RETRACTION

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Article Title: The prevention of hip fracture with menatetrenone and risedronate plus calcium supplementation in elderly patients with Alzheimer disease: a randomized controlled trial
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The Prevention of Hip Fracture with Menatetrenone and Risedronate Plus Calcium Supplementation in Elderly Patients with Alzheimer Disease: A Randomized Controlled Trial

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Summary: 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 vitamin K deficiency and low 25-hydroxyvitamin D (25-OHD) with compensatory hyperparathyroidism cause reduced bone mineral density (BMD) in female patients with AD. This may be modifiable by intervention with menatetrenone (vitamin K2) and risedronate sodium; we addressed the possibility that treatment with menatetrenone, risedronate and calcium may reduce the incidence of nonvertebral fractures in elderly patients with AD. A total of 231 elderly patients with AD were randomly assigned to daily treatment with 45 mg of menatetrenone or a placebo combined with once weekly risedronate sodium, and followed up for 12 months. At baseline, patients of both groups showed high undercarboxylated osteocalcin (ucOC) and low 25-OHD insufficiency with compensatory hyperparathyroidism. During the study period, BMD in the treatment group increased by 5.7% and increased by 2.1% in the control group. Nonvertebral fractures occurred in 15 patients (10 hip fractures) in the control group and 5 patients (2 hip fractures) in the treatment group. The relative risk in the treatment group compared with the control group was 0.31 (95% confidence interval, 0.12-0.81). Elderly AD patients with hypovitaminosis K and D are at increased risk for hip fracture. The study medications were well tolerated with relatively few adverse events and effective in reducing the risk of a fracture in elderly patients with AD.

Key words Alzheimer disease, fall, hip fracture, vitamin K deficiency, osteoporosis

INTRODUCTION

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 falls [4] 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 management. We previously demonstrated that deficiency of 25-hydroxyvitamin D (25-OHD) due to sunlight deprivation and vitamin K deficiency due to malnutrition contributed to reduced bone mineral density (BMD) in patients with AD and were associated with a high risk of hip fracture [10,11].

Our previous study demonstrated that menatetrenone (vitamin K2) reduced the risk of hip fracture in patients with AD [11]. We also showed that risedronate and vitamin D plus calcium supplementation prevented the hip fracture in patients with AD [12].

These studies demonstrated vitamin K deficiency with compensatory hyperparathyroidism contribute to reduced BMD in patients with AD. Nutritional vitamin K1 deficiency may reduce carboxylation of osteocalcin, which may cause reduced BMD in elderly patients with AD [14]. Low dietary vitamin K1 intake was associated with low BMD in women leading to an increased risk of hip fracture [15], and treatment with menatetrenone increases metacarpal BMD in senile osteoporosis [16] and reduces the incidence of fractures in patients with postmenopausal osteoporosis [17]. Menatetrenone therapy would be beneficial for increasing BMD in patients with AD. Risedronate sodium, a pyridinyl bisphosphonate, is known to reduce bone resorption through the inhibition of osteoclastic activity [18]. Risedronate decreases the risk of fractures and increases BMD in postmenopausal women with osteoporosis [19]. According to a recent review [20], the effectiveness of risedronate in preventing osteoporotic fractures has been clearly demonstrated in many trials.

We therefore conducted a 12-month randomized, double-blind trial to evaluate the efficacy of menatetrenone and risedronate for preventing the progression of osteoporosis and decreasing the risk of a non-vertebral fractures in elderly patients with AD. Also, biochemical indexes of bone metabolism were measured to assess the effectiveness of the therapy. Although reduced vitamin D is one of the cause of hip fracture in AD [21], we did not administer vitamin D in the present study because the purpose of the study is to determine effectiveness of menatetrenone, risedronate and calcium without vitamin D supplementation in reducing hip fracture in AD. The Institutional Review Board approved the study with reservation that required the usage of an external hip protector on patients with the baseline serum 25-OHD level of below 10 ng/mL. The rate of nonvertebral fractures was not determined in this study because many vertebral fractures are asymptomatic in elderly patients with AD and the interpretation of spinal X-ray films may be the presence of osteoarthritis or scoliosis.

METHODS

Study population

This study compared the incidence of vertebral fractures in 2 groups of elderly patients with AD of both genders who were administered menatetrenone or a placebo, combined with risedronate and calcium. The menatetrenone and placebo capsules in this trial were identical in size, weight, color and taste. We recruited 231 ambulatory patients 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 [22]. Patients were recruited from August 2007 to July 2008, and each patient was followed up for 12 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. At baseline, we determined body mass index (BMI), and the Mini-Mental State Examination (MMSE) [23] was given to the patients. Activities of daily living were assessed by the Barthel index (BI), in which a functional dependence score of 100 represents independence [24]. Mean weekly intake of dietary vitamin K1 (phyloquinone) during the previous 12 months was calculated for each individual from a questionnaire filled by patients or family members. Daily dietary intake of phylloquinone was assessed by a 126-item semiquantitative food frequency questionnaire (FFQ) [25,26]. Patients who fell at least once in the 3 months before recruitment were defined as “fallers”. We assessed the degree sunlight deprivation according to the method of Komar et al. [27]; i.e. sunlight exposure was assessed by the family members and graded as almost none, less than 15 min per week, or 15 min or longer per week. The sunlight exposure...
during the preceding year was assessed by the family members when patients spent a time in homes, whereas it was assessed by staff of day care centers (DCC) during patients stay in DCC. This study was approved by the ethics committee of the Mitate Hospital. All patients and controls were informed of the nature of the study. Written informed 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 treatment group (n=116) received a daily dose of 45 mg menatetrenone/day in capsule (Glakay, Eizai Pharmaceuticals, Tokyo, Japan) 3 times a day after meals and risedronate (Actonel, Eizai Pharmaceuticals, Tokyo Japan) 17.5 mg once weekly in a tablet and 1200 mg of elemental calcium. The control group received a daily dose of risedronate 17.5 mg once weekly and 1200 mg of elemental calcium (n=115). 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.

Follow-up

Assessment of the patients' condition was performed by physicians (Y.S. and Y.H.) who did not participate in the initial randomization. Both groups were observed for 12 months. General medical evaluation and laboratory values were assessed on entry and after 12 months later. Metacarpal BMD measurement was assessed on entry and after 6 and 12 months. Computed x-ray densitometry (CXD, Teijin Diagnostics, Tokyo, Japan) [28] utilizing an improved microdensitometric method was used to quantify BMD in the left second metacarpal 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 [29]. In the morning, blood and urine samples were obtained from the 231 patients after an overnight fast at study entry and 12 months later. Blood samples were analyzed for ionized calcium, intact parathyroid hormone (PTH), 25-OHD and undercarboxylated osteocalcin (ucOC; a sensitive marker of vitamin K status [30,31]). The cut off value of ucOC in Japanese people is 4.5 ng/mL [32]. Ionized calcium concentration was determined in fresh serum processed under anaerobic conditions using an ion-selective electrode and an ionized calcium analyzer (Jokoh Co., Tokyo, Japan). Serum PTH concentration was measured by an immunoradiometric assay (Sumitomo Biomedical, Osaka, Japan). Ionized calcium was measured in freshly prepared serum collected under anaerobic conditions. An ion-selective electrode was used as part of an ionized calcium analysis system (NOVA Biochemical, Newton, MA, USA). Serum 25-OHD concentration was determined by a radioimmunoassay (DiaSorin, Stillwater, Mich, USA). An electro-chemiluminescence immunoassay was used to measure ucOC in serum samples (Sanko-Biochemicals, Tokyo, Japan). Urinary deoxypyridinoline (D-Pyr) was measured with a commercially available, specific enzyme immunoassay kit (Metra Biosystems Inc, Calif, USA). Urinary D-Pyr was expressed relative to urinary creatinine.
concentration. These analyses were carried out in the Central Hormone Reference Laboratory in Kita-kyusyu. The normal ranges of the BMD and biochemical indexes in elderly persons are given in Table 2 [11].

**Study end points and statistical analysis**

The primary end point was defined as the incidence of a hip fracture. An intention-to-treat analysis was performed on all randomized subjects to determine relative risk (RR), absolute risk reduction (ARR) and the number needed to treat (NNT). 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 ucOC, 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.

The sample size was based on an expected nonvertebral fracture incidence of 10% in the control group over 12 months. Assuming a 10% dropout rate over 12 months, the study had at least 80% power to detect a 70% reduction in fracture risk, with a 2-sided significance level of \( \alpha = .05 \).

**RESULTS**

**Baseline characteristics of study subjects (Table 1)**

Of 263 assessed subjects, 231 were randomized into the treatment groups (Fig. 1). Twenty-three patients in the treatment group and 27 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 180 patients (92 in the treatment group

![Flow of participants through the study](Fig. 1. Flow of participants through the study.)
and 89 in the control group) completed the trial. We included 231 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 age, sex, duration of illness, BMI, MMSE, numbers of fallers, BI, sunlight exposure and dietary intake of vitamin K1. BMI was low in both groups. Many of the patients in both groups had been exposed to sunlight for less than 15 min per week or had almost no sun exposure because of being home-bound. The average values of dietary intake of vitamin K1 in the 2 groups were lower compared with the previous reported data [11]. 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 ucOC or urinary D-Pyr were high compared with the reference range of the normal Japanese population [11]. Metacarpal BMD in the two patients groups was significantly lower compared with reference range of the normal Japanese population [11].

When both patient groups were analyzed together, the BMD correlated positively with BMI (r=0.392; P<.01), and 25-OHD (r=0.428; P<.01) concentrations, whereas BMD correlated negatively with ucOC (r=–0.701; P<.0001) and PTH (r=–0.303; P<.01).

### Table 1.
**Demographic and baseline clinical characteristics of the patients with Alzheimer’s disease at study entry**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n=115)</th>
<th>Treated group (n=116)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80.6±7.4</td>
<td>80.8±7.2</td>
<td>.91</td>
</tr>
<tr>
<td>Sex (Men/Women)</td>
<td>38/77</td>
<td>40/76</td>
<td>.82 §</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>5.2±2.3</td>
<td>5.1±2.1</td>
<td>.84</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>19.0±2.7</td>
<td>19.1±2.5</td>
<td>.92</td>
</tr>
<tr>
<td>Mini-Mental State Examination†</td>
<td>17±4</td>
<td>17±5</td>
<td>.95</td>
</tr>
<tr>
<td>Barthel index</td>
<td>83±5</td>
<td>85±4</td>
<td>.73</td>
</tr>
<tr>
<td>Dietary intake of vitamin K1 (μg/day)</td>
<td>98±18</td>
<td>95±19</td>
<td>.81</td>
</tr>
<tr>
<td>Sunlight exposure/week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 min</td>
<td>25 (22%)</td>
<td>28 (24%)</td>
<td></td>
</tr>
<tr>
<td>&lt;15 min</td>
<td>90 (78%)</td>
<td>88 (76%)</td>
<td>.66 §</td>
</tr>
<tr>
<td>Faller (%)</td>
<td>36 (31%)</td>
<td>38 (33%)</td>
<td>.87 §</td>
</tr>
</tbody>
</table>

Values are mean±SD. *unpaired t test; †The mean standard deviation of Mini-Mental Examination scores in cognitively normal subject (mean age 80.3 years, 70% women) has been reported as 28.5±1.4.; §chi-squared analysis between treated and control groups. Normal Japanese dietary intake of vitamin K1 is 247±102 (μg/day).11

### Table 2.
**Bone mineral density and various biochemical tests of control subjects and two groups of patients with Alzheimer’s disease at baseline**

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Treated group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized calcium (mEq/L)</td>
<td>2.42±0.11</td>
<td>2.42±0.12</td>
<td>.92</td>
</tr>
<tr>
<td>Intact PTH (pg/mL)</td>
<td>71±14</td>
<td>69±15</td>
<td>.98</td>
</tr>
<tr>
<td>25-OHD (ng/mL)</td>
<td>12.6±2.5</td>
<td>12.8±2.8</td>
<td>.90</td>
</tr>
<tr>
<td>Deoxypyridinoline (μmol/mol creatinine)</td>
<td>10.0±4.0</td>
<td>10.5±3.7</td>
<td>.87</td>
</tr>
<tr>
<td>ucOC (ng/mL)</td>
<td>8.7±2.9</td>
<td>8.9±2.4</td>
<td>.84</td>
</tr>
<tr>
<td>Bone mineral density (mm Al)</td>
<td>1.74±0.49</td>
<td>1.74±0.42</td>
<td>.94</td>
</tr>
</tbody>
</table>

Values are mean±SD. * unpaired t test; PTH, parathyroid hormone; 25-OHD, 25-hydroxyvitamin D; ucOC, undercarboxylated osteocalcin.

The reference range [11]: ionized calcium, 2.45 to 2.63 mEq/L (ion-selective electrode); intact PTH, 35-63 pg/mL (immunoradiometric assay); 25-OHD, 18.5 to 30.5 ng/mL (competitive protein-binding assay); Deoxypyridinoline, 4.0 to 8.2 μmol/mol creatinin (enzyme immunoassay); bone mineral density, 1.89 to 2.37 mm Al (computed X-ray densitometer).
There were negative correlations between serum 25-OHD and PTH (r = −0.213; P < .01), suggesting the presence of compensatory hyperparathyroidism.

**Fracture incidence**

**Hip fractures:** There were 2 hip fractures in the treatment group and 10 hip fractures in the control group; this difference was statistically significant (P < .001, log-rank test). The number of the hip fractures per 1000 patient-years was 17 and 86 for the treatment and control groups, respectively. The RR, ARR and the NNT in the treatment group as compared with the control group for hip fractures were 0.19 (95% CI, 0.04 to 0.85), 0.09 (95% CI, 0.02 to 0.17) and 11 (95% CI, 6 to 52), respectively.

**All fractures:** There were 5 fractures in the treatment group and 15 fractures in the control group; this difference was statistically significant (P < .001, log-rank test). The unadjusted RR, ARR and NNT in the treatment group as compared with the control group for all fractures were 0.31 (95% CI, 0.12 to 0.81), 0.12 (95% CI, 0.03 to 0.21) and 8 (95% CI, 5 to 36), respectively.

There was no significant difference between the two groups in the number of falls per subject during the 12 months (2.2 ± 1.8 in the control group and 2.3 ± 1.9 in the treated group).

**Bone changes and blood biochemical markers**

Figure 2 shows the percentage changes from the baseline in metacarpal BMD during the 12 months. The mean ± SD percentage changes in BMD were +5.7 ± 0.8 in the treatment group and +2.2 ± 0.5 in the control group. The difference between the 2 groups was statistically significant (P < .001). Changes in various parameters during the 1-year study period are summarized in Table 3. UcOC levels decreased significantly in the treatment group but not in the control group. Urinary levels of D-Pyr decreased while ion-

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**TABLE 3.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated group</th>
<th>Treated group</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized calcium (mEq/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated group</td>
<td>+5.8±0.9 (2.43±0.79)</td>
<td></td>
<td>.94</td>
</tr>
<tr>
<td>Treated group</td>
<td>+5.9±0.4 (2.43±0.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated group</td>
<td>−1.3±1.7 (70±11)</td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>Treated group</td>
<td>+3.2±2.3 (71±10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-OHD (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated group</td>
<td>−5.6±3.8 (11.9±2.9)</td>
<td></td>
<td>.68</td>
</tr>
<tr>
<td>Treated group</td>
<td>−7.1±4.2 (11.7±2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deoxypyridinoline (μmol/mol creatinine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated group</td>
<td>−57.0±13.8 (5.7±1.8)</td>
<td></td>
<td>.55</td>
</tr>
<tr>
<td>Treated group</td>
<td>−46.7±15.5 (5.6±1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ucOC (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated group</td>
<td>+2.3±1.4 (8.9±2.2)</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Treated group</td>
<td>−31.4±9.7 (2.8±1.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are the mean±SEM. *Wilcoxon rank sum test. Abbreviations are as in Table 2.
ized calcium, PTH, and 25-OHD levels remained unchanged in the 2 groups. Serum ionized calcium remained unchanged in the both groups. There was no significant difference between the 2 groups in the mean ± SD number of falls per subject during the 12 months (2.2±0.9 in the control group and 2.1±1.1 in the treatment 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 treatment group, 3 patients experienced gastrointestinal symptoms such as epigastric discomfort and nausea, 2 patients had esophagitis, and 2 patients experienced eruption of extremities, which eventually disappeared with appropriate therapy without discontinuation of the treatment. Three patients in the control group experienced headache, but this subsided within a week without discontinuing medication.

**DISCUSSION**

Prevention of fractures is one of the important issues in the management of elderly patients with AD. The high incidence of hip fractures in elderly patients with AD may be attributed to frequent falls [4] and osteoporosis due to low vitamin K1, and 25-OHD deficiency with compensatory hyperparathyroidism [11]. Indeed, serum levels of ucOC, 25-OHD and PTH and BMI were found to correlate with BMD in patients with AD.

Indeed, RRs for hip and nonvertebral fractures were low in the treatment group compared with the control group. This difference may be explained by a larger increase in BMD in the present study: the average values of BMD increased by 5.7% in the treatment group over 12 months. This may reflect a synergistic effect of menatetrenone and risedronate. The hip fracture rate in the control group was calculated as 87 per 1000 patient-years. The rate of hip fracture in an elderly reference population over ages 80 years was reported to be 22.9 per 1000 patient-years [33]. Although the mean age of our AD subjects (80.6 years) was within this range, the fracture rate in the present series was far higher than that reported in the reference population [33]. In addition to sunlight deprivation, 25-OHD deficiency and low vitamin K1 in these patients was considered to reflect generally poor nutrition, as also evidenced by lower BMIs. It has been reported that patients with dementia had malnutrition and decreased body weight [34]. Also, 25-OHD deficiency with compensatory hyperparathyroidism resulted in high urinary excretion of D-Pyr, which was corrected by risedronate in both groups. The decrease in bone turnover variables was more pronounced in the menatetrenone group. This may be caused by inhibition of bone resorption of menatetrenone [11].

In our previous study on stroke patients [35], with both vitamins D and K1 deficiency, treatment with menatetrenone for 1 year resulted in an increase in second metacarpal BMD by 4.3%, and the BMD in untreated controls decreased by 4.7%. Similar results were obtained by menatetrenone therapy in Parkinson’s disease patients [36], and the odds ratio of nonvertebral fractures in the untreated controls and the menatetrenone group was 11.5 [36].

We conclude that AD patients with low serum vitamins K and 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 menatetrenone and risedronate may be safe and effective in increasing bone mass and reducing the risk of fractures in elderly patients with AD.

**ACKNOWLEDGMENTS:** This study was supported by a grant of Eizai Pharmaceuticals, Tokyo.


