

The Prevention of Hip Fracture With Risedronate and Ergocalciferol Plus Calcium Supplementation in Elderly Women With Alzheimer Disease

A Randomized Controlled Trial

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Background: A high incidence of fractures, particularly of the hip, represents an important problem in patients with Alzheimer disease (AD), who are prone to falls and have osteoporosis. We previously found that deficiency of 25-hydroxyvitamin D and compensatory hyperparathyroidism cause reduced bone mineral density in female patients with AD. We address the possibility that treatment with risedronate sodium and ergocalciferol plus calcium supplementation may reduce the incidence of nonvertebral fractures in elderly women with AD.

Methods: A total of 500 elderly women with AD were randomly assigned to daily treatment with 2.5 mg of risedronate sodium or a placebo, combined with 1000 IU of ergocalciferol and 1200 mg of elementary calcium, and followed up for 18 months.

Results: At baseline, patients of both groups showed 25-

hydroxyvitamin D deficiency with compensatory hyperparathyroidism. During the study period, bone mineral density in the risedronate group increased by 4.1% and decreased by 0.9% in the control group. Vertebral fractures occurred in 29 patients (24 hip fractures) in the control group and 8 patients (5 hip fractures) in the risedronate group. The relative risk in the risedronate group compared with the control group was 0.28 (95% confidence interval, 0.13-0.59).

Conclusions: Elderly patients with AD hypovitaminosis D are at increased risk for hip fracture. Treatment with risedronate and ergocalciferol may be safe and effective in reducing the risk of a fracture in elderly patients with AD.

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ALZHEIMER DISEASE (AD) IS a common neurodegenerative disorder characterized by progressive loss of memory and cognitive function, and far-advanced AD is associated with generalized weakness. A high incidence of fractures, particularly of the hip,¹⁻³ represents an important problem in patients with AD, who are prone to falls⁴ and may have osteoporosis. The odds ratio reported for fracture prevalence between elderly persons with and without AD is 6.9.⁴ Hip fractures are associated with higher medical costs compared with all other osteoporosis-related fractures combined.⁵ Functional recovery after hip fracture in AD is poor,⁶⁻⁸ and patients with dementia have increased mortality during the first 6 months after a hip fracture.⁹

The physical condition of patients with AD has increasingly become one of the critical issues in their treatment. We previously¹⁰ demonstrated that deficiency of 25-hydroxyvitamin D (25-OHD) due to sunlight deprivation contributes to the reduced bone mineral density (BMD) in pa-

tients with AD in nursing homes. Also, elderly female patients with AD with low BMD and serum 25-OHD concentrations of 5 ng/mL or lower with secondary hyperparathyroidism had a high risk of hip fracture.¹¹ Kipen et al¹² examined women with dementia in the community and found that they have normal BMD, hypovitaminosis D, and compensatory hyperparathyroidism.

Thus, vitamin D deficiency with compensatory hyperparathyroidism contributes to reduced BMD in patients with AD. Risedronate sodium, a pyridinyl bisphosphonate, is known to reduce bone resorption through the inhibition of osteoclastic activity.¹³ Its antiresorptive action is more potent than that of a related compound, etidronate disodium. Risedronate decreases the risk of fractures and increases BMD in postmenopausal women with osteoporosis.¹⁴⁻¹⁶ According to a recent review,¹⁷ the effectiveness of the risedronate in preventing osteoporotic fractures has been clearly demonstrated in many trials. Risedronate therapy would be beneficial particularly in reducing accelerated osteoclastic bone re-

Table 1. Demographic and Baseline Clinical Characteristics of the Female Patients With Alzheimer Disease at Study Entry*

Characteristic	Control Group (n = 250)	Risedronate Group (n = 250)	P Value†
Age, y	77.7 ± 5.1	77.7 ± 5.3	.99
Duration of illness, y	4.4 ± 2.0	4.4 ± 1.9	.98
Mini-Mental State Examination score	16.4 ± 4.5	16.5 ± 5.2	.80
Interval since menopause, y	25.0 ± 3.6	25.0 ± 3.7	.95
Barthel index‡	85.8 ± 9.0	85.7 ± 8.6	.88
Body mass index, kg/m ²	19.6 ± 2.3	19.7 ± 2.0	.61
Faller§	90 (36)	88 (35)	.90
Sunlight exposure per wk			
>15 min	14 (6)	13 (5)	.93
≤15 min	26 (10)	24 (10)	
None	210 (84)	213 (85)	
Dietary intake of calcium, mg/d	864 ± 167	862 ± 161	.85
Dietary intake of vitamin D, IU/d	80 ± 19	80 ± 18	.96
Bone mineral density,¶ mm Al	1.90 ± 0.29	1.90 ± 0.32	.96

*Values are given as mean ± SD or number (percentage) of patients unless otherwise specified. Risedronate group, treated with risedronate sodium + ergocalciferol + calcium supplementation; control group, treated with placebo + ergocalciferol and + calcium supplementation.

†Unpaired *t* test.

‡Activities of daily living were evaluated by the Barthel index.²⁰

§Patients who fell at least once in the 3 months before recruitment or study period.

||Fisher exact test.

¶Bone thickness was calculated as an aluminum equivalent (mm Al) (reference range, 2.19-2.91 mm Al).

sorption in patients with AD. We therefore conducted an 18-month randomized, double-blind trial to evaluate the efficacy of risedronate and ergocalciferol with calcium supplementation in preventing the progression of osteoporosis and decreasing the risk of vertebral fractures in elderly women with AD. Also, biochemical indexes of bone metabolism were measured to assess the effectiveness of the therapy. The rate of vertebral fractures was not determined in this study because many vertebral fractures are asymptomatic among elderly patients with AD and the interpretation of spinal x-ray films may be complicated by osteoarthritis or scoliosis.

METHODS

STUDY POPULATION

This study compared the incidence of vertebral fractures in the 2 groups of elderly female patients with AD who were administered risedronate or a placebo, combined with ergocalciferol and calcium supplementation. We recruited 500 ambulatory women from consecutive patients in our outpatient clinic who were 70 years or older, living in the community and cared for by their family caregivers, and who met criteria for dementia and probable AD according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*.¹⁸ Patients were recruited from March 2003 to April 2003, and each patient was followed up for 18 months. Patients younger than 70 years were excluded from the study. Patients with impairment of hepatic, renal, cardiac, or thyroid function or those who had known causes of osteoporosis, such as primary hyperparathyroidism,

renal osteodystrophy, or familial osteoporosis, were excluded from this study. Also, patients were excluded if they had received any drug known to alter bone metabolism, such as corticosteroids, anticonvulsants, estrogens, calcitonin, bisphosphonate, calcium, or vitamins D and K (all forms), for 3 months or longer during the 12 months preceding the study. The study neurologist (Y.S.), who remained blind to the results of biochemical assays of bone metabolism, diagnosed AD.

Baseline demographic data and duration of illness were obtained (Table 1). At baseline, we determined body mass index, and the Mini-Mental State Examination¹⁹ was given to the patients. Activities of daily living were assessed by the Barthel index, in which a functional dependence score of 100 represents independence.²⁰ Patients who fell at least once in the 3 months before recruitment were defined as "fallers." Daily intake of calcium and vitamin D was calculated, by comparing with the Japanese Standard Food Table, for each participant on the basis of a food-frequency questionnaire filled out by a family member. Patients who consumed less calcium and vitamin D than the Japanese recommended daily allowance (1000 mg and 100 IU, respectively) were defined as low dietary consumers of vitamin D. Sunlight exposure during the preceding year was assessed by the family members and graded as almost none, less than 15 minutes per week, or 15 minutes or longer per week.²¹

This study was approved by the local ethics committee (Human Investigation Committee of the Mitate Hospital, Tagawa, Japan). All patients and controls were informed of the nature of the study. Consent was obtained from each participant or from family members when patients were unable to understand because of dementia.

STUDY PROTOCOL

The patients were assigned to 1 of the 2 study groups by means of computer-generated random numbering. Random allocation sequence was implemented using numbered containers, and the sequence was concealed until interventions were assigned. The patients and all study personnel were blinded to treatment assignment and biochemical measurements. The randomization code was generated using a permuted block size of 4 (stratified by site) by a consulting statistician not otherwise involved in the trial. No other restrictions were used in the randomization procedure. Physicians who performed the follow-up assessment of the patients' condition were blinded to randomization and study group. Patients in the risedronate group (n=250) received a daily dose of 2.5-mg risedronate sodium in a tablet (Actonel; Aventis Pharmaceuticals, Tokyo, Japan) and 1000 IU of ergocalciferol and 1200 mg of elemental calcium after breakfast. The control group received a placebo and 1000 IU of ergocalciferol and 1200 mg of elemental calcium (n=250). Patients were instructed to take the tablet with a cup of water (180 mL), 30 to 60 minutes before breakfast, and to remain sitting or maintain an upright position for 60 minutes thereafter. Adherence to study medication was assessed by counting the returned tablets. No dose adjustments were made at any time during the study. Patients were prohibited from taking any other drugs that could affect bone metabolism during the study period, except for those for whom it was decided to be necessary for accompanying conditions. Such exceptions included an anti-inflammatory therapy with a corticosteroid in 2 patients (1 each in the 2 groups) for connective tissue diseases. Follow-up assessment of the patients' condition was performed by a physician (Y.S.) who did not participate in the initial randomization. Both groups were observed for 18 months. General medical evaluation and laboratory values were assessed on entry and after 18 months. The patients' clinical status was assessed at baseline, and all patients were followed up every 4 weeks in the outpatient clinic, at which times nonver-

Table 2. Falls and Biochemical Tests in the Risedronate and Control Groups at Baseline and After 6, 12, 18 Months of Follow-up*

Fallers/Biochemical Indexes†	Baseline	Follow-up, mo		
		6	12	18
Fallers‡				
Risedronate group	88 (35)§	69 (29)§	48 (20)§	27 (12)¶
Control group	90 (36)	71 (29)	47 (20)	24 (10)
Ionized calcium, mEq/L				
Risedronate group	2.38 ± 0.13	2.45 ± 0.09§	2.46 ± 0.08§	2.48 ± 0.09§
Control group	2.38 ± 0.14	2.51 ± 0.08	2.52 ± 0.07	2.54 ± 0.09
Intact parathyroid hormone, pg/mL				
Risedronate group	79.2 ± 17.5	43.0 ± 3.9	39.4 ± 6.9	37.3 ± 6.0
Control group	79.1 ± 18.5	43.1 ± 3.8	39.6 ± 6.0	37.2 ± 5.6
25-hydroxyvitamin D, ng/mL				
Risedronate group	9.1 ± 3.0	19.4 ± 3.5	21.9 ± 3.0	23.0 ± 2.6
Control group	9.1 ± 3.5	19.4 ± 3.3	22.1 ± 2.3	23.0 ± 2.5
Intact bone Gla protein, ng/mL				
Risedronate group	14.5 ± 4.5	7.6 ± 2.2§	7.0 ± 2.1§	6.6 ± 2.2§
Control group	14.5 ± 3.2	9.6 ± 2.2	9.1 ± 2.1	8.8 ± 2.4
Deoxypyridinoline, µmol/mol creatinine				
Risedronate group	13.6 ± 2.1	4.4 ± 2.4§	3.5 ± 1.5§	3.1 ± 1.5§
Control group	13.6 ± 2.4	6.5 ± 3.4	6.0 ± 2.8	5.5 ± 2.9

*Values are given as number (percentage) of patients or mean ± SD. Risedronate group, treated with risedronate sodium + ergocalciferol + calcium supplementation; control group, treated with placebo + ergocalciferol + calcium supplementation.

†The reference ranges of healthy elderly women: ionized calcium, 2.44 to 2.60 mEq/L; intact parathyroid hormone, 35 to 52 pg/mL; 25-hydroxyvitamin D, 18.9 to 24.9 ng/mL; intact bone Gla protein, 4.2 to 11.2 ng/mL; deoxypyridinoline, 2.1 to 6.3 µmol/mol creatinine.

‡Patients who fell at least once in the 3 months before recruitment or study period.

§ $P < .01$ vs control group.

|| $P < .01$ for the comparison with baseline.

¶ $P < .001$ for the comparison with baseline.

tebral fractures were recorded. Symptomatic nonvertebral fractures confirmed by radiological examinations were considered adverse clinical events, with no attempt to exclude fractures related primarily to trauma. Falls were registered by means of monthly "fall calendars." The family members of participants were instructed to complete the calendar daily, marking an "X" for each fall on the date when the fall occurred. In addition, the characteristics of each fall were recorded according to the timing, direction, and severity of the fall, and the activity in which the fall occurred and injuries due to the fall were also recorded.

Both groups were observed for 18 months. General medical evaluation, metacarpal BMD measurement, and laboratory values were assessed on entry and after 6, 12, and 18 months later.

Computed x-ray densitometry (CXD; Teijin Diagnostics, Tokyo)²² via an improved microdensitometric method was used to quantify BMD in the left second metacarpals of each patient as described previously.¹⁰ The computer algorithm for CXD compares bone radiodensity with the gradations of an aluminum step wedge, calculating bone thickness as an aluminum equivalent (mm Al) showing the same x-ray absorption. The validity and accuracy of this method have been described elsewhere.²³

In the morning of the day of bone evaluation, blood and urine samples were obtained from the 500 patients after an overnight fast. Blood samples were analyzed for ionized calcium, intact parathyroid hormone (PTH), and 25-OHD. Ionized calcium concentration was determined in fresh serum processed under anaerobic conditions using an ion-selective electrode and an ionized calcium analyzer (Jokoh, Tokyo). Serum PTH concentration was measured by an immunoradiometric assay (Sumitomo Biomedical, Osaka, Japan). Serum 25-OHD concentration was determined by a radioimmunoassay (DiaSorin, Stillwater, Mich). Urinary deoxypyridinoline (D-Pyr) was measured with a commercially available, specific enzyme immunoassay kit (Metra Biosystems Inc, Calif). Urinary D-Pyr was

expressed relative to urinary creatinine concentration. The normal ranges of the BMD and biochemical indexes in elderly women are given in **Table 2**.^{24,25}

STUDY END POINTS AND STATISTICAL ANALYSIS

The sample size was based on an expected nonvertebral fracture incidence of 10% in the control group over 18 months. Assuming a 10% dropout rate over 18 months, the study had at least 80% power to detect a 70% reduction in fracture risk, with a 2-sided significance level of $\alpha = .05$. The primary end point was defined as the incidence of a nonvertebral fracture. An intention-to-treat analysis was performed on all randomized participants to determine relative risk (RR), and the difference between the 2 groups was analyzed by the log-rank test. The within-group changes from the baseline values were assessed by the paired *t* test. Group differences of the categorical data were tested by the Fisher exact test. Spearman rank correlation coefficients were calculated to determine the relationships between BMD and serum 25-OHD or intact PTH. Laboratory values and BMD were expressed as percentage change from the baseline, and the 2 groups were compared by the Wilcoxon rank sum test. $P < .05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF STUDY SUBJECTS

Figure 1 illustrates the flow of participants through the study. Nineteen patients in the risedronate group and 20

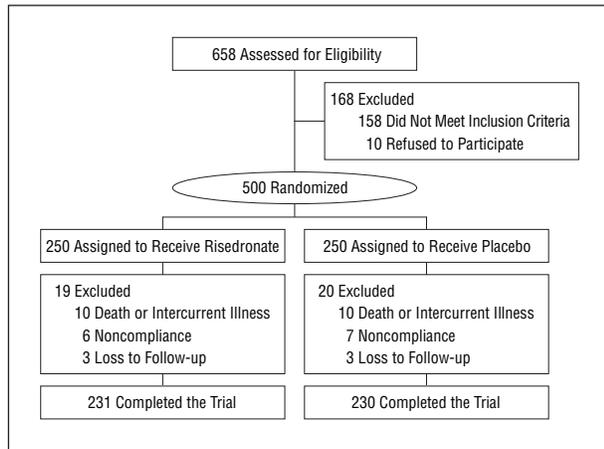


Figure 1. Flow of participants through the study.

in the control group dropped out or withdrew from the study owing to noncompliance, loss to follow-up, intercurrent illness, or death. Thus, a total of 461 patients (231 in the risedronate group and 230 in the control group) completed the trial. We included 250 patients in each treatment group in the final intention-to-treat analysis.

Table 1 lists the baseline characteristics of the participants. There was no significant difference between the 2 groups in duration of illness, Mini-Mental State Examination, Barthel index, body mass index, BMD, and numbers of fallers. Body mass index was low in both groups. Many of the patients in both groups had been exposed to sunlight for less than 15 minutes per week or had almost no sun exposure because of being homebound. Mean daily dietary intake of vitamin D and calcium in both groups were less than the Japanese recommended daily allowance (100 IU and 1000 mg, respectively). The average values of metacarpal BMD in the 2 groups were lower compared with the reference range of the normal Japanese population.^{24,25}

As shown in Table 2, in the 2 groups, the baseline values of serum ionized calcium, 25-OHD concentrations were low, whereas serum PTH and bone Gla-protein (BGP) or urinary D-Pyr were high compared with the reference range of the normal Japanese population.^{24,25}

When both patient groups were analyzed together, the BMD correlated positively with body mass index ($r=0.250$; $P<.01$), and 25-OHD ($r=0.261$; $P<.01$) concentrations, whereas BMD correlated negatively with PTH ($r=-0.260$; $P<.01$). There were negative correlations between serum 25-OHD and PTH ($r=-0.213$; $P<.01$), suggesting the presence of compensatory hyperparathyroidism.

FRACTURES

Nonvertebral fractures occurred in 8 patients in the treatment group (5 hip fractures and 1 fracture each at the distal forearm, proximal humerus, and ankle) and 27 patients in the control group (19 with hip fractures; 3 fractures at the distal forearm; 2 fractures at the proximal femur; and 1 fracture each at the proximal humerus, ribs, and pelvis).

There were 5 hip fractures in the treatment group and 19 in the control group (**Figure 2**); this difference was

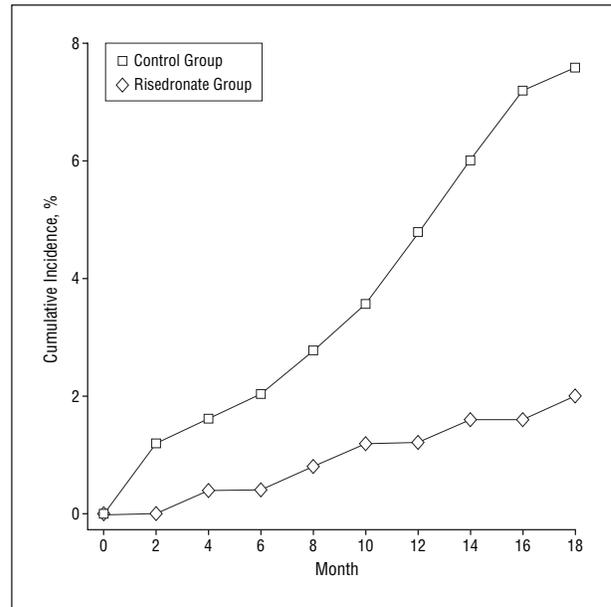


Figure 2. Cumulative incidence of hip fractures in the risedronate sodium and ergocalciferol with calcium supplementation (risedronate) group and the placebo and ergocalciferol with calcium supplementation (control) group. During 18 months, 19 subjects in the control group and 5 in the risedronate group had a hip fracture (log-rank, $P<.001$).

statistically significant (log-rank test, $P<.001$). The number of hip fractures per 1000 patient-years for the risedronate and control groups was 15 and 57, respectively. The RR in the risedronate group vs control group for hip fractures was 0.26 (95% confidence interval, 0.10-0.69).

There were 8 nonvertebral fractures in the treatment group and 29 in the control group; this difference was statistically significant (log-rank test, $P<.001$). The RR in the risedronate group vs control group for nonvertebral fractures was 0.28 (95% confidence interval, 0.13-0.59).

Table 2 summarizes time-dependent changes in the number of fallers, who fell at least once in 3 months because of sudden loss balance. The numbers of fallers after 6 months remained similar to those at baseline in the 2 groups; however, the numbers in the 2 groups after 12 and 18 months were significantly smaller compared with the baseline number in each group ($P<.01$). There was no significant difference between the 2 groups in the mean \pm SD number of falls per subject during the 18 months (1.9 ± 0.8 in the control group and 1.9 ± 0.9 in the risedronate group).

BONE CHANGES AND BLOOD BIOCHEMICAL MARKERS

Figure 3 shows the percentage changes from the baseline in metacarpal BMD during the 18 months. The mean \pm SD percentage changes in BMD were $+4.1 \pm 0.2$ in the risedronate group and -0.9 ± 0.1 in the placebo group. The difference between the 2 groups was statistically significant ($P<.001$).

Changes in various parameters during the 18-month study period are summarized in Table 2. In both groups,

serum calcium and 25-OHD concentrations increased significantly compared with the baseline values, and serum PTH and BGP or urinary D-Pyr concentrations decreased significantly compared with the baseline values in both groups. A significant decrease of serum ionized calcium, BGP, and urinary D-Pyr concentrations in the risedronate group was observed compared with those in control group.

ADVERSE EFFECTS

Serious adverse events including death, overdose, and any other event that was life threatening or permanently disabling or that required intervention to prevent permanent impairment were not observed in either group. In the risedronate group, 2 patients experienced leukopenia, 1 patient had esophagitis, and 3 patients experienced abdominal pain, which eventually disappeared with appropriate therapy without discontinuation of the treatment. Three patients in the control group experienced gastrointestinal symptoms such as epigastric discomfort and nausea, but they subsided within a week without discontinuing ergocalciferol.

COMMENT

Prevention of fractures is one of the important issues in the treatment of elderly women with AD. The high incidence of hip fractures in elderly patients with AD may be attributed to frequent falls⁴ and osteoporosis due to 25-OHD deficiency with compensatory hyperparathyroidism as suggested in the present study. Serum levels of 25-OHD and PTH and body mass index were found to correlate with BMD in patients with AD. In the present study, the number of falls during the follow-up period was similar and reduced compared with baseline values in the 2 groups, indicating that ergocalciferol may have prevented falls in both groups. A recent study suggested that vitamin D supplementation reduces the risk of falls among ambulatory or institutionalized older individuals.²⁶ This implies that the frequency of fractures due to falls in patients with AD is related to hypovitaminosis D. Despite the reduced incidence of falls and normalization of 25-OHD, incidence of nonvertebral fractures was higher in the control group. Indeed, RRs for hip and nonvertebral fractures were low in the risedronate group compared with the control group. Also, the RR of the risedronate group in the present study (0.26) was low compared with that reported in a recent meta-analysis of 7 trials (0.73) on the effect of risedronate for osteoporotic fractures.¹⁷ This difference may be explained by a larger increase in BMD in the present study: the average values of BMD increased by 4.1% in the risedronate group over 18 months. This may reflect a synergistic effect of risedronate and ergocalciferol.

The hip fracture rate in the control group was calculated as 57 per 1000 patient-years. The rate of hip fracture in an elderly reference population between ages 70 and 79 years was reported to be 6.6 per 1000 patient-years.²⁷ Although the mean age of our AD subjects (77.7 years) was within this range, the fracture rate in the pres-

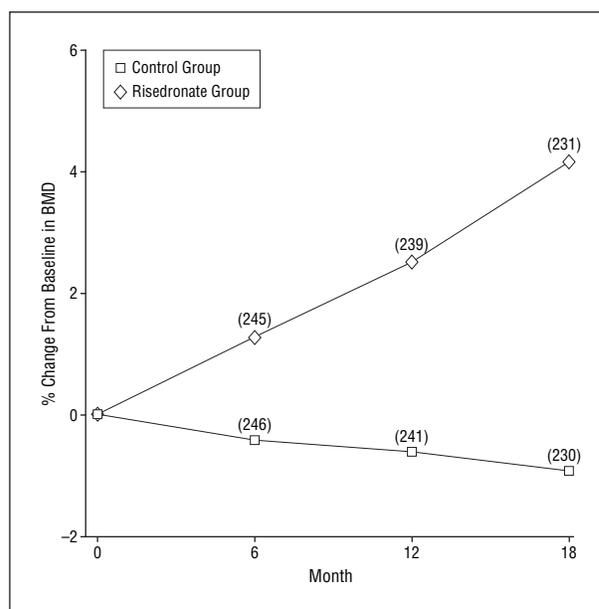


Figure 3. Percentage changes from baseline in metacarpal bone mineral density (BMD) after 6, 12, and 18 months in the 2 groups of patients. During the 18 months, the differences in the percentage changes in the BMD among the 2 groups were statistically significant (based on Wilcoxon rank sum test; $P < .001$). Numbers in parentheses are the numbers of the subjects followed.

ent series was far higher than that reported in the reference population.²⁷ In addition to sunlight deprivation, 25-OHD deficiency in these patients was considered to reflect generally poor nutrition, as also evidenced by lower body mass index. It has been reported that patients with dementia had malnutrition and decreased body weight.²⁸ In the present study, 25-OHD deficiency with compensatory hyperparathyroidism resulted in high serum BGP and urinary excretion of D-Pyr, which was corrected by ergocalciferol in both groups. Thus, normalization of 25-OHD, ionized calcium, and bone turnover variables was observed in both groups. The decrease in bone turnover variables was more pronounced in the risedronate group, indicating that greater inhibition of bone resorption may have brought about significant improvement of BMD in the risedronate group.

The patients with deficient 25-OHD levels in the risedronate group benefited from the therapy in terms of increased BMD and prevention of nonvertebral fractures. This implies that treatment with risedronate may be particularly effective in patients with vitamin D deficiency.

We conclude that female patients with AD with low serum vitamin D levels and high bone remodeling due to compensatory hyperparathyroidism are at an increased risk for nonvertebral fractures, particularly in the hip. Combined treatment with risedronate, ergocalciferol, and calcium supplementation may be safe and effective in increasing bone mass and reducing the risk of fractures in elderly women with AD.

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