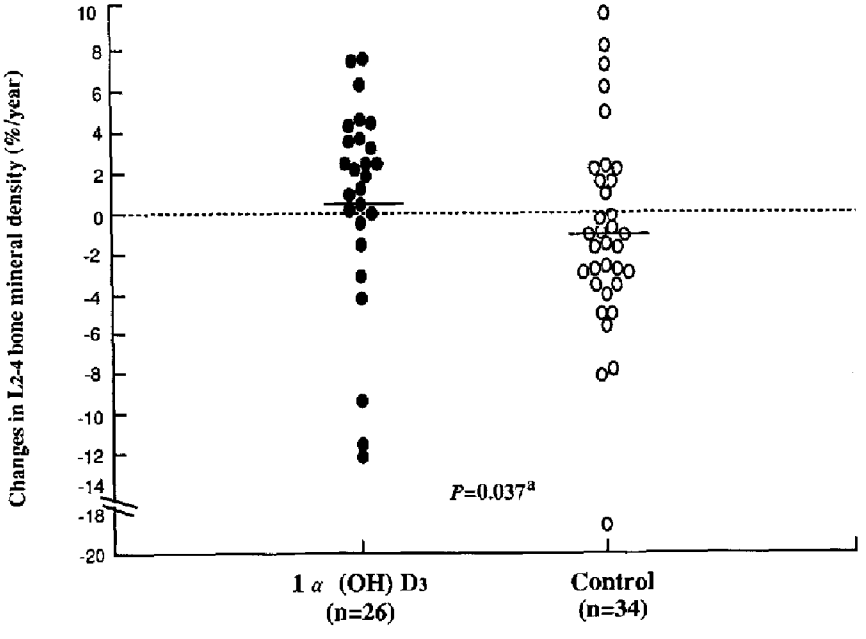

Fig. 2. Percentage changes of L2-L4 BMD in the 1α(OH)D3 group (filled circle) and the control group (open circle) after 1 year. [a]By Wilcoxon rank sum test.

Table 4. Changes in serum and urine chemistry at baseline and changes at 6 and 12 months

Variable	Group	Baseline value	Changes 6 months	Changes 12 months
Serum chemistry				
Calcium (mg/dl)	1α(OH)D_3	9.41 ± 0.42 (34)	0.14 ± 0.55 (32)	0.13 ± 0.59 (32)
	Control	9.31 ± 0.49 (35)	0.04 ± 0.45 (34)	0.03 ± 0.52 (32)
Phosphate (mg/dl)	1α(OH)D_3	3.58 ± 0.52 (34)	−0.09 ± 0.48 (32)	−0.11 ± 0.59 (32)
	Control	3.61 ± 0.51 (34)	−0.03 ± 0.51 (33)	0.08 ± 0.52 (31)
Alkaline phosphatase (mU/ml)	1α(OH)D_3	225 ± 61 (24)	−36 ± 35[b,d] (17)	−18 ± 34[c] (18)
	Control	226 ± 66 (30)	−10 ± 36 (22)	−1 ± 50 (22)
Creatinine (mg/dl)	1α(OH)D_3	0.75 ± 0.19 (33)	0.04 ± 0.11 (31)	0.04 ± 0.14 (31)
	Control	0.76 ± 0.18 (36)	0.00 ± 0.10 (35)	0.02 ± 0.09 (31)
BUN (mg/dl)	1α(OH)D_3	17.8 ± 5.5 (33)	0.7 ± 4.6 (31)	−0.1 ± 5.3 (31)
	Control	16.5 ± 4.3 (36)	−0.8 ± 4.3 (34)	0.1 ± 5.4 (31)
Parathyroid hormone (pg/ml)	1α(OH)D_3	501 ± 225 (27)	−44 ± 121 (18)	−80 ± 187 (20)
	Control	504 ± 223 (31)	−14 ± 97 (23)	−44 ± 102[c] (23)
Calcitonin (pg/ml)	1α(OH)D_3	26.3 ± 15.6 (28)	4.8 ± 10.3 (19)	−5.0 ± 18.4 (20)
	Control	27.8 ± 12.9 (33)	1.5 ± 12.2 (24)	−6.7 ± 14.0[c] (23)
TRAP (mU/ml)	1α(OH)D_3	6.4 ± 1.8[a] (27)	−1.1 ± 2.3 (19)	−0.9 ± 2.1 (20)
	Control	5.3 ± 1.5 (31)	0.2 ± 1.8 (23)	−0.1 ± 1.7 (23)
Al-P type III (mU/ml)	1α(OH)D_3	107 ± 45 (19)	−18 ± 34 (12)	−26 ± 26[d] (13)
	Control	105 ± 42 (26)	−3 ± 28 (17)	−12 ± 28 (16)
Osteocalcin (ng/ml)	1α(OH)D_3	7.7 ± 4.8 (28)	−1.3 ± 3.7 (19)	−1.3 ± 4.5 (20)
	Control	7.2 ± 5.4 (33)	0.2 ± 4.7 (24)	0.2 ± 4.5 (23)
Urine chemistry				
Ca/Creatinine	1α(OH)D_3	0.20 ± 0.10 (26)	0.09 ± 0.11[a,d] (17)	0.11 ± 0.16[d] (21)
	Control	0.17 ± 0.12 (30)	−0.00 ± 0.10 (22)	0.04 ± 0.13 (23)
P/Creatinine	1α(OH)D_3	0.74 ± 0.34 (29)	0.06 ± 0.44 (18)	−0.02 ± 0.37 (22)
	Control	0.69 ± 0.34 (32)	−0.01 ± 0.45 (23)	0.03 ± 0.51 (23)
Na/Creatinine	1α(OH)D_3	2.25 ± 1.25 (29)	0.68 ± 1.59 (18)	−0.10 ± 1.22 (22)
	Control	2.74 ± 3.04 (32)	−0.26 ± 3.90 (23)	−0.35 ± 3.94 (23)
Hydroxyproline/Creatinine	1α(OH)D_3	0.15 ± 0.04 (24)	0.00 ± 0.08 (16)	−0.02 ± 0.04 (19)
	Control	0.22 ± 0.27 (30)	−0.08 ± 0.32 (22)	−0.09 ± 0.32 (23)

Data are mean ± SD, with the number of subjects in parentheses
[a] $P < 0.05$; [b] $P < 0.01$: by unpaired t-test against the control group
[c] $P < 0.05$; [d] $P < 0.01$: by paired t-test against baseline

cortical BMDs after 1α(OH)D_3 treatment, there has been no data available on the effect of 1α(OH)D_3 treatment on trabecular bone mass. We have found an increase of 0.65% in lumbar bone density (difference between the 1α(OH)D_3 and the control was + 1.79%, $P = 0.037$) and a significant reduction of vertebral fracture rate from 277 fractures per 1000 patient years to 75 (73% reduction, $P = 0.029$) after 1 year treatment with 1α(OH)D_3 in postmenopausal osteoporosis. In the femoral neck, BMDs tended to be sustained (2.15% in femoral neck, 4.20% in trochanter, and 3.26% in Ward's triangle) in the 1α(OH)D_3 group and to decrease (−0.31, −2.37, and −0.01%, respectively) in the control group after 1 year of treatment, but these were not statistically different. These results agree with the previous reports in which the effects of 1,25$(OH)_2D_3$ on lumbar BMD were evaluated by other investigators. For example, Aloia et al. [2] conducted a 2-year trial with 0.8 μg/day of 1,25$(OH)_2D_3$ and showed a gain in bone mass of +1.7%/year. Gallagher and Goldgar [3] also showed a +2.06% gain over 2 years of treatment with 0.62 μg/day, but a trial by Ott and Chesnut [20] at a dose of 0.43 μg/day showed a loss of about 1% over 2 years. However, they [21] reanalyzed their data and reported that certain patients who were taking thyroid hormone preparation might easily have developed hypercalciuria with 1,25$(OH)_2D_3$ and therefore lost bone mass. They also showed that patients who could tolerate more than 0.55 μg/day of 1,25$(OH)_2D_3$ gained spinal bone mass of about 10%, as determined by dual photon absorptiometry.

There are no reports regarding the effects of active forms of vitamin D on femoral bone mass. Effects of active forms of vitamin D on radial bone mass have been reported by many investigators. Significant gains in radial bone mass have been found by treatment with 1,25$(OH)_2D_3$ at a daily dose of 0.7 μg or more [2, 21]. Treatment with 0.5 μg/day or less did not show a gain in radial bone mass [6, 20, 22, 23]. The minimal effective dose of 1,25$(OH)_2D_3$ (0.5 μg/day) was about half that of 1α(OH)D_3 (1 μg/day), quite reasonable because the bioactivity of 1α(OH)D_3 appears to be half that of 1,25$(OH)_2D_3$. Therefore, we can conclude that 1α(OH)D_3 administration in osteoporosis is effective for increasing or at least sustaining bone mass not only in cortical but also in trabecular bone.

Recently, treatment of osteoporosis has been required to show a preventive effect on bone fractures. In the present study, the vertebral fracture rate in the treated group was about one-third of that in the control group. These results agree with our previous study [10] and the results reported by Tilyard et al. [4]. Furthermore, Chapuy et al. [24] also reported that supplementation of Vitamin D_3 and Ca prevented hip fractures in elderly women.

1α(OH)D_3 treatment resulted in a decrease in serum bone-derived alkaline phosphatase by 26% from the basal value. TRAP, osteocalcin, and urinary excretion of hydroxyproline also tended to decrease after treatment. These results may indicate that 1α(OH)D_3 has a depressive effect on bone turnover and this fact coincides with our previous re-

port, as determined by serum chemistry [9] and with reports determined by bone histomorphometric data [2, 24]. There were two possible explanations as to why 1α(OH)D_3 depresses bone turnover: indirect inhibition, because it has been reported that 1α(OH)D_3 administration results in inhibition of PTH secretion [25]; and direct inhibition of bone turnover, because our results showed no significant decrease in PTH levels after treatment. Urinary calcium excretion increased significantly after 1α(OH)D_3 treatment. This might be caused by increased calcium absorption from intestine, because there was no evidence to show increase in bone resorption.

There were no serious adverse effects seen in the patients given 1α(OH)D_3. Thus, we can conclude that 1α(OH)D_3 treatment is safe and effective for preventing the progression of osteoporosis in the entire skeleton, judging from bone density and fracture incidence after treatment.

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