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Vitamin D Deficiency and Risk of Hip Fractures Among Disabled Elderly Stroke Patients

Yoshihiro Sato, MD; Takeshi Asoh, MD; Izumi Kondo, MD; Kei Satoh, MD

Background and Purpose—Risk of hip fracture after stroke is 2 to 4 times that in a reference population. Osteomalacia is present in some patients with hip fractures in the absence of stroke, while disabled elderly stroke patients occasionally have severe deficiency in serum concentrations of 25-hydroxyvitamin D (25-OHD) (≤5 ng/mL). To determine the effects of vitamin D status on hip fracture risk, we prospectively studied a cohort of patients with hemiplegia after stroke who were aged at least 65 years.

Methods—We compared baseline serum indices of bone metabolism, bone mineral density, and hip fracture occurrence in stroke patients with serum 25-OHD ≤25 nmol/L (≤10 ng/mL; deficient group, n=88) with findings in patients from the same cohort who had 25-OHD levels 26 to 50 nmol/L (10 to 20 ng/mL; insufficient group, n=76) or ≥51 nmol/L (≥21 ng/mL; sufficient group, n=72).

Results—Over a 2-year follow-up interval, hip fractures on the paretic side occurred in 7 patients in the deficient group and 1 patient in the insufficient group ($P<0.05$; hazard ratio=6.5), while no hip fractures occurred in the sufficient group. The 7 hip fracture patients in the deficient group had an osteomalacic 25-OHD level of <5 ng/mL. Higher age and severe immobilization were noted in the deficient group. Serum 25-OHD levels correlated positively with age, Barthel Index, and serum parathyroid hormone.

Conclusions—Elderly disabled stroke patients with serum 25-OHD concentrations ≤12 nmol/L (≤5 ng/mL) have an increased risk of hip fracture. Immobilization and advanced age cause severe 25-OHD deficiency and consequent reduction of BMD. (*Stroke*. 2001;32:1673-1677.)

Key Words: bone diseases ■ elderly ■ hemiplegia ■ osteoporosis

The number of disabled elderly stroke survivors has recently been increasing.[1] The poststroke physical state has become an increasingly important concern in stroke management. A recent report has documented that the risk of hip fracture after stroke is 2 to 4 times as high as that in a reference population.[2] These fractures usually occur relatively late after stroke onset and affect the paretic side.[1] Hip fractures are associated with more deaths, disability, and medical costs than all other osteoporosis-related fractures combined. Our previous investigations[3] have disclosed low serum 25-hydroxyvitamin D (25-OHD) concentration in 45 patients during long-term hospitalization after stroke (mean, 5.9 ng/mL). Among the patients, 21 (47%) had 25-OHD concentrations <5 ng/mL, which are considered osteomalacic levels. This 25-OHD deficiency resulted from malnutrition and sunlight deprivation.[3] Indeed, a hip fracture was the presenting event in 11 of 37 cases of osteomalacia in a report concerning elderly individuals without stroke.[4]

Osteomalacia is a generalized bone disorder characterized by impaired mineralization evident as accumulation of unmineralized matrix (osteoid) in the skeleton. The major cause of osteomalacia is vitamin D deficiency,[4–6] which most often is due to reduced cutaneous production of vitamin D in housebound or hospitalized patients with advanced age or neurological disorders.[7–12] Serum 25-OHD concentrations have been shown to range from 5 ng/mL to undetectable in osteomalacia related to vitamin D deficiency.[12] In patients with such osteomalacia, calcium absorption is low; this leads to mild hypocalcemia causing secondary hyperparathyroidism.[6,12]

To determine the effects of vitamin D status on the risk of hip fracture, we prospectively studied a cohort of patients with hemiplegia after stroke who were aged at least 65 years.

Subjects and Methods

All the cases in this study were first admitted as emergency patients with acute stroke to the Kurume University Medical Center or the Futase Social Insurance Hospital in Japan. They were consecutive cases followed, as outpatients, in these hospitals for management and training for functional disability from November 1996 to February 1997. All of them had poststroke hemiplegia involving both the

upper and lower extremities for >1 month. Patients younger than 65 years, those with diseases or medications that might interfere with vitamin D metabolism, those with a previous history of hip fracture or stroke, and those with a primary disease other than stroke were excluded from the study. Patients with stroke were excluded if they showed other known causes of osteoporosis such as hyperparathyroidism, hepatic dysfunction, or renal dysfunction (serum creatinine concentration, ≥1.5 mg/dL). Patients with cardiac failure also were excluded. Patients with a duration of illness <1 month or total disability (ie, a bedridden state) were excluded. The diagnosis of stroke was made on the basis of CT performed in both acute and chronic phases, as well as by clinical examination. Twelve patients showed no evidence of stroke on CT performed during both acute and chronic phases and were diagnosed as having brain infarction because they had rapidly developed hemiplegia lasting >1 month with no apparent cause other than a vascular origin. Strokes were classified according to the Classification of Cerebrovascular Diseases (version III) of the US National Institute of Neurological Disorders and Stroke.[13] On the basis of previously reported data,[14,15] serum 25-OHD concentration was defined as deficient when ≤25 nmol/L (≤10 ng/mL), insufficient when 26 to 50 nmol/L (10 to 20 ng/mL), and sufficient when ≥51 nmol/L (≥21 ng/mL). Patients with serum 25-OHD concentration ≤12 nmol/L (≤5 ng/mL) were considered to have severe vitamin D deficiency (osteomalacic levels). We compared subsequent hip fracture occurrence among stroke patients who had been classified into the 3 subgroups according to their serum 25-OHD levels. We also compared baseline data of indices of bone metabolism and bone mineral density (BMD) in the 3 groups.

The Barthel Index (BI)[16] was assessed in each patient. Clinical severity of hemiplegia was evaluated with the long-term score of the Scandinavian Stroke Scale.[17] Osteomalacic myopathy presents with weakness of the limbs, particularly the legs.[18] To determine the presence or absence of vitamin D–deficient (osteomalacic) myopathy, the strength of the gluteus maximus and iliopsoas muscles was evaluated on the nonhemiplegic side with the British Medical Research Council scale,[19] in which a score of 0 is defined as no contraction of the tested muscle, while a score of 5 represents normal power. The sum of the scores for the 2 muscles was calculated (maximum total points, 10). Patients completed a questionnaire concerning diet and sunlight exposure. The mean weekly dietary vitamin D intake was calculated for each individual, and patients who consumed less vitamin D than the Japanese recommended daily allowance (100 IU) were defined as low dietary consumers of the vitamin. Sunlight exposure in the preceding year was assessed by patients and graded as almost none, <15 minutes per week, or >15 minutes per week.[20]

Metacarpal BMD measurements and laboratory values were assessed on study entry to obtain baseline values. Computed x-ray densitometry (CXD) (Teijin Diagnostics)[21] employing an improved microdensitometric method was used to quantify BMD in both second metacarpals of each patient, as previously described.[22] 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 reference range for BMD for both sexes combined aged 65 to 75 years was 2.69 to 2.71 mm Al.

On the day of bone evaluation, fasting blood samples were obtained from the 236 patients as previously described.[23–25] Serum 25-OHD was determined with a competitive protein-binding assay, and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] was determined by a radioreceptor assay with the use of calf thymus receptor [Nichols Institute Diagnostics; reference ranges at 65 to 75 years, 46.2 to 61.6 nmol/L for 25-OHD and 105.0 to 152.9 pmol/L for 1,25-$(OH)_2$D]. When 25-OHD was undetectable, attempts were made to measure it in concentrated serum. Ionized calcium in serum prepared freshly under anaerobic conditions was measured with an ion-selective electrode and an ionized calcium analyzer (NOVA Biochemical; reference range in elderly individuals, 1.178 to 1.245 mmol/L). Serum intact parathyroid hormone (PTH) was measured with a 2-site immunoradiometric assay (Nichols Institute Diagnostics; reference

TABLE 1. Hip Fracture Rate in 3 Stroke Patient Groups Defined by Serum 25-OHD Concentration

Group	No. of Cases	No. of Fractures (%)	Fracture Rate/ 1000 Patient-Years
Deficient group (25-OHD ≤10 ng/mL)	82	7 (8.5)*	42.7
Insufficient group (25-OHD 10 to 20 ng/mL)	71	1 (1.4)	7.0
Sufficient group (25-OHD ≥21 ng/mL)	63	0 (0)	0

*$P<0.05$ vs insufficient 25-OHD group.

range for elderly individuals, 20 to 32 ng/L). Intact bone Gla protein (BGP), an osteoblastic bone formation marker,[26] was measured with an enzyme immunoassay with the use of antibodies to N- and C-terminal regions of human BGP (Teijin Diagnostics; reference range in the elderly, 2.5 to 11.5 μg/L). The pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP), an osteoclastic bone resorption marker,[27] was measured by radioimmunoassay (Orion Diagnostica; reference range for elderly subjects, 6.0 to 8.2 μg/L). These analyses were performed in the Creative Research Hormone Reference Laboratory at Kurume University. All data obtained were withheld from all authors until completion of the study period to avoid bias.

Informed consent was obtained from all study subjects in the presence of a witness. The protocol for the study was approved by the Human Investigation Committee at the Kurume University and Futase Social Insurance hospitals.

During the 2-year study period, patients were assessed clinically every 2 weeks. In addition to overall clinical status, the question of hip fracture occurrence was specifically addressed at each visit.

Data are presented as mean±SD. Differences in fracture rate among the 3 groups during the 2 years were tested by Fisher's exact test. Baseline differences for categorical data were tested by χ^2 analysis. One-way ANOVA and Fisher's protected least significant difference were used to assess differences among the 3 stroke groups. Differences of BMD in the hemiplegic and contralateral sides were calculated by paired t test. Spearman's rank correlation coefficients were calculated to determine the relationship between 25-OHD and each variable. Probability values <0.05 were considered statistically significant.

Results

Fracture Incidence

Of the 236 patients initially enrolled, 6 patients in the deficient group, 5 in the insufficient group, and 9 in the sufficient group left the study because of loss to follow-up (5 in the sufficient group and 3 each in the insufficient and deficient groups) or intercurrent illness (4 in the sufficient group, 2 in the insufficient group, and 3 in the deficient group) (Table 1).

The results for the 216 patients who completed the study are shown in Table 1. During the 2 years of study, a fall resulting in hip fracture on the hemiplegic side occurred in 7 patients (5 women and 2 men) in the deficient group, while 1 male patient in the insufficient group sustained hip fracture on the hemiplegic side ($P<0.05$). In contrast, no hip fractures occurred in the sufficient group. The hazard ratio for hip fractures among patients in the deficient group compared with those in the insufficient group was 6.5 (95% CI, 2.5 to 14.8). Numbers of hip fractures per 1000 patient-years were

TABLE 2.   Clinical Profiles of Stroke Patients

| | 25-OHD Concentration | | | |
Variables	Sufficient Group (≥21 ng/mL) (≥51 nmol/L) (n=72)	Insufficient Group (10 to 20 ng/mL) (26 to 50 nmol/L) (n=76)	Deficient Group (≤10 ng/mL) (≤25 nmol/L) (n=88)	P*
Age, y	68±3	71±4§	74±9‖¶	<0.0001
Sex, M/F	30/42	34/42	39/49	NS
Duration of illness, mo	9.3±8.3	11.7±9.7	9.9±7.3	0.26
BI	94±15	78±32§	55±33‖#	<0.0001
Degree of hemiplegia†				
Hand	5.5	5.0‖	3.5‖#	<0.0001
	(5.0 to 6.0)	(2.8 to 5.0)	(2.0 to 5.0)	
Leg	6.0	5.0‖	4.0‖#	<0.0001
	(5.0 to 6.0)	(3.0 to 6.0)	(3.0 to 6.0)	
Muscle strength on intact side‡	9.9	9.8	8.5‖#	<0.0001
	(9.0 to 10.0)	(9.0 to 10.0)	(8.0 to 9.0)	
Brain infarction/brain hemorrhage	43/29	45/31	52/36	NS

Values are mean±SD or median with interquartile ranges in parentheses.
*Difference among the 3 groups (ANOVA).
†Degree of hemiplegia was evaluated by the Scandinavian Stroke Scale.[17]
‡Strength of the gluteal maximus and iliopsoas muscles of the intact side was evaluated by the British Medical Research Council Scale.[19]
§$P<0.01$ vs sufficient 25-OHD group.
‖$P<0.0001$ vs sufficient 25-OHD group.
¶$P<0.01$ vs deficient 25-OHD group.
#$P<0.0001$ vs insufficient 25-OHD group.

42.7 and 7.0 for the deficient and insufficient groups, respectively.

Baseline Characteristics of Study Subjects
Characteristics of the patients are shown in Table 2. No differences were observed among the 3 patient groups in terms of sex, illness duration, or type of stroke. The average age was significantly higher in the deficient group than in the insufficient group. BI and hemiplegia score were significantly lower in the deficient group than in the insufficient and sufficient groups. Additionally, hip muscle strength on the nonhemiplegic side was significantly lower in the deficient group than in the insufficient and sufficient groups. Dietary intakes of vitamin D and sunlight exposure were significantly lower in the deficient group than in the insufficient and sufficient groups (data not shown).

Baseline Serum Biochemical Indices and Bone Changes
Mean serum 25-OHD levels were 10 nmol/L (4.4 ng/mL) in the deficient group, 36 nmol/L (14.5 ng/mL) in the insufficient group, and 59 nmol/L (23.6 ng/mL) in the sufficient group. The mean serum calcium concentration was significantly higher in the deficient and insufficient groups than in the sufficient group (Table 3). The serum PTH concentration in the deficient group was significantly higher than in the insufficient and sufficient groups. No significant differences in serum concentration of BGP were evident among the 3 groups. Mean serum concentrations of ICTP and creatinine in

the deficient group were significantly higher than in the sufficient group.

BMD on both sides was significantly lower in the deficient group than in the insufficient and sufficient groups. In addition, there was a significant difference between the insufficient and sufficient groups. As previously reported,[3] BMD on the hemiplegic side was significantly lower than on the contralateral, nonhemiplegic side in all 3 groups.

Relationships Between 25-OHD and Clinical Variables
Serum 25-OHD concentration correlated positively with BI ($r=0.535$, $P<0.0001$), muscle strength on the intact side ($r=0.517$, $P<0.0001$), and BMD on hemiplegic ($r=0.582$, $P<0.0001$) and contralateral sides ($r=0.499$, $P<0.0001$); serum 25-OHD concentration correlated negatively with age ($r=-0.282$, $P<0.0001$).

When analyzed separately for the 2 stroke groups, serum PTH concentrations correlated negatively with serum concentrations of 25-OHD ($r=-0.409$, $P=0.0002$) and ionized calcium ($r=-0.374$, $P=0.0007$) and positively with ICTP ($r=0.276$, $P=0.0125$) in the deficient group, while these correlations were not observed in the insufficient group (data not shown). A negative correlation was seen between serum calcium concentration and illness duration only in the deficient group ($r=-0.444$, $P<0.0001$).

Discussion
Metacarpal CXD measurement has been validated and found to be generalizable by comparison with the better-known but

TABLE 3.   Serum Biochemical Parameters and BMD

	25-OHD Concentration			
Variables	Sufficient Group ($\geq$21 ng/mL) ($\geq$51 nmol/L) (n=72)	Insufficient Group (10 to 20 ng/mL) (26 to 50 nmol/L) (n=76)	Deficient Group ($\leq$10 ng/mL) ($\leq$25 nmol/L) (n=88)	P*
1,25-[OH]$_2$D, pmol/L (105.0–152.9)	133$\pm$24	64$\pm$31†	62$\pm$34†	<0.0001
Ionized Ca, mmol/L (1.178–1.245)	1.18$\pm$0.06	1.27$\pm$0.07†	1.26$\pm$0.08†	<0.0001
Intact PTH, ng/L (20–32)	25$\pm$10	20$\pm$9	43$\pm$29†‡	<0.0001
Intact BGP, μg/L (2.5–11.5)	7.0$\pm$4.5	5.4$\pm$5.6	5.7$\pm$5.6	0.15
ICTP, μg/L (6.0–8.2)	7.1$\pm$1.1	7.4$\pm$7.3	9.4$\pm$4.1§‖	0.0003
Creatinine, μmol/L (50.5–84.5)	78$\pm$12	77$\pm$4	98$\pm$18†‡	<0.0001
BMD, mm Al (2.69–2.71)				
Hemiplegic side	2.53$\pm$0.37	2.21$\pm$0.50‖	1.76$\pm$0.53†‡	<0.0001
Intact side	2.59$\pm$0.36¶	2.45$\pm$0.44¶	2.01$\pm$0.54†‡¶	<0.0001

Values are mean$\pm$SD. Values in parentheses are reference range in elderly subjects.
*Difference among the 3 groups (ANOVA).
†P<0.0001 vs sufficient 25-OHD group.
‡P<0.0001 vs insufficient 25-OHD group.
§P<0.001 vs sufficient 25-OHD group.
‖P<0.001 vs sufficient 25-OHD group.
¶P<0.0001 vs hemiplegic side.

less-available method of dual energy x-ray absorptiometry.[28] Precision errors in measuring BMD by CXD (coefficients of variation) have been determined to be 0.2% to 1.2%.[21] We previously found in stroke patients that the second metacarpal BMD of the hemiplegic side determined by the CXD method correlated with the risk of hip fracture on that side.[29] Therefore, reduction in second metacarpal BMD in stroke patients appears to reflect a decreased BMD throughout the appendicular skeleton.[30]

In the present study we found that disabled elderly stroke patients with serum 25-OHD concentration $\leq$10 ng/mL had an increased risk of hip fracture. The number of hip fractures was 7.1 times higher in the deficient group than the insufficient group. Hip fracture incidence in the deficient group was 8.5%, and the fracture rate was 42.7 per 1000 patient-years. In contrast, the fracture incidence during 2 years in the insufficient group was 1.4%, with a fracture rate of 7.0 per 1000 patient-years. Ramnemark et al[2] reported that the fracture rate on either side per 1000 patient-years was 19.8 for stroke patients aged 70 to 79 years and 47.3 for patients older than 80 years. Although the mean age of the deficient group in the present study was 74 years, the fracture rate was similar to that in subjects older than 80 years in the aforementioned study.[2] In a group aged 69 years or younger, the fracture rate was reported to be 5.7,[2] which is similar to the fracture rate in our insufficient group with mean age of 68 years. The high incidence of hip fracture in the deficient group may be attributable to osteopenia due to severe 25-OHD deficiency caused by immobilization and compensatory hyperparathyroidism. Additionally, vitamin D–deficient (osteomalacic) myopathy may have contributed to a high incidence of hip fractures in the severe vitamin D deficiency group by causing gait instability leading to frequent falls.

In the present study we found that immobilization was more severe in the deficient group. Dietary intake of vitamin D was significantly lower in the deficient group than in the insufficient and sufficient groups. The deficient group also had lower sunlight exposure, which may be due to a high degree of immobilization. These factors may have resulted in severely deficient 25-OHD concentrations.

At baseline, serum 25-OHD concentration was at an osteomalacic level ($\leq$5 ng/mL) in many patients in the deficient group. However, histological proof of osteomalacia was not sought in these patients.[31] There were significant differences among the 3 groups in metacarpal BMD: the lowest in the deficient group and the highest in the sufficient group. Age, BI, muscle strength on the nonhemiplegic side, and BMD on both sides correlated with 25-OHD.

In isolated vitamin D deficiency, serum ionized calcium concentration is chronically low, and this leads to the feedback stimulation of the parathyroid glands to cause secondary hyperparathyroidism. However, serum ionized calcium levels in the insufficient group were increased, which may imply the presence of immobilization-related hypercalcemia. Despite hypovitaminosis D, serum PTH was also normal in this group. Thus, hypercalcemia in the insufficient group may inhibit compensatory PTH secretion that otherwise would occur in response to hypovitaminosis D. These findings were virtually similar to our previous studies on the vitamin D state and calcium metabolism in disabled stroke patients.[23,24,32] On the other hand, we found increased serum calcium and PTH levels in the deficient group of the present study. This may imply that compensatory hyperparathyroidism does occur in this group and explains the negative correlation between 25-OHD and PTH found only in the deficient group. The parathyroid response to hypovitaminosis D overrides the effect of immobilization-induced hypercalcemia when serum

25-OHD levels are in the osteomalacic range. Hyperparathyroidism may result in increased bone resorption, as evidenced by a positive correlation between PTH and ICTP.

It is noteworthy that many stroke patients with 25-OHD deficiency suffered a hip fracture. A previous study found that daily nutritional supplementation with vitamin D_3 (cholecalciferol, 800 IU) and calcium (1200 mg) reduced hip fracture by 43% in postmenopausal women compared with placebo controls.[33] Investigation is required to determine whether the incidence of hip fracture can be reduced by use of vitamin D (cholecalciferol) and calcium supplementation in poststroke patients with 25-OHD deficiency.

We conclude that disabled stroke patients 65 years and older whose serum 25-OHD concentrations are <10 ng/mL are at increased risk for hip fracture. Immobilization and advanced age may cause 25-OHD deficiency with compensatory hyperparathyroidism, leading to reduced BMD, which in turn is responsible for the increased risk of fracture.

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