Original article

Serum 25-hydroxyvitamin D concentrations in Japanese postmenopausal women with osteoporotic fractures

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ABSTRACT

Objectives: To assess the vitamin D status in postmenopausal women with osteoporotic fractures, determine its concentration by fracture site at the clinical setting, and compare the proportion of vitamin D deficiency with that reported in literature.

Methods: The prospective study included 317 postmenopausal women with osteoporotic fractures who were treated consecutively from 2016 to 2018. After obtaining informed consent for participation in the seamless treatment of osteoporosis against fractures study, which is our initiative to prevent secondary osteoporotic fractures, we registered the patients, examined bone mineral density (BMD) at the unfractured femoral neck and lumbar spine, serum 25-hydroxyvitamin D (25(OH)D) concentration, blood chemistry, and bone turnover markers.

Results: The mean age of the patients was 80.7 years. Moreover, 78% of patients of all fractures had 25(OH)D concentration < 20 ng/mL, whereas 12% of patients had 25(OH)D concentration ≥ 30 ng/mL 25(OH)D concentration in hip fractures was significantly lower than that in vertebral or distal radius fractures (P < 0.05). Multiple regression analysis revealed that 25(OH)D concentration is significantly associated with femoral neck BMD (β = 0.16; 95% confidence interval [CI], 0.78–12.17, P = 0.03) and serum albumin concentration (β = 0.21; 95% CI, 0.62–2.96, P < 0.001) in patients with 25(OH)D concentration < 30 ng/mL.

Conclusions: The results of this study show that the proportion of postmenopausal women with osteoporotic fractures who had vitamin D deficiency was higher than the proportion in previous reports that examined general postmenopausal women (35.2%–52.0%).

1. Introduction

Vitamin D is a fat-soluble vitamin that is taken orally as a dietary supplement or produced in the skin when the skin is exposed to direct ultraviolet radiation from sunlight. Vitamin D is first hydroxylated in the liver, forming 25-hydroxyvitamin D (25(OH)D; calcidiol), and the 1α-position is subsequently hydroxylated in the kidney to form active 1,25-dihydroxyvitamin D (1,25(OH)$_2$D; calcitriol). The serum 25(OH)D level is the most commonly used indicator of vitamin D supply by oral intake and ultraviolet-induced skin synthesis. Therefore, in the guidelines of many countries, the definitions of vitamin D deficiency and insufficiency are based on serum 25(OH)D concentrations [1–5]. Based on these foreign guidelines and domestic data, vitamin D sufficiency criteria using

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serum 25(OH)D concentrations have been established in Japan [5]. Serum 25(OH)D concentration of ≥ 30 ng/mL is a sufficient level of vitamin D; serum 25(OH)D concentration of < 30 ng/mL, but ≥ 20 ng/mL, is regarded as vitamin D insufficiency; and serum 25(OH)D concentration < 20 ng/mL is defined as vitamin D deficiency.

According to the longitudinal Aging Study Amsterdam, which involved 643 men and 676 women aged 65–88 years, 48.4% of the participants had serum vitamin D deficiency [6]. The cross-sectional, community-based epidemiological study in Japan revealed that, among 600 ambulatory postmenopausal women, 35.2% showed vitamin D deficiency and the mean serum 25(OH)D concentration was 22.2 ng/mL [7]. The longitudinal study in Japan revealed that, in 1470 postmenopausal women, 49.6% showed vitamin D deficiency [8]. The more recent Japanese epidemiological investigation demonstrated that, among 1211 community-dwelling women aged ≥ 50 years without early menopause or diseases affecting bone metabolism, 52.0% showed vitamin D deficiency [9]. In a Hong Kong osteoporosis study of 5276 participants (70% female) aged 20 years or above, 43.8% of participants showed vitamin D deficiency [10]. All 5 previous studies and the present one utilized the same definition of vitamin D deficiency.

It is reported that individuals with 25(OH)D concentration < 20 ng/mL showed higher prevalence of accumulated fractures in 15 years compared to those with 25(OH)D concentration ≥ 20 ng/mL and that individuals with 25(OH)D concentration < 10 ng/mL had 6.55 times higher fracture risk in 5 years than those with 25(OH)D concentration ≥ 30 ng/mL [7]. The measurement of serum 25(OH)D concentration is important for the evaluation of nutritional status and prediction of fracture risk.

There is a need for evidence regarding 25(OH)D concentrations in postmenopausal women with osteoporotic fractures to prevent subsequent osteoporotic fractures. We hypothesized that the proportion of vitamin D deficiency in postmenopausal women with osteoporotic fractures was greater than that previously reported in postmenopausal women. We consecutively registered patients with osteoporotic fractures and measured serum 25(OH)D concentration. We also investigated the association of 25(OH)D concentration with age, calcium, bone turnover markers, and bone mineral density (BMD) in the clinical setting.

2. Methods

2.1. Subjects and study design

This study was approved by the ethical review board of the University of Occupational and Environmental Health, Fukuoka, Japan (H27-190), and followed the Declaration of Helsinki. All patients agreed to participate in the study and provided written informed consent.

We have made efforts, such as the seamless treatment of osteoporosis against fractures (STOP-Fx) study, to prevent secondary osteoporotic fractures since October 2016. All patients were postmenopausal Japanese women with new osteoporotic fractures, including vertebral, hip, distal radius, and proximal humerus fractures, who were treated at our 6 nearby hospitals consecutively from October 2016 to February 2018. After obtaining informed consent from all participants in the STOP-Fx study, we registered the patients, interviewed them and their family regarding their history of fracture and residence (home, hospital, facility), and examined BMD in the unfractured femoral neck and lumbar spine, serum 25(OH)D concentration, blood chemistry, and bone turnover markers. Patients administered with agents such as supplemental vitamin D that could affect 25(OH)D concentration were excluded.

This prospective study included 317 postmenopausal women with osteoporotic fractures, including 132 new vertebral fractures, 121 hip fractures, 46 distal radius fractures, and 18 proximal humeral fractures. All fractures were caused by low impact falls, such as falls at standing height. The characteristics of all subjects are presented in Table 1. The mean age was 80.7 years (range, 45–101 years) for all patients, 80.1 years (range, 45–101 years) for those with vertebral fractures, 83.9 years (range, 49–100 years) for those with hip fractures, 76.1 years (range, 53–97 years) for those with distal radius fractures, and 75.6 years (range, 62–91 years) for those with proximal humerus fractures.

2.2. Serum 25(OH)D

Venous blood was obtained from all participants. Serum content was extracted using a routine centrifuge method and kept frozen at −70 °C. All serum samples were measured for 25(OH)D concentration, using the chemiluminescence immunoassay kit by LIAISON analyzer (25 OH vitamin D total assay, DiaSorin Liaison, Hitachi Chemical Diagnostics Systems Co., Ltd., Tokyo, Japan).

2.3. Serological indices

Serum albumin, calcium, phosphorus, tartrate-resistant acid phosphatase-5b (TRACP-5b), and undercarboxylated osteocalcin (ucOC) concentrations were measured.

The concentration of TRACP-5b, a bone resorption marker, was measured by a fragment-resorbing immunocapture enzyme assay, Osteolinks TRACP-5b kit (DS Pharma Biomedical Co., Ltd., Osaka, Japan); this assay can specifically measure TRACP-5b without causing a cross-reaction with TRACP-5a derived from macrophages. Serum ucOC was assayed using the Picolumi ucOC kit (Eisai Co., Ltd., Tokyo, Japan).

Table 1
Patient characteristics.

Characteristic	All	Vertebral fracture	Hip fracture	Distal radius fracture	Proximal humeral fracture	P-value
Number of patients	317	132	121	46	18	
Age, yr	80.7 ± 0.54	80.1 ± 0.84	83.9 ± 0.77	76.1 ± 1.50	75.6 ± 2.07	<0.001
Albumin, g/dL	3.94 ± 0.26	3.36 ± 0.06	3.36 ± 0.06	4.04 ± 0.06	3.61 ± 0.08	0.34
Albumin-corrected calcium, mg/dL	9.19 ± 0.03	9.22 ± 0.04	9.21 ± 0.07	9.19 ± 0.09	9.17 ± 0.14	0.63
Phosphate, mg/dL	3.37 ± 0.04	3.43 ± 0.04	3.32 ± 0.07	3.32 ± 0.08	3.25 ± 0.17	0.48
25-hydroxyvitamin D, ng/mL	17.3 ± 0.82	16.4 ± 1.07	17.1 ± 1.45	19.5 ± 2.34	20.3 ± 3.90	0.51
Tartrate-resistant acid phosphatase 5b, mU/dL	391 ± 12.2	345 ± 15.0	449 ± 23.4	398 ± 29.9	310 ± 34.1	<0.001
Undercarboxylated osteocalcin, ng/mL	8.41 ± 1.84	9.25 ± 4.00	9.05 ± 1.98	5.49 ± 0.71	4.14 ± 1.02	0.87
Lumbar spine BMD, g/cm^2	0.74 ± 0.01	0.71 ± 0.01	0.74 ± 0.02	0.78 ± 0.02	0.78 ± 0.03	0.07
Femoral neck BMD, g/cm^2	0.49 ± 0.01	0.49 ± 0.01	0.46 ± 0.01	0.57 ± 0.02	0.54 ± 0.03	<0.001

Values are presented as mean ± standard error.
BMD, bone mineral density.

2.4. Bone mineral density

BMD of the lumbar spine (L1–4) and femoral neck were measured using Hologic Horizon (Hologic, Inc., Marlborough, MA, USA) with dual-energy X-ray absorption after registering of the STOP-Fx study. BMD of the femoral neck was measured at the unfractured side.

2.5. Statistical analysis

Results are expressed as means ± standard error. The differences in patient characteristics among the 4 fracture groups were evaluated using 1-way analysis of variance (ANOVA). The differences in 25(OH)D concentrations among the 4 groups were evaluated using 1-way ANOVA with a Tukey *post hoc* analysis and analysis of covariance (ANCOVA) with 25(OH)D as the dependent variable and age, albumin-corrected calcium, lumbar spine BMD, and femoral neck BMD as covariates in patients with 25(OH)D concentrations < 30 ng/mL (vitamin D insufficiency). Pearson correlation and multiple stepwise linear regression analyses were used to determine correlates of 25(OH)D concentration. The independent variables were age, BMD (lumbar spine and femoral neck, unfractured side), blood chemistry (albumin, albumin-corrected calcium, phosphate), and bone turnover markers (TRACP-5b, ucOC) for Pearson's correlation analysis and age, BMD (lumbar spine and femoral neck, unfractured side), blood chemistry (albumin, albumin-corrected calcium, phosphate), bone turnover markers (TRACP-5b, ucOC), existing fragility fracture, fracture site (vertebral fracture, hip fracture, distal radius fracture, proximal humerus fracture), and residence (home, hospital, facility) for the multiple stepwise linear regression analysis. A P-value < 0.05 was considered significant. The analysis was performed using Excel version 2016 (Microsoft, Redmond, WA, USA) and IBM SPSS Statistics ver. 21.0 (IBM Japan, Tokyo, Japan).

3. Results

3.1. General patient characteristics

There were significant differences in age, TRACP-5b concentration, and femoral neck BMD among the 4 groups of fracture sites (P < 0.001) (Table 1). Patients with hip fractures had the greatest age, highest TRACP-5b concentration, and lowest femoral neck BMD among the 4 groups of fracture sites.

3.2. 25(OH)D concentration

In this study, 78% of patients with 4 osteoporotic fractures including vertebral fractures, hip fractures, distal radial fractures, and proximal humeral fractures, 80% with vertebral fractures, 79% with hip fractures, 76% with distal radius fractures, and 72% with proximal humerus fractures had 25(OH)D concentration < 20 ng/mL (vitamin D deficiency), while 12% of patients with all fractures, 9% with vertebral fractures, 14% with hip fractures, 13% with distal radius fractures, and 22% with proximal humerus fractures had 25(OH)D concentration ≥ 30 ng/mL (vitamin D sufficiency) (Fig. 1). For patients with 25(OH)D concentrations < 30 ng/mL (vitamin D insufficiency), 1-way ANOVA with a Tukey *post hoc* analysis revealed that 25(OH)D concentrations in hip fractures were significantly lower than those in vertebral and distal radial fractures (P < 0.05) (Fig. 2). ANCOVA revealed that 25(OH)D concentrations in hip fractures were significantly lower than those in vertebral fractures (P < 0.05).

3.3. Significant factors associated with 25(OH)D concentration

Simple linear regression and multiple linear stepwise regression analyses revealed that lower 25(OH)D concentration was significantly associated with higher serum albumin-corrected calcium concentration (P = 0.02 and P = 0.04, respectively) (Table 2).
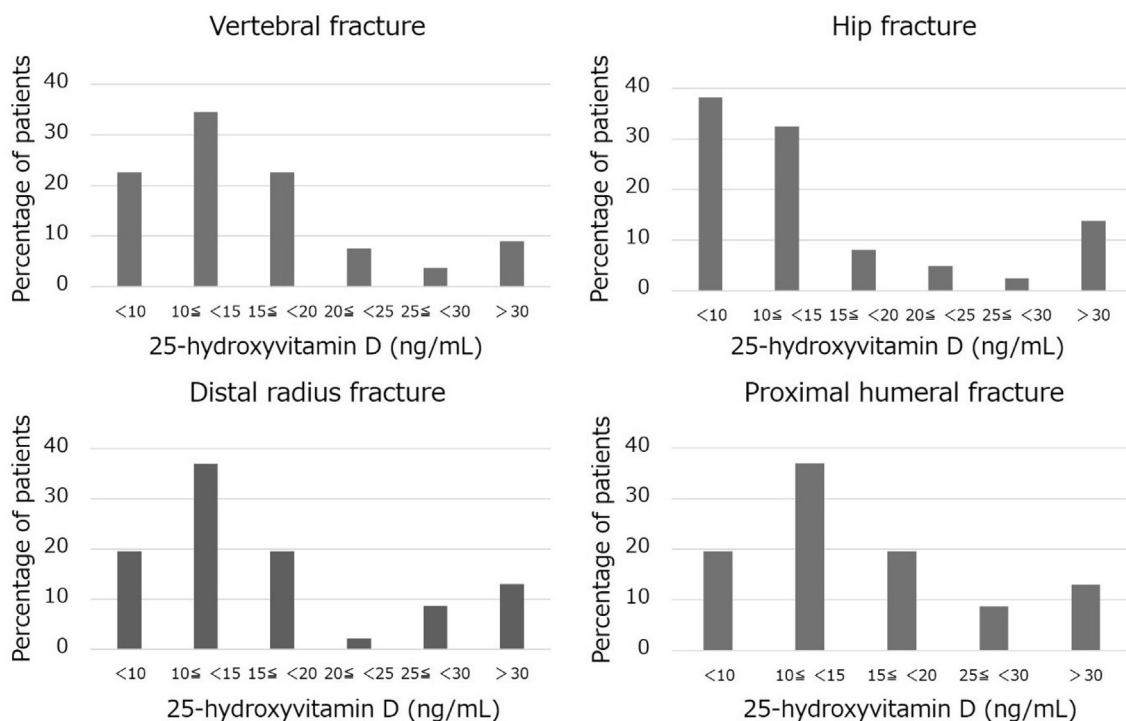

Fig. 1. Percentage of patients by serum 25-hydroxyvitamin D concentration in each osteoporotic fracture site.
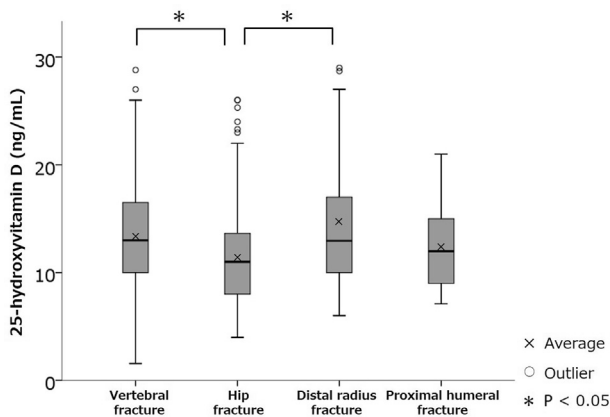
Fig. 2. Comparison of 25-hydroxyvitamin D (25(OH)D) serum concentrations in each osteoporotic fracture site in patients with 25(OH)D concentrations < 30 ng/mL (vitamin D insufficiency).

In patients with 25(OH)D concentration < 30 ng/mL (vitamin D deficiency and insufficiency), simple linear regression analysis revealed that lower 25(OH)D concentration was significantly associated with lower femoral neck BMD (P < 0.001) and lower serum albumin concentration (P < 0.001) (Table 3). Moreover, multiple linear stepwise regression analysis revealed that lower 25(OH)D concentration was significantly associated with lower femoral neck BMD (P = 0.03) and lower serum albumin concentration (P < 0.001) (Table 3).

4. Discussion

This study demonstrated that 78% of the Japanese postmenopausal women with osteoporotic fractures had vitamin D deficiency, while only 12% of them had vitamin D sufficiency. Lower serum 25(OH)D concentration is significantly associated with lower femoral neck BMD in patients with vitamin D deficiency or insufficiency. The percentage of vitamin D deficiency in Japanese postmenopausal women with osteoporotic fractures (78%) was higher than those in Japanese ambulatory postmenopausal women (35.2%) [7], Japanese postmenopausal women (49.6%) [8], and Japanese community-dwelling women aged ≥ 50 years without metabolic bone disease or premature menopause (52.0%) [9]. The percentage of vitamin D sufficiency in Japanese postmenopausal women with osteoporotic fractures (12%) was similar to that in Japanese community-dwelling women aged ≥ 50 years without early menopause or diseases affecting bone metabolism (10%) [9]. Thus, we can consider that vitamin D insufficiency in postmenopausal women leads to vitamin D deficiency, thus increasing fracture risks.

Most patients have serum vitamin D deficiency independent of osteoporotic fracture sites. Regarding the 4 sites of fractures, 25(OH)D concentration in patients with hip fractures was significantly lower than that in those with vertebral and distal radius fractures. Tanaka et al. [8] reported that serum 25(OH)D concentration < 25 ng/mL was significantly associated with long bone fractures (P < 0.01) and moderately associated with hip fractures (P = 0.07), but not associated with vertebral fractures (P = 0.88) in 1470 Japanese postmenopausal women. Bischoff-Ferrari et al. [11] reported that individuals with 25(OH)D concentration > 24 ng/mL had low risk of hip fractures (hazard ratio, 0.63; 95% confidence interval, 0.46–0.87) (P = 0.02) compared with those with 25(OH)D concentration < 12 ng/mL and aged > 65 years. It has been reported that when serum 25(OH)D concentration is high, the cortical bone of the femoral neck becomes thick and the medullary volume decreases [12]. The e-ADVANCED study compared the use of alendronate 35 mg/wk combined with eldecalcitol 0.75 μg/d (eldecalcitol is a strong analogue of vitamin D) and the use of plain vitamin D 400 IU/d combined with calcium 610 mg/d; the results of that study showed a significant increase in femoral neck BMD in the group receiving eldecalcitol. However, lumbar BMD did not significantly differ between the 2 groups [13]. The serum 25(OH)D concentration and exogenous application of vitamin D are closely associated with fractures, bone structure, and BMD in the femoral neck.

There was a significant difference in age among the 4 groups of fracture sites, while 25(OH)D concentration was not associated with age. Intestinal calcium absorption gradually decreased with age in women and men [14]. To maintain homeostasis of serum calcium, it is necessary to increase serum 25(OH)D concentration.

Table 2
Simple linear regression analysis and multiple linear stepwise regression analysis (n = 317).

Variable	25-hydroxyvitamin D (ng/mL)				
	Simple linear regression analysis		Multiple linear stepwise regression analysis		
	R	P-value	β (95% CI)	t-value	P-value
Age, yr	0.00	0.50	-	−0.10	0.92
Lumbar spine BMD, g/cm^2	−0.04	0.30	-	−0.53	0.60
Femoral neck BMD, g/cm^2	−0.02	0.40	-	−0.07	0.95
Albumin, g/dL	0.10	0.08	-	0.97	0.34
Albumin-corrected calcium, mg/dL	−0.14	0.02	−0.137 (−6.55 to −0.10)	−2.03	0.04
Phosphate, mg/dL	−0.04	0.27	-	−0.32	0.75
Tartrate-resistant acid phosphatase 5b, mU/dL	0.04	0.29	-	0.58	0.56
Undercarboxylated osteocalcin, ng/mL	−0.09	0.10	-	−1.15	0.25
Existing fragility fracture	-	-	-	0.06	0.96
Fracture site					
Vertebral fracture	-	-	-	−0.29	0.77
Hip fracture	-	-	-	−0.96	0.34
Distal radius fracture	-	-	-	1.08	0.28
Proximal humerus fracture	-	-	-	0.97	0.33
Place of residence					
Home	-	-	-	−0.88	0.38
Hospital	-	-	-	0.56	0.57
Facility	-	-	-	0.67	0.51

R = correlation coefficient; β = standardized correlation coefficients (95% confidence interval [CI]); BMD, bone mineral density.

Table 3
Simple linear regression analysis and multiple linear stepwise regression analysis (25-hydroxyvitamin D < 30 ng/mL) (n = 279).

Variable	25-hydroxyvitamin D (ng/mL)				
	Simple linear regression analysis		Multiple linear stepwise regression analysis		
	R	P-value	β (95% CI)	t-value	P-value
Age, yr	−0.12	0.05	-	0.41	0.68
Lumbar spine BMD, g/cm^2	0.06	0.19	-	−0.62	0.54
Femoral neck BMD, g/cm^2	0.20	<0.001	0.16 (0.78−12.17)	2.24	0.03
Albumin, g/dL	0.24	<0.001	0.21 (0.62−2.96)	3.01	<0.001
Albumin-corrected calcium, mg/dL	0.04	0.29	-	1.21	0.23
Phosphate, mg/dL	0.07	0.15	-	0.98	0.33
Tartrate-resistant acid phosphatase 5b, mU/dL	−0.15	0.02	-	−1.37	0.17
Undercarboxylated osteocalcin, ng/mL	−0.08	0.12	-	−0.86	0.39
Existing fragility fracture	-	-	-	−1.56	0.12
Fracture site					
Vertebral fracture	-	-	-	1.57	0.12
Hip fracture	-	-	-	−1.67	0.10
Distal radius fracture	-	-	-	0.17	0.87
Proximal humerus fracture	-	-	-	−0.32	0.75
Place of residence					
Home	-	-	-	−0.27	0.79
Hospital	-	-	-	−0.83	0.41
Facility	-	-	-	0.78	0.44

R = correlation coefficient; β = standardized correlation coefficients (95% confidence interval [CI]); BMD, bone mineral density.

In elderly individuals, increase in 25(OH)D concentration after sunlight exposure was slower compared to that in the young adults [15], and intestinal calcium absorption was increased after supplementation with active vitamin D or eldecalcitol, compared to supplementation with plain vitamin D [16]. Thus, in elderly individuals, it is difficult for 25(OH)D concentration to increase after sunlight exposure and to affect intestinal calcium absorption.

Miu and Lam [17] reported that 79% of patients with hip fractures are at risk of malnutrition, and serum albumin concentration significantly decreased in the malnourished group compared with that in the well-nourished group. Bohl et al. [18] reported that the prevalence of hypoalbuminemia (serum albumin concentration < 3.5 g/dL) was 45.9% in patients with geriatric hip fractures. Hypoalbuminemia is also a risk factor of vertebral fracture [19]. In this study, the average serum albumin concentration of vertebral and hip fractures was >3.5 g/dL, and it was considered that malnutrition may be involved in both fractures. However, 25(OH)D concentrations in hip fractures were significantly lower than that in vertebral fractures (P < 0.05). A decrease in vitamin D concentration in patients with hip fractures may be caused by lesser sunlight exposure time due to decline in activities of daily living, in addition to malnutrition.

The measurement of serum 25(OH)D concentration is greatly important, and it is essential to determine the status of dietary habits and lifestyle of patients, presume the response to bisphosphonate [20,21], and predict fracture risk [8,9,11]. Thus, we have to measure serum 25(OH)D concentration at the start of osteoporosis treatment. In individuals with a 25(OH)D concentration < 30 ng/mL, osteoid volume per bone volume, osteoid surface per bone surface, and osteoid thickness were increased [22]. Mineralization was impaired histologically in those with 25(OH)D concentration < 30 ng/mL. Bisphosphonate has affinity to the mineralized surface of the bone but does not have affinity to the osteoid surface. In this study, because approximately 88% of patients had 25(OH)D concentration < 30 ng/mL, they seem to show increased osteoid tissue (so-called osteoporomalacia) histologically. These patients with osteoporotic fractures must be treated with bisphosphonate together with or after improving calcium metabolic status appropriately.

This study had 2 limitations. First, we recruited patients throughout the year and did not consider seasonal variation. The serum 25(OH)D concentration varies seasonally [23]. Synthesis of vitamin D by the skin upon exposure to ultraviolet light directly affects serum 25(OH)D deficiency [24]. However, the difference in serum 25(OH)D concentration between summer and winter is only about 7 ng/mL [23], which is considered to have a small effect in this study. Second, physical performance was not routinely assessed in this study. There is a positive correlation between serum 25(OH)D concentration and body performance, such as grip strength and short physical performance battery (SPPB) [25,26]. In this study, we evaluated the residence at the time of injury, and it was considered that physical performance of the home residents was better than that of facility and hospital residents. However, the evaluation of physical performance was considered insufficient in the evaluation of only the place of residence.

5. Conclusions

In this study, 78% of the postmenopausal women with osteoporotic fractures showed serum vitamin D deficiency. The proportion of vitamin D deficiency in postmenopausal women with osteoporotic fractures was greater than that in postmenopausal women reported by previous literatures. Serum vitamin D concentration was significantly associated with femoral neck BMD in patients with vitamin D deficiency or insufficiency. We should be aware that almost all postmenopausal patients with osteoporotic fractures have vitamin D deficiency or insufficiency independent of the fracture site.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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