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Amelioration of Osteoporosis and Hypovitaminosis D by Sunlight Exposure in Hospitalized, Elderly Women With Alzheimer's Disease: A Randomized Controlled Trial

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ABSTRACT: In a random and prospective study, Alzheimer's disease (AD) patients were assigned to regular sunlight exposure ($n = 132$) or sunlight deprivation ($n = 132$) and followed for 1 year. Serum 25-OHD level increased by 2.2-fold in the sunlight-exposed group. Eleven patients sustained fractures in the sunlight-deprived group, and three fractures occurred among the sunlight-exposed group ($p = 0.0362$; odds ratio = 3.7).

Introduction: A high incidence of fractures, particularly of the hip, represents an important problem in patients with Alzheimer's disease (AD), who are prone to falls and have osteoporosis. We previously showed that 25-hydroxyvitamin D (25-OHD) deficiency caused by sunlight deprivation with compensatory hyperparathyroidism causes reduced BMD in elderly women with AD. This study was undertaken to address the possibility that sunlight exposure with calcium supplementation may maintain BMD and reduce the incidence of nonvertebral fractures in elderly women with AD.

Materials and Methods: In a random and prospective study, AD patients were assigned to regular sunlight exposure ($n = 132$) or sunlight deprivation ($n = 132$) and followed for 1 year. BMD of the second metacarpal bone was measured using a computed X-ray densitometer (CXD). The CXD method measures BMD and cortical thickness at the middle of the second metacarpal bone on a radiogram of the hand and an aluminum step wedge as a standard (20 steps; 1 mm/step). Incidence of nonvertebral fractures in the two patient groups during the 1-year follow-up period was assessed.

Results and Conclusion: At baseline, average hospitalization period was 1.7 years in both groups, and activity of daily living (ADL) was decreased. Patients of both groups showed vitamin D deficiency caused by sunlight deprivation and decreased dietary intake of vitamin D with compensatory hyperparathyroidism. The exposed group patients were exposed to sunlight (3615 minutes/year). BMD increased by 2.7% in the sunlight-exposed group and decreased by 5.6% in the sunlight-deprived group ($p < 0.0001$). Serum 25-OHD level increased from 24.0 to 52.2 nM in the sunlight-exposed group. Eleven patients sustained fractures in the sunlight-deprived group, and three fractures occurred among the sunlight-exposed group ($p = 0.0362$; odds ratio = 3.7). Sunlight exposure can increase the BMD of vitamin D-deficient bone by increasing 25-OHD concentration and lead to the prevention of nonvertebral fractures.

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Key words: Alzheimer's disease, hip fracture, osteoporosis, sunlight exposure, vitamin D

INTRODUCTION

ALZHEIMER'S DISEASE (AD) is a common neurodegenerative disorder characterized by progressive loss of memory and cognitive function. Also, far advanced AD is associated with generalized weakness. A high incidence of fractures, particularly of the hip,^(1–3) represents an important problem in AD patients, who are prone to falls⁽⁴⁾ and have osteoporosis.^(5,6) The odds ratio of 6.9 for fracture prevalence between elderly persons with and without AD is reported.⁽⁴⁾

In addition, functional recovery after hip fracture in AD is poor,^(7–9) and patients with dementia have increased mortality during the 6 months after hip fracture.⁽¹⁰⁾ The physical state of AD patients has increasingly become one of the critical issues in their clinical management. Our previous study⁽⁵⁾ showed that deficiency of 25-hydroxyvitamin D (25-OHD) caused by sunlight deprivation contributes to the reduced BMD in AD patients in nursing homes, in which duration of admission was 0.9 months. Also, we have shown that elderly female AD patients with low BMD and vitamin D deficiency with secondary hyperparathyroidism have a high risk of hip fracture.⁽⁶⁾ Kipen et al.⁽¹¹⁾ examined

The authors have no conflict of interest.

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demented women in the community and found that they have normal BMD, hypovitaminosis D, and compensatory hyperparathyroidism.

Serum 25-OHD is derived from both dietary intake and sunlight-induced production by the skin^(12,13) and is the most abundant circulating vitamin D metabolite.⁽¹⁴⁾ It is the most sensitive and useful index of the body's vitamin D supply.

We conducted a 12-month randomized trial to evaluate the efficacy of sunlight exposure in increasing serum 25-OHD, reducing the severity of the osteoporosis in the second metacarpals, and in decreasing the risk of nonvertebral fractures in chronically hospitalized elderly women with AD. Rate of vertebral fractures was not determined in this study, because many vertebral fractures are asymptomatic among elderly AD patients and because the interpretation of spinal X-ray films may be complicated by osteoarthritis or scoliosis.

MATERIALS AND METHODS

The institutional review board approved the study with some reservations, in which all the patients should receive calcium supplementation, and the patients of the deprived group are to wear an external hip protector during study period if baseline serum 25-OHD is <5 ng/ml. All patients and control subjects 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.

For this study, we selected 264 chronically hospitalized ambulatory women, 65 years of age or older, with AD, and who had been hospitalized at the Mitate Hospital in Tagawa City in Japan (32.0° N). The clinical condition in each patient met the criteria listed in the DSM-III R for dementing disease and probable AD.⁽¹⁵⁾ Exclusion criteria included total disability, <1 year of hospitalization, diseases or use of medications that might interfere with vitamin D metabolism, primary disease other than dementia, or time spent outside the hospital during the prior 6 months. Also, patients with AD were excluded if they showed other known causes of osteoporosis, such as primary hyperparathyroidism or renal osteodystrophy or impairment of hepatic, renal (serum creatinine > 1.5 mg/dl), cardiac, or thyroid function.

At baseline, we assessed duration of hospitalization and body mass index (BMI). The Mini-Mental State Examination (MMSE)⁽¹⁶⁾ was given to the patients, and functional dependence was assessed by the Barthel index (BI), in which a score of 100 represents independence and a score of 0 represents total dependence.⁽¹⁷⁾ The mean of MMSE scores in cognitively normal elderly subjects (mean age, 80.3 years; 70% women) has been reported as 28.5 ± 1.4 (SD).⁽¹⁸⁾ A physical therapist blinded to patients' information evaluated, using the British Medical Research Council (MRC) scale,⁽¹⁹⁾ the muscle strength of the lateral and medial rotators of the hip and flexion and extension of the thigh with the hip and knee flexed 90°. The British MRC scale defines a score of 0 as no contraction of the tested muscle, and a score of 5 represents normal power. The

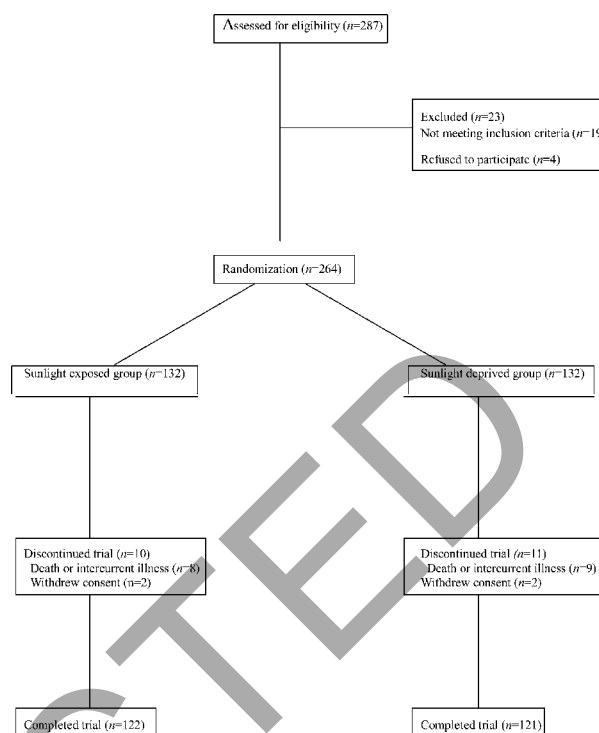


FIG. 1. Flow of participants through the study.

evaluation was performed on the right side. The total points for muscle strength of the four different movements of the hip joint were calculated in each patient. Mean weekly intake of dietary calcium and vitamin D during the previous 12 months was calculated for each individual from a questionnaire filled by patients or family members.

Sunlight exposure was assessed from patient charts in the hospital and was determined using nurses' notes in the charts that described the behavior of individuals during every 60-minute period of the day regarding time spent outdoors. Thus, sunlight exposure in the previous year was assessed at baseline and graded as almost none, <15 minutes per week, or longer.⁽²⁰⁾ Falls were defined as incidents where the subject fell because of an unexpected loss of balance; patients who fell at least once in the 3 months before recruitment were defined as "fallers." The number of fallers was also recorded during the 1-year follow-up period.

Age-matched healthy volunteers from the community, 132 postmenopausal women, served as the comparison group to discriminate BMD variations related to the treatment from those related to methods of measurement. The same exclusion criteria for the patients were used in excluding subjects from the comparison group. Spinal radiologic studies of these subjects did not detect any vertebral abnormalities.

A computer-assisted randomization was used to assign the participants to the sunlight-exposed group ($n = 132$) or the sunlight-deprived group ($n = 132$). Elemental calcium was given twice a day, at a dose of 1200 mg/day, to both groups. Figure 1 shows the flow of participants through the study. These determinations were performed by the chair-

man of the Human Clinical Study Committee of the Mitate Hospital who was completely blind to patients' information and follow-up. Ancillary care was provided by nurses who were also blinded to patients' information. Sunlight exposure outdoors for 15 minutes each day was given to the exposed group during clear weather. Nurses took the patients outside each day using a wheelchair if the patients could not walk without assistance, and the face, forearms, and hands (total exposed skin area was $426 \pm 32 \text{ cm}^2$) were exposed to sunlight for 15 minutes. Although the deprived group members were not prohibited from venturing outdoors, the interventional sunlight exposure was not performed. Sunlight exposure was assessed from the patients care documents. The document was completed by nurses who recorded the daily behavior of individuals during every 60-minute period. If the patients were taken outdoors by a nurse, time spent outdoors was obtained from notes in the medical records.

Follow-up assessment of patients' condition was performed by physicians who did not participate in the initial randomization. Both groups were observed for 12 months, and the incidence of nonvertebral fractures was assessed. In addition to general medical evaluation, laboratory values were assessed on entry into the study (in the morning) to obtain baseline values and again after 12 months. Metacarpal BMD measurements were assessed on entry into the study to obtain baseline values and again after 6 and 12 months. The patients' clinical status was assessed at baseline and every 2 weeks in the hospital, and the timing of nonvertebral fractures was carefully recorded. Members of the comparison group visited the clinic 6 and 12 months after enrollment, and 10 of them dropped out. The starting and final data of the subjects who completed the study were analyzed. Medical and bone evaluations performed before randomization were used for the determination of baseline values.

Using a computed X-ray densitometer (CXD; Teijin, Tokyo, Japan),⁽²¹⁾ the BMD of the second metacarpal bone of the left hand was measured on the day of study entry and 6 and 12 months later. The CXD method measures BMD and cortical thickness at the middle of the second metacarpal bone, using a radiogram of the hand and an aluminum step wedge as a standard (20 steps; 1 mm/step). The computer-calculated BMD was determined on the basis of the pattern expressed as gradations along the aluminum step wedge. BMD was expressed as the thickness of an aluminum equivalent (mm Al) showing corresponding X-ray absorption.

The CXD method for measuring BMD has been validated by comparing with DXA. Precision has been established with CVs ranging 0.2–1.2%.⁽²¹⁾ In our hospital, the intermediate-term precision errors were 0.3–0.9%, and the short-term precision errors were 0.5–1.3%. In osteoporotic patients, the reproducibility ranged from 1.4% to 2.6%.⁽²²⁾

On the day of bone evaluation, a fasting blood sample was obtained from all patients in both groups. Blood samples were analyzed for ionized calcium, 25-OHD, 1,25-dihydroxyvitamin D [$1,25\text{-(OH)}_2\text{D}$], intact PTH, and intact bone Gla protein (BGP). Ionized calcium was measured in freshly prepared serum collected under anaerobic condi-

tions. An ion-selective electrode was used as part of an ionized calcium analysis system (NOVA Biochemical, Newton, MA, USA). Serum 25-OHD was determined using a competitive protein-binding assay, and $1,25\text{-(OH)}_2\text{D}$ was determined by a radioreceptor assay using calf thymus receptor (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Intact PTH was measured by radioimmunoassay (Nichols Institute Diagnostics). Serum concentration of intact BGP was measured using an enzyme immunoassay kit (Teijin Diagnostics). Urinary deoxypyridinoline (D-Pyr) was measured using a commercially available, specific enzyme immunoassay kit (Metra Biosystems). Urinary D-Pyr was expressed relative to the urinary creatinine concentration ($\text{D-Pyr/creat.}/\mu\text{mol/mol creatinine}$).⁽²³⁾ The normal ranges of the BMD and biochemical indices in elderly women are described in Table 2.^(6,24) These analyses were carried out in the Special Reference Hormone Reference Laboratory in Tokyo. All data obtained were withheld from all authors until completion of the study period to avoid bias.

All statistical procedures were performed using Statview J 5.0 and SuperANOVA 1.11 software packages (Abacus Concepts, Berkeley, CA, USA). Values are given as the mean \pm SD unless otherwise indicated. The unpaired *t*-test was used to determine the significance of any difference between the two groups of patients with AD. Baseline differences of categorical data were tested by χ^2 analysis. Spearman's rank correlation coefficients (SRCCs) were calculated to examine possible correlations between BMD and various parameters such as PTH and 25-OHD, between PTH and ionized calcium or 25-OHD, and between BI and 25-OHD. The paired *t*-test was used to assess the difference of biochemical indices between baseline values and values after 12 months. The BMD measurements values were computed and expressed as a percentage change from the baseline. All three groups (the two AD groups and comparison group) were compared with respect to BMD by analysis of covariance (ANCOVA). The difference in the incidence of nonvertebral fracture between the two patient groups during the 12 months was tested by χ^2 analysis. *p* values <0.05 were considered significant.

RESULTS

Baseline characteristics of study subjects

Demographic and baseline clinical features of study patients are presented in Tables 1 and 2. There were no significant differences between the two patient groups in age, BMI, BI, MMSE, muscle strength, interval since menopause, fallers, illness duration, duration of hospitalization, sunlight exposure, dietary intake of calcium and vitamin D, BMD, and biochemical indices of bone metabolism. BMI was lower in both patient groups. Mean daily dietary intake of vitamin D and calcium in both groups were less than the Japanese recommended daily allowance (100 IU) of vitamin D and calcium (1000 mg). In addition, many patients in both groups had sunlight exposure <15 minutes per week or no exposure at all because of long-term hospitalization.

Compared with the reference range of the normal Japa-

TABLE 1. DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS OF THE AD PATIENTS AT STUDY ENTRY

Characteristic	Deprived (n = 132)	Exposed (n = 132)	p*
Age (years)	72.2 ± 5.8	72.4 ± 5.0	0.93
Body mass index (kg/m ²)	21.3 ± 1.9 [†]	21.3 ± 1.9 [†]	0.99
BI	81.7 ± 13.4	81.7 ± 16.6	0.97
MMSE	16.4 ± 3.4 [†]	16.6 ± 3.9 [†]	0.91
Interval since menopause (years)	15.0 ± 6.6	15.6 ± 6.3	0.90
Faller (%)	43 (33%)	41 (31%)	0.85 [†]
Duration of illness (years)	3.0 ± 0.7	3.0 ± 0.9	0.97
Duration of hospitalization (years)	1.7 ± 0.4	1.7 ± 0.4	0.97
Sunlight exposure/week			
>15 minutes	12 (9%)	10 (8%)	
<15 minutes	11 (8%)	12 (9%)	
None	109 (83%)	110 (83%)	0.89 [†]
Dietary intake of vitamin D (IU/day)	85 ± 22	86 ± 21	0.90
Dietary intake of calcium (mg)	722 ± 65	726 ± 63	0.93

Values are mean ± SD

* Unpaired *t*-test.[†] χ^2 analysis between unexposed and exposed groups.

TABLE 2. BMD AND VARIOUS BIOCHEMICAL TESTS OF CONTROL SUBJECTS AND TWO GROUPS OF AD PATIENTS AT BASELINE

	Deprived	Exposed	p*
BMD (mm Al)	2.06 ± 0.22	2.06 ± 0.23	0.95
Ionized calcium (mM)	1.15 ± 0.05	1.15 ± 0.04	0.86
Intact PTH (ng/liter)	55.8 ± 19.0	55.1 ± 18.9	0.89
25-OHD (nM)	24.0 ± 7.0	24.0 ± 5.7	0.98
1,25-(OH) ₂ D (pM)	169.3 ± 52.0	170.8 ± 50.0	0.99
BOP (μg/liter)	15.5 ± 2.8	15.8 ± 3.0	0.86
Deoxypyridinoline (μmol/mol creatinine)	10.7 ± 2.9	10.7 ± 2.7	0.98

Values are mean ± SD

* Unpaired *t*-test.

The reference range^(6,23): BMD, 2.32–2.88 mm Al; ionized calcium, 2.41–2.57 mM; intact PTH, 24.8–42.2 ng/liter; 25-OHD, 47–61 nM; 1,25-(OH)₂D, 104–162 pM; BGP, 6.9–12.9 μg/liter; deoxypyridinoline, 2.1–6.3 μmol/mol creatinine.

nese population,^(6,24) both groups of patients had high serum concentrations of PTH, 1,25-(OH)₂D, and BGP and low ionized calcium at baseline. Urinary D-Pyr concentration was high. The 25-OHD levels in both groups were in the deficient range. The average values of metacarpal BMD in the two patient groups were lower compared with the reference range of the normal Japanese population.⁽⁶⁾

When the sunlight-exposed and sunlight-deprived patients were analyzed together, the BMD correlated positively with 25-OHD ($r = 0.857$, $p < 0.0001$) concentrations and negatively with PTH concentrations ($r = -0.864$, $p < 0.0001$). The PTH correlated negatively with calcium ($r = -0.821$, $p < 0.0001$) and 25-OHD ($r = -0.905$, $p < 0.0001$) concentrations. The 25-OHD correlated negatively with

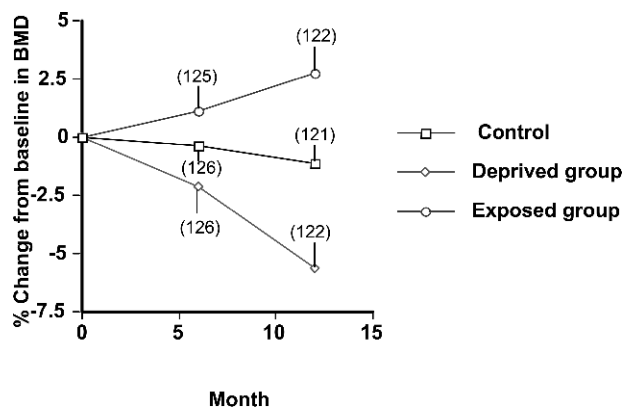


FIG. 2. Mean ± SE percent changes from baseline in metacarpal BMD after 1 year in the exposed, deprived, and control groups. The differences in the percent changes in BMD among the three groups were statistically significant (ANCOVA, $p < 0.0001$; exposed group vs. deprived group, $p < 0.0001$; exposed group vs. control group, $p < 0.0001$; deprived group vs. control group, $p < 0.0001$). Numbers in parentheses are the subjects followed.

1,25-(OH)₂D ($r = -0.846$, $p < 0.0001$). There was a positive correlation between BI and serum concentrations of 25-OHD ($r = 0.142$, $p = 0.0210$).

Frequency of sunlight exposure

During the 1 year, the exposed group received sunlight on 241 clear weather days (3615 minutes/year), whereas in the sunlight-deprived group, sunlight exposure was none in 85 patients (70%), <15 minutes/week in 32 patients (26%), and >15 minutes/week in 4 patients (4%).

Bone changes and serum biochemical markers

Figure 2 shows percent changes from the baseline in the metacarpal BMD during the 12 months. The changes in the BMD were $+2.7 \pm 0.3\%$ in the sunlight-exposed group, $-5.6 \pm 0.4\%$ in the sunlight-deprived group, and $-1.1 \pm 0.2\%$ in the control group. The differences among the three groups were statistically significant (ANCOVA, $p < 0.0001$; sunlight-exposed group vs. sunlight-deprived group, $p < 0.0001$; sunlight-exposed group vs. control group, $p < 0.0001$; sunlight-deprived group vs. control group, $p < 0.0001$).

The changes in blood levels of ionized calcium, PTH, 25-OHD, 1,25-(OH)₂D, and BGP and urinary D-Pyr are summarized in Table 3. Serum ionized calcium and 25-OHD increased, and PTH and 1,25-(OH)₂D decreased in the exposed group; the changes in these parameters in the deprived group were totally opposite. Notably, at the end-point of the study, serum 25-OHD levels in the deprived group were at an osteomalacic level (<5 ng/ml). Serum BGP and urinary D-Pyr levels decreased in the exposed group and increased in the deprived group.

Fallers, muscle strength, and fracture incidence

In the sunlight-exposed group, the number of fallers decreased from 41 at baseline to 21 after 12 months ($p < 0.0001$), whereas the number of fallers in the deprived group increased from 43 to 59 ($p < 0.0001$). Also, in the

TABLE 3. BIOCHEMICAL INDICES OF BONE AND CALCIUM METABOLISM BEFORE AND AFTER THE 12-MONTH PERIOD IN THE 243 SUBJECTS WHO COMPLETED THE STUDY

	Deprived group			Exposed group		
	Before (n = 132)	After (n = 121)	p*	Before (n = 132)	After (n = 122)	p*
Ionized calcium (mM)	1.15 ± 0.05	1.10 ± 0.051	<0.0001	1.15 ± 0.04	1.25 ± 0.05	<0.0001
Intact PTH (ng/liter)	55.8 ± 19.0	67.2 ± 13.8	<0.0001	55.1 ± 18.9	34.1 ± 11.0	<0.0001
25-OHD (nM)	24.0 ± 7.0	10.7 ± 5.2	<0.0001	24.0 ± 5.7	52.2 ± 9.7	<0.0001
1,25-(OH) ₂ D (pM)	169.3 ± 52.0	214.5 ± 42.1	<0.0001	170.8 ± 50.0	141.2 ± 40.6	<0.0001
BGP (ng/ml)	15.5 ± 2.8	18.1 ± 3.5	<0.0001	15.8 ± 3.0	10.5 ± 2.2	<0.0001
Deoxypyridinoline (μmol/mol creatinine)	10.7 ± 2.9	135 ± 3.4	<0.0001	10.7 ± 2.7	7.1 ± 2.2	<0.0001

Values are the mean ± SD

* Paired *t*-test.

sunlight-exposed group, the muscle strength increased from 7.0 ± 2.2 at baseline to 14.3 ± 3.8 after 12 months ($p < 0.0001$), whereas the muscle strength in the deprived group decreased from 7.0 ± 2.3 to 4.1 ± 1.1 ($p < 0.0001$).

During the 12 months of the study, nonvertebral fractures occurred in 11 of 121 patients in the deprived group (9 with hip fractures, 1 fracture each at the distal forearm and proximal femur), whereas fractures occurred in 3 of 122 patients in the exposed group (2 with hip fractures, 1 at the proximal femur). There was a difference in the fracture incidence between the two groups: 11/121 versus 3/122 ($p = 0.0362$). The odds ratio for nonvertebral fractures among patients in the deprived group compared with those in the exposed group was 3.7 (95% CI, 2.1–6.6). The number of nonvertebral fractures per 1000 patient-years was 25 and 91 for the sunlight-exposed and -deprived groups, respectively. There was a difference in the hip fracture incidence between the two groups: 9/121 versus 2/122 ($p = 0.0377$). All hip fractures were caused by falls. The odds ratio for hip fractures in the deprived group and exposed group was 4.5 (95% CI, 3.3–9.0). The number of hip fracture per 1000 patient-years was 16 and 74 for the exposed group and deprived group, respectively. The numbers of all nonvertebral fractures and hip fractures in the exposed group was lower than the deprived group by 73% and 78%, respectively.

DISCUSSION

In this study, we examined elderly female patients who were hospitalized chronically for the dementia of AD to assess the effect of regular sunlight exposure on serum 25-OHD concentration and BMD of this population.

At baseline, vitamin D deficiency with compensatory hyperparathyroidism and stimulation of skeletal turnover were important contributing factors to osteoporosis risk in elderly women with AD. In addition to frequent falls, these factors may be the cause of the high incidence of nonvertebral fractures in AD.

Among the elderly AD patients who completed the 12-month study, the numbers of all nonvertebral fractures and hip fractures in the exposed group was lower than the deprived group by 73% and 78%, respectively. This study was confined to elderly AD patients, which explains the higher

incidence of hip fractures compared with the previously reported data obtained in the general population.^(25,26) The hip fracture rate in the untreated group was calculated as 74 per 1000 patient-years. The rate of hip fracture in an elderly reference population between 70 and 79 years old is reported to be 6.6 per 1000 patient-years.⁽²⁶⁾ Although the mean age of our AD subjects (72 years) was within this range, with no subjects <65 or >84 years, the fracture rate in this series was far higher than that reported in the reference population.⁽²⁶⁾

The high incidence of hip and all nonvertebral fractures in elderly AD patients may be attributable to frequent falls and osteoporosis because of deficiency of vitamin D. The beneficial effect of sunlight exposure through increased serum 25-OHD concentrations in reducing the incidence of hip and nonvertebral fractures in this population is noteworthy. A recent study suggested that vitamin D supplementation reduces the risk of falls among ambulatory or institutionalized older individuals.⁽²⁷⁾ Indeed, the number of fallers decreased in the exposed group and increased in the deprived group during the study period. This implies that the frequency of fractures caused by falls in AD patients is related to hypovitaminosis D. Based on recent studies,^(28,29) serum 25-OHD <80 nM is considered as insufficient. Intestinal calcium absorption with 25-OHD at 50 nM was significantly reduced relative to that at a 25-OHD level of 86 nM.⁽²⁸⁾ In this study, serum 25-OHD in the exposed group increased but still remained in an insufficient range (52 nM), and this was probably because of lowered cutaneous production of vitamin D₃ associated with aging.⁽³⁰⁾ However, serum calcium and PTH normalized, and BMD increased. The increase in serum calcium was mainly caused by calcium supplementation, whereas compensatory hyperparathyroidism may have been corrected by the increase in 25-OHD.⁽³¹⁾ Also, it is documented that BMD correlates positively with 25-OHD levels, particularly in the subjects with insufficient levels of 25-OHD; this is consistent with this study, which showed effectiveness of even a mild increase in 25-OHD in improving BMD.⁽³²⁾

These data show in elderly women with AD that daily sunlight exposure is associated with a marked reduction in nonvertebral fractures and an increase in metacarpal BMD. The risk of fractures is very high in women with AD and severe vitamin D deficiency. We previously reported a simi-

lar effectiveness of sunlight exposure in chronically hospitalized stroke patients.⁽³³⁾ The most prominent difference in the results between the previous and present studies is that the stroke patients are immobilized, but this is rather uncommon in AD patients. The immobilization-induced hypercalcemia in stroke patients inhibits compensatory hyperparathyroidism, and its important consequence is the suppression of renal 1,25-(OH)₂D generation. The immobilization-induced hypercalcemia persisted after sunlight exposure in stroke patients.⁽³³⁾ AD patients, on the contrary, have hypocalcemia and compensatory hyperparathyroidism; sunlight exposure enhanced 25-OHD levels, which resulted in the correction of hyperparathyroidism and bone turnover. Arguably, this may suggest that sunlight exposure is more effective in improving BMD of AD patients compared with stroke patients.

The loss of BMD in the femoral neck, spine, and total body in untreated, community-dwelling elderly stroke patients of both sexes has been reported to be <1% over 3 years.⁽²⁴⁾ In this study, we found more pronounced bone loss in elderly women with AD. Over 1 year, the metacarpal BMD decreased by 5.6% in the deprived group and 1.1% in the comparison group, whereas the BMD increased by 2.7% in the exposed group. The sunlight exposure may reduce the risk of fractures, especially of the hip in elderly AD patients, probably by increasing BMD of the femoral neck. In previous studies on elderly women with AD, we found second metacarpal BMD by CXD to correlate with risk of hip fracture.⁽⁶⁾ Therefore, reduced second metacarpal BMD in AD patients seems to reflect a decrease throughout the appendicular skeleton.⁽³⁴⁾ Hip fractures are associated with more medical costs than all other osteoporosis-related fractures combined. Although various agents had been used to prevent hip fracture, regular sunlight exposure may be safe and beneficial without any medical cost.

We conclude that elderly women with AD having low serum 25-OHD with compensatory hyperparathyroidism and stimulation of skeletal turnover are at increased risk for nonvertebral fracture particularly in the hip. Regular sunlight exposure and calcium supplementation may be safe and effective in increasing BMD and reducing the risk of fracture in chronically hospitalized elderly women with AD.

REFERENCES

- Johansson C, Skoog I 1996 A population-based study on the association between dementia and hip fractures in 85-year olds. *Aging (Milano)* **8**:189–196.
- Melton LJ III, Beard CM, Kokmen E, Atkinson EJ, O'Fallon WM 1994 Fracture risk in patients with Alzheimer's disease. *J Am Geriatr Soc* **42**:614–619.
- van Staa TP, Leufkens HG, Cooper C 2000 Utility of medical and drug history in fracture risk prediction among men and women. *Bone* **31**:508–514.
- Buchner DM, Larson EB 1987 Falls and fractures in patients with Alzheimer-type dementia. *JAMA* **257**:1492–1495.
- Sato Y, Asoh T, Oizumi K 1998 High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. *Bone* **25**:555–557.
- Sato Y, Kanoko T, Satoh K, Iwamoto J 2004 Risk factors for hip fracture among elderly patients with Alzheimer's disease. *J Neurol Sci* **223**:107–112.
- Holmes J, House A 2000 Psychiatric illness predicts poor outcome after surgery for hip fracture: A prospective cohort study. *Psychol Med* **30**:921–929.
- Matsueda M, Ishii Y 2000 The relationship between dementia score and ambulatory level after hip fracture in the elderly. *Am J Orthop* **29**:691–693.
- Morrison RS, Siu AL 2000 Mortality from pneumonia and hip fractures in patients with advanced dementia. *JAMA* **284**:2447–2448.
- Nightingale S, Holmes J, Mason J, House A 2001 Psychiatric illness and mortality after hip fracture. *Lancet* **357**:1264–1265.
- Kipen E, Helme RD, Wark JD, Flicker L 1995 Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. *J Am Geriatr Soc* **43**:1088–1091.
- Beadle PC 1977 Sunlight, ozone and vitamin D. *Br J Dermatol* **97**:585–591.
- Lester E, Skinner RK, Foo AY, Lund B, Sorensen OH 1980 Serum 25-hydroxyvitamin D levels and vitamin D intake in healthy young adults in Britain and Denmark. *Scand J Clin Lab Invest* **49**:145–150.
- Bouillon R, Van Herck E, Jans I, Tan BK, Van Baelen H, De Moor P 1984 Two direct (nonchromatographic) assays for 25-hydroxyvitamin D. *Clin Chem* **30**:1731–1736.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM 1984 Clinical diagnosis of Alzheimer's disease: Report on the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* **34**:939–944.
- Folstein MF, Folstein SF, McHugh PR 1975 "Mini Mental State." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**:189–198.
- Mahoney FI, Barthel DW 1965 Functional evaluation: The Barthel index. *Md Med J* **14**:61–65.
- Smith GE, Bohac DL, Waring SC, Kokmen E, Tangalos EG, Ivnik RJ, Petersen RC 1998 Apolipoprotein E genotype influences cognitive 'phenotype' in patients with Alzheimer's disease but not in healthy control subjects. *Neurology* **50**:355–362.
- Medical Research Council of the United Kingdom 1978 Aids to the Examination of the Peripheral Nervous System, Pendragon House, London, UK.
- Komar L, Nieves J, Cosman F, Rubin A, Shen V, Lindsay R 1993 Calcium homeostasis of an elderly population upon admission to a nursing home. *J Am Geriatr Soc* **41**:1057–1064.
- Matsumoto C, Kushida K, Yamazaki K, Imose K, Inoue T 1994 Metacarpal bone mass in normal and osteoporotic Japanese women using computed X-ray densitometry. *Calcif Tissue Int* **55**:324–329.
- Sato Y, Asoh T, Oizumi K 1998 High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. *Bone* **23**:555–557.
- Robins SP, Black D, Petersen CR 1991 Evaluation of urinary hydroxypyridinium cross-link measurements as resorption markers in metabolic bone disease. *Eur J Clin Invest* **21**:310–315.
- Sato Y, Kanoko T, Yasuda H, Satoh K, Iwamoto J 2004 Beneficial effect of etidronate therapy in immobilized hip fracture patients. *Am J Phys Med Rehabil* **83**:298–303.
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE 1997 Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* **337**:670–676.
- Rannemark A, Nyberg L, Borssén B, Olsson T, Gustafson Y 1998 Fractures after stroke. *Osteoporos Int* **8**:92–95.
- Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB 2004 Effect of vitamin D on falls. A meta-analysis. *JAMA* **291**:1999–2006.
- Heaney RP, Dowell MS, Hale CA, Bendich A 2003 Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* **22**:142–146.
- Meier C, Woitge HW, Witte K, Lemmer B, Seibel MJ 2004 Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: A randomized controlled open-label prospective trial. *J Bone Miner Res* **19**:1221–1230.

30. MacLaughlin J, Holick MF 1985 Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* **76**:1536–1538.
31. Vieth R, Ladak Y, Walfish PG 2003 Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* **88**:185–191.
32. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B 2004 Positive association between 25-hydroxy vitamin D levels and bone mineral density: A population-based study of younger and older adults. *Am J Med* **116**:634–639.
33. Sato Y, Metoki N, Iwamoto J, Satoh K 2003 Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. *Neurology* **61**:338–342.
34. Derisquebourg T, Dubois P, Devogelaer JP, Meys E, Duquesnoy B, Nagant de Deuxchaisnes C, Delcambre B, Marchandise X 1994 Automated computerized radiogrammetry of the second metacarpal and its correlation with absorptiometry of the forearm and spine. *Calcif Tissue Int* **54**:461–465.

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