FISEVIER

Contents lists available at ScienceDirect

Journal of Orthopaedic Science

journal homepage: http://www.elsevier.com/locate/jos



Original Article

Different types of hip fragility fractures have different values of 25-hydroxyvitamin D and parathyroid hormone*



Atsuko Kanno a, b, *, Toshitake Aizawa b, Yu Mori c, Toshimi Aizawa c

- ^a Department of Orthopaedic Surgery, Japan Community Health Care Organization Sendai South Hospital, Japan
- b Department of Orthopaedic Surgery, Iwaki City Medical Center, Japan
- ^c Department of Orthopaedic Surgery, Tohoku University Graduate School of Medicine, Japan

ARTICLE INFO

Article history:
Received 9 April 2022
Received in revised form
11 October 2022
Accepted 3 November 2022
Available online 24 November 2022

Keywords:
Osteoporosis
25-Hydroxyvitamin D
Parathyroid hormone
Hip fracture
Femoral neck fracture
Trochanteric fracture

ABSTRACT

Background: Vitamin D insufficiency/deficiency is related to fragility fracture. In most previous studies, there was no assessment of vitamin D deficiency status separately for hip fracture types. The first aim is to evaluate vitamin D and parathyroid hormone (PTH) status in patients with hip fracture. The second objective is to determine whether there are differences in vitamin D and PTH between the femoral neck fracture and the femoral metaphyseal fracture group.

Methods: 62 men and 248 women with fragility hip fractures were enrolled. 25-hydroxyviamin D [25(OH)D] and intact PTH (iPTH) values were evaluated, and femoral neck bone mineral density (BMD) was measured on the uninjured side. Vertebral fractures (VFs) were assessed using radiographs of the thoracic and lumbar spine. We examined the relationships of 25(OH)D value with the number of prevalent VFs, T-score of femoral neck, and iPTH level. These analyses were also performed, neck fracture and trochanteric fracture separately.

Results: Mean age was 85 years. The mean 25(OH)D was 11.2 (range, 4.0-26.1) ng/ml, whereas the mean iPTH value was 48.9 pg/ml (range, 9-429 pg/ml). The mean number of VFs was 1.5 (range, 0-11), and the mean T-score was -3.3 (range, -5.2 to -0.5). There was a weak correlation between the 25(OH)D value and the number of VFs. There was a weak but significant correlation between 25(OH)D and iPTH values. In the patients with trochanteric fractures, 25(OH)D value was significantly lower and iPTH value was significantly higher than those with neck fractures. There was a significant correlation between the 25(OH)D value and number of the VFs, 25(OH)D, and iPTH values only in trochanteric fractures. Conclusions: Vitamin D deficiency was severe and PTH levels were higher in the trochanteric fractures.

Both vitamin D deficiency was severe and PTH levels were higher in the trochanteric fractures. Both vitamin D deficiency and high PTH levels were suggested to have association with bone fragility.

© 2022 The Japanese Orthopaedic Association. Published by Elsevier B.V. All rights reserved.

1. Introduction

Osteoporosis is a skeletal disorder of reduced bone strength that leads to fragility fracture [1]. These fractures, especially hip fractures diminish their quality of life and increases mortality [2].

Vitamin D deficiency is related to insufficient calcium absorption from the intestine and deficient bone mineralization. It is also associated with the subsequent development of osteoporosis [3]. Vitamin D deficiency also results in secondary hyperparathyroidism, which leads to excessive bone resorption and osteomalacia [3]. Because 25-hydroxyvitamin D [25(OH)D] is the primary form of

E-mail address: akkanchan428@gmail.com (A. Kanno).

vitamin D in the human body, its value is used to assess vitamin D status [3].

It was reported that vitamin D insufficiency and deficiency increased the risks of falls and fragility fractures [4,5]. Vitamin D insufficiency and deficiency are widely observed in community-dwelling healthy people in Japan and Singapore [6,7], although there were differences in the degree of decrease in 25(OH)D values by ethnicity. In vitro, it has been reported that vitamin D administration promotes myocyte differentiation [8]. Although there are reports of improved lower extremity muscle strength in osteoporosis patients treated with vitamin D, the effect of vitamin D administration in preventing falls is controversial [9]. However, there have been a few reports on vitamin D status in Japanese patients with hip fragility fractures [10,11].

Hip fracture is classified into neck fracture and trochanteric fracture. In a previous report, the association between the 25(OH)D value and intact parathyroid hormone (iPTH) value is different

^{*} This research has been approved by the IRB of the authors' affiliated institutions. The approval numbers are H28-22, 2017-8.

^{*} Corresponding author. 143, Aza-Maeoki, Nakadamachi, Taihaku Ward, Sendai, 981-1103, Japan.

between these fracture types [12]. However, most previous studies did not analyze these hip fracture types separately.

According to the criteria of the Japanese Osteoporosis Society, we diagnose patients with hip or vertebral fracture (VF) as osteoporosis if index fracture occurs after a fall from a standing position [13]. Approximately only one-fourth of postmenopausal women with radiographic VF are symptomatic [14]. The assessment of VF is also crucial in diagnosing osteoporosis.

Therefore, the purpose of this study was to clarify the relationship between vitamin D insufficiency/deficiency and fragility fractures. This study mainly focused on examining 25(OH)D levels in patients with fragility hip fractures. The relationship between VFs, bone mineral density (BMD), iPTH value, and the 25(OH)D value was examined. These analyses were also analyzed separately due to fracture type.

2. Materials and methods

2.1. Participants

This retrospective study was performed in two institutes by the ethical standards of the Declaration of Helsinki and approved by the Institutional Review Board of the authors' affiliated institutions. The participants in this study were patients with fragility hip fractures. Patients were enrolled from April 2017 to March 2020. Sixty-two men and 248 women, who experienced a fall from a standing position or a low-energy fall, were enrolled. Patients with a high energy injury (i.e., traffic accident or fall from height), or those with pathological hip fracture were excluded. Written informed consent has been obtained from all the patients and their families.

Two-hundred ninety-one patients were surgically treated and the other 19 patients were conservatively managed. In total, 60 patients had previous fragility fractures before enrollment. Of these patients, 22 had contralateral hip fractures, and 20 had experienced symptomatic VFs. Eight patients had suffered fragility fracture several times. Detailed information was shown in Table 1.

Using a plain radiograph and computed tomography (CT), the type of hip fracture site was diagnosed. CT imaging was performed in the emergency department to diagnose hip fractures. The number of patients with femoral neck, intertrochanteric, and subtrochanteric fractures was 139, 159, and 12. These patients were divided into the neck and trochanteric groups: the latter contains patients with intertrochanteric fracture and those with subtrochanteric fracture. Fracture at head-neck junction was classified into trochanteric group.

Table 1Prevalent fracture and number of patients.

Prevalent fracture site	Number of patients
Vertebra	20
Contralateral proximal femur	22
Distal radius	8 ^a
Proximal humerus	2^{b}
Clavicle	1
Rib	2
Pubis	1
Contralateral distal femur	1 ^c
patella	1 ^d
Unknown upper limb	5 ^e
Unknown lower limb	1
Unknown upper and lower limbs	1

- ^a One patient had suffered bilateral distal radius fracture.
- ^b One patient had suffered vertebral fracture.
- ^c This patient had suffered contralateral proximal femur fracture.
- ^d This patient had suffered distal radius fracture.
- ^e One patient had suffered contralateral proximal femoral fracture. Another patient had suffered vertebral fracture. Another one patient had suffered shoulder and elbow fracture; however, there was no detailed information.

2.2. Clinical parameters

General characteristics included age, body weight, height, body mass index (BMI), and comorbidities at enrollment. During admission, the value of serum 25(OH)D, iPTH, alkaline phosphatase (ALP), calcium, phosphate, albumin, blood urea nitrogen (BUN), and creatinine (Cr) were evaluated. A corrected calcium value was calculated when the serum level of albumin was less than 4.0 g/dl. The estimated glomerular filtration rate (eGFR) was calculated from BUN and Cr. eGFR was calculated by the Japanese Society of Nephrology equation [15]. eGFR (ml/min/1.73 m²) = 194 × serum creatinine(mg/dL) $^{-1.094}$ × age $^{-0.287}$. For women, the figure was multiplied by 0.739. The mean period between surgery and serum sample collection was 6.1 days after surgery (range, ten days before surgery to 34 days after surgery).

The mean period from the admission to serum sample collection was 7.9 days in 19 patients who did not undergo surgery (3–15 days).

To measure the 25(OH)D value, a chemiluminescent immunoassay was performed using the Riezon® kit (Hitachi Chemical Diagnostic Systems Co.Ltd., Tokyo, Japan), and a radioimmunoassay was performed at another institute using the 25-hydroxyvitamin D 125I RIA kit (DiaSorin, Saluggia, Italy). The exact 25(OH)D value could not be measured in seven patients because the level was below the lower limit of quantification of the instrument (<4.0 ng/ml). In these patients, 25(OH)D value was defined as 4.0 ng/ml.

An electrochemiluminescence immunoassay was performed in both institutes to measure the iPTH value using the ECLusys® kit (Roche Diagnostics, Basel, Switzerland). TBA-FX8 (Canon Medical Systems, Ohtawara, Japan) and TBA C-8000 (Canon Medical Systems, Ohtawara, Japan) were used for all other clinical chemical analysis according to standard automated laboratory methods.

Based on the criteria of the Endocrine Society Clinical practical guidelines [3], 25(OH)D values ≥ 30 ng/ml, 20-30 mg/ml, and <20 ng/ml were defined as vitamin D sufficiency, insufficiency, and deficiency, respectively.

Because major source of vitamin D is exposure of natural sunlight [3], season can influence 25(OH)D value. To assess the seasonal changes, the patients were divided into four groups by time of injury: March to May (spring), June to August (summer), September to November (autumn), and December to February (winter). The differences in 25(OH)D values among these four groups were evaluated.

The numbers of patients with a serum level of iPTH above or below the reference value were determined (reference value: 10–65 pg/ml). The relationship between the iPTH value and osteoporosis drug treatment was also examined.

2.3. Radiographic assessment

Plain radiographs of the thoracic and lumbar spine were obtained. Anteroposterior and lateral views were evaluated. Prevalent VF was detected using Genant's semiquantitative grade (SQ grade) [16]. Briefly, this grade is defined from the anterior, middle and posterior height of vertebral body: grade 1 (mild deformity), grade 2 (moderate deformity), grade 3 (severe deformity) is approximately 20–25%, 25–40%, more than 40% reduction in any height, respectively. The total number of VF and the number of SQ grade 2 and 3 VFs were recorded.

2.4. BMD assessment

The BMD of the contralateral proximal femoral neck was measured in 275 patients using dual-energy X-ray absorptiometry (DXA). This measurement was not performed in patients with a history of contralateral proximal femoral fractures and those with

poor general conditions. The Discovery A DXA system (version 13.0, Hologic, Marlborough, USA) and the Discovery SL (version 13.3.0.1, Hologic, Marlborough, USA) were used in the study. All procedures were performed according to the manufacturer's standardized protocols. All BMD results were expressed as the T-score values.

2.5. Statistics

The Kruskal-Wallis test was used to evaluate differences in 25(OH)D values among the four seasons to evaluate the influence of season to 25(OH)D values. Mann-Whitney test was used to examine the differences in patients' age, 25(OH)D value, number of all VFs, number of SQ grade 2 and 3 VFs, T-score of the femoral neck, and iPTH value between neck group and trochanteric group.

Spearman's rank correlation coefficient was used to evaluate the correlation of the serum level of 25(OH)D with the number of all VFs, number of SQ grade 2 and 3 VFs, and T-score of the proximal femoral neck. This analysis was performed in all the subjects, neck and trochanteric group, respectively. Excel 2019® (Microsoft, Washington, USA) and BellCurve for Excel (SSRI, Tokyo, Japan) were used for statistical analysis. Significant differences were defined as p<0.05.

3. Results

3.1. Baseline characteristics

The mean age at injury was 85 (65–100) years. The age distribution and the ratio of men and women are shown in Table 2. Approximately three-fourths of patients were 80 years or older. Mean BMI was 20.6 (range, 12.0–31.3) kg/m². Comorbidities are shown in Table 3. The most common comorbidity was hypertension, followed by cerebral infarction and central nerve disease, and heart disease. Sixty-eight patients had osteoporosis treatment: activated vitamin D3 and bisphosphonate were most used. The various treatment drugs are shown in Table 4.

Table 2Age distribution and sex ratio of the participants.

Total	Neck fractures	Trochanteric fractures
12 (3.9%)	7 (5.0%)	5 (2.9%)
61 (19.7%)	40 (28.8%)	21 (12.3%)
152 (49.0%)	70 (50.4%)	82 (48.0%)
85 (27.4%)	22 (15.8%)	63 (36.8%)
1:4	1:3.5	1:4.5
	12 (3.9%) 61 (19.7%) 152 (49.0%) 85 (27.4%)	12 (3.9%) 7 (5.0%) 61 (19.7%) 40 (28.8%) 152 (49.0%) 70 (50.4%) 85 (27.4%) 22 (15.8%)

Table 3 Participants' comorbidities.

Comorbidity	n
Hypertension	167
Heart disease	75
Cerebral infarction, central nerve system disease	77
Dementia	53
Psychological disease other than dementia	13
Vascular disease other than heart and brain	18
Lung disease other than cancer	19
Liver disease other than cancer	10
Diabetes mellitus	64
Thyroid disease	12
Parathyroid disease	1
Rheumatoid Arthritis/collagen disease	5
Chronic kidney disease ^a	20
Malignant tumor	56

^a 10 patients were getting dialysis.

Table 4 Osteoporosis drug at injury.

Osteoporosis drug	No. of patients
Alfacalcidol (0.25 μg) Alfacalcidol (0.5 μg) Alfacalcidol (0.5 μg), Menatetrenone Alfacalcidol (1.0 μg)	3 6 1 5
Alfacalcidol (1.0 μg), Ca ι-aspartate 400 mg	1
Eldecalcitol (0.5 μg) Eldecalcitol (0.5 μg), Ca ι-aspartate 400 mg Eldecalcitol (0.75 μg) Eldecalcitol (0.75 μg), Ca ι-aspartate 400 mg	1 2 11 1
Raloxifene Raloxifene, Alfacalcidol (1.0 μg) Raloxifene, Eldecalcitol (0.75 μg)	4 2 1
Bazedoxifene, Eldecalcitol (0.75 μg)	2
Alendronate (weekly) Alendronate (monthly)	1 2
Risedronate (daily) Risedronate (weekly) Risedronate (weekly), Eldecalcitol (0.75 µg) Risedronate (weekly), Eldecalcitol (0.5 µg), Ca L-aspartate 400 mg Risedronate (monthly) Risedronate (monthly), Alfacalcidol (0.5 µg) Risedronate (monthly), Eldecalcitol (0.75 µg)	1 5 2 1 1 1
Minodronate (monthly) Minodronate (monthly), alfacalcidol (0.25 μg) Minodronate (monthly), Eldecalcitol (0.5 μg), Ca ι-aspartate 400 mg Minodronate (monthly), Eldecalcitol (0.75 μg), Ca ι-aspartate 400 mg Minodronate (monthly), Eldecalcitol (0.75 μg), Ca ι-aspartate 400 mg Minodronate (monthly), Ca ι-aspartate hydrate 400 mg	3 1 1 2 1
Daily teriparatide Weekly teriparatide, alfacalcidol (0.5 μg) Denosumab, alfacalcidol (0.5 μg) Denosumab, Eldecalcitol (0.75 μg), Ca ι-aspartate 600 mg (after 2-year daily teriparatide)	1 1 1

Table 5 biochemical examination.

	Average (range)
25(OH)D (ng/ml)	11.2 (4.0–26.1)
iPTH (pg/ml)	48.9 (9-428)
ALP (IU/L)	271.3 (29-1582)
corrected calcium (mg/dL)	9.7 (7.8-12.0)
phosphate (mg/dL)	3.4 (1.3-6.3)
albumin (g/dL)	2.72 (1.4-4.1)
eGFR (ml/min/1.73m ²)	67.0 (4.3-151.1)

The mean age at injury was 82 and 87 in the neck and trochanteric fracture groups, respectively. The age distribution and the ratio of men and women in each group are shown in Table 1. The trochanteric group patients were significantly older than neck group (p < 0.001). The ratio of patients over 90 years was higher in the trochanteric group.

3.2. 25(OH)D value

The results of all biochemical examinations are shown in Table 5.

The mean 25(OH)D value was 11.2 (4.0–26.1) ng/ml. The value of 25(OH)D is shown in Fig. 1. None of the cases was vitamin D sufficient. Nineteen patients (6.1%) were vitamin D insufficiency, and the remaining 291 patients (93.9%) were vitamin D deficiency. The mean 25(OH)D values in the patients injured in the spring, summer, autumn, and winter were 10.3 ng/ml, 11.6 ng/ml, 12.7 ng/

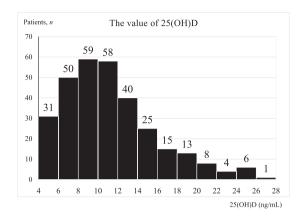


Fig. 1. Histogram of the 25(OH)D concentration. Vitamin D deficiency (less than 20 ng/ml) is evident in 93.9% of the patients.

ml, and 11.6 ng/ml, respectively. There was a significant difference between spring and autumn values (p=0.03).

3.3. iPTH value and osteoporosis drug administration

The mean iPTH value was 48.9 (9–428) pg/ml. The serum level of iPTH exceeded the reference value in 53 patients. One of these patients had already been diagnosed with primary hyperparathyroidism. Among these 53 patients, drugs for osteoporosis treatment were administered to 11 patients: alfacalcidol in 1 patient, eldecalcitol in 3 patients, eldecalcitol and calcium in 1 patient, bisphosphonate in 5 patients, and denosumab in 1 patient, respectively. One patient had the iPTH value below the reference value, and eldecalcitol was administered.

3.4. Concomitant VFs and BMD of the contralateral femoral neck

Prevalent VFs of any grade were observed in 294 patients (94.8%). Fig. 2 demonstrates that the mean number of VFs was 3.0 (0–12). SQ grade 2 or 3 VFs were detected in 189 patients (61.0%). The mean number of SQ grade 2 or 3 VFs was 1.5 (0–11) in Fig. 3.

The mean T-score of the contralateral femoral neck was -3.3 (-5.2 to -0.5) in Fig. 4. The number of patients with a T-score greater than -2.5 was 51, accounting for 18.5% of patients who underwent BMD measurement.

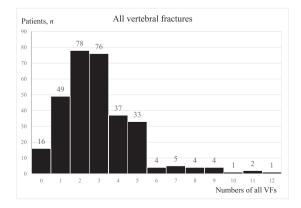


Fig. 2. Histogram of the number of all prevalent VFs (VF: vertebral fracture). There had been any prevalent VF in 94.8% of the patients. Most patients had had plural number of VFs.

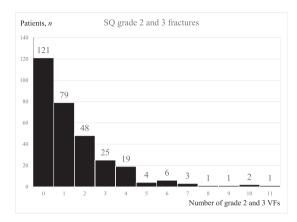


Fig. 3. Histogram of the number of prevalent SQ grade 2 and 3 VFs (VF: vertebral fracture). 61.0% of the patients had SQ grade 2 and 3 VFs.

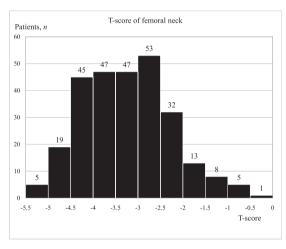


Fig. 4. Histogram of the T-score of the contralateral femoral neck. Bone mineral density was measured in 275 patients. 51 patients (18.5%) showed higher T-score (greater than -2.5).

3.5. Correlation of the 25(OH)D value with concomitant fracture, BMD, and the iPTH value in all the subjects

There was no significant correlation between the 25(OH)D value and the number of all VFs. In contrast, there was a weak negative correlation between the 25(OH)D value and the number of grade 2 and 3 VFs (p = 0.004, r = -0.16). There was no significant correlation between the 25(OH)D value and the T-score of the femoral neck. There was a weak negative correlation between the 25(OH)D and iPTH values (p \leq 0.001, r = -0.25).

3.6. Comparison of 25(OH)D value and other factors between neck group and trochanteric group, correlation of these factors

Mean 25(OH)D value in neck group and trochanteric group was 11.7 ng/ml (4.0–26.1 ng/ml) and 10.7 ng/ml (4.0–25.4 ng/ml), respectively. There was a significant difference between the two groups (p = 0.047). Both numbers of VFs and SQ grade 2,3 VFs were significantly greater in the trochanteric group. T-score of the femoral neck was significantly lower in the trochanteric group. The mean value of iPTH was significantly higher in the trochanteric group. The detailed figure is shown in Table 6.

There was no correlation between the mean 25(OH)D value and other factors in the neck group. On the contrary, there was a

Table 6 25(OH)D value and other factors in neck group and trochanteric group. *: p < 0.05, **: p < 0.01 compared to neck group.

	Neck fractures	Trochanteric fractures
25(OH)D value (ng/ml)	11.7 (4.0-26.1)	10.7* (4.0-25.4)
Numbers of all VF	2.4 (0-12)	3.4** (0-11)
Numbers of SQ grade 2 and 3 VFs	1.1 (0-10)	1.8** (0-11)
T-score of the femoral neck	−3.1 (−4.8 to −1.5)	-3.5** (−4.4 to −1.9)
iPTH value (pg/ml)	46.4 (14-428)	50.9** (9-272)

Table 7 p value, Spearman's rank correlation coefficient between 25(OH)D value and other factors in trochanteric group. r_s : Spearman's rank correlation coefficient. *: p < 0.05, **: p < 0.01.

	p value	r_s between 25(OH)D value
number of all VFs	0.13	-0.12
number of SQ grade 2 and 3 VFs	0.03*	-0.17
T-score of the femoral neck	0.15	0.12
iPTH value	p < 0.001**	-0.32

significant correlation between the mean 25(OH)D value in the trochanteric group and the factors of the number of SQ grade 2 and 3 VF and iPTH value (Table 7).

4. Discussion

The present study showed severe 25(OH)D deficiency in fragility hip fracture patients. The mean 25(OH)D value was 11.2 ng/ml, and the value of 25(OH)D in 94% of patients was deficient (<20 ng/ml) and that in 6% of patients was insufficient (20—30 ng/ml). Differences in 25(OH)D values related to seasonal differences in ultraviolet intensity demonstrated, but low vitamin D levels were severe and differences were limited.

Nuti et al. reported that the mean serum level of 25(OH)D was 33.4 ng/ml in elderly patients with hip fractures in Italy [17]. Sakuma et al. reported that the level was 16.6 ng/ml in patients with hip fractures in Japan [10]. In another report from Japan, the mean 25(OH)D values were 9.1 ng/ml and 19.0 ng/ml in 72 female patients and 27 male patients with hip fracture, respectively, and vitamin D deficiency was apparent in 90% of these patients [11]. From those previous studies and the present study, the 25(OH)D value of elderly Japanese patients with fragility hip fractures was much lower than that of Caucasian patients.

There was no significant correlation between the number of all VFs and 25(OH)D values. On the other hand, there was a significant correlation between the serum 25(OH)D value and the number of SQ grade 2 and 3 VFs. According to asymptomatic VF, the relationship between SQ grade and 25(OH)D value seems to be controversial. Healthy postmenopausal women with vitamin D insufficiency or deficiency showed a higher prevalence of SQ grade 2 and 3 asymptomatic VFs than those with vitamin D sufficiency [18]. In another study, the value of 25(OH)D in postmenopausal community-dwelling women with any prevalent VF was no significant difference compared to women without VF [19]. In a recent report, VF of SQ grade 1 is not associated with a non-vertebral osteoporotic fracture [20]. A significant correlation was lost in our study, including grade 1 VF: this result might be consistent with the previous report.

There was no significant correlation between the 25(OH)D value and the T-score of the femoral neck BMD patients with fragility hip fracture. The association between the 25(OH)D value and BMD seems controversial. Some previous studies also indicated no association between the 25(OH)D value and BMD in healthy

postmenopausal women [18]. On the other hand, another study showed a significant relationship between healthy Caucasians and Asians [21]. In another report, in addition to vitamin D deficiency, hypersecretion of PTH is related to lower BMD in the women with fragility hip fracture [22]. These discrepancies in previous studies might be related to response of PTH to vitamin D deficiency.

In the trochanteric fractures group, the 25(OH)D value was lower, the number of VF was higher, and the T-score of the femoral neck was lower than the neck fractures group. Previous reports showed more prevalent VF in patients with trochanteric fractures than neck fractures [23]. In another report, the T-score of the femoral neck was lower in trochanteric fracture [24]. Our results were consistent with these results. On the contrary, 25(OH)D value was not significantly different between neck and trochanteric fracture in another report [12,25], although vitamin D deficiency was evident in both fracture type. In a previous report, 25(OH)D value is correlated to number of VF [26]. In our study, the patients in trochanteric group had had more prevalent VF compared to those in neck group. This might affect the 25(OH)D value. Furthermore, another possible reason for the difference in vitamin D levels between the trochanteric fracture group and the femoral neck fracture group is that the patients in this study had the severe deficiency of 25(OH)D. We believe that vitamin D should be administered to Japanese patients with osteoporosis. Further research will be necessary to clarify the relationship between 25(OH)D value and hip fracture type.

As mentioned above, PTH was normal in most patients regardless of vitamin D deficiency. In our results, the iPTH value was significantly higher in the trochanteric fractures group than in the neck fractures group. Furthermore, there was significant correlation between 25(OH)D and iPTH value only in the trochanteric group. In a previous study, the PTH value was higher in patients with trochanteric fracture [12]. In another study, the correlation between 25(OH)D and PTH value was more robust in the patients with trochanteric fractures than those with neck fractures [27]. These results suggested that the response of PTH to vitamin D deficiency was different between patients with neck fractures and trochanteric fractures. Our results were consistent with these results.

Cortical thinning and porosity occur due to increased PTH, although cancellous is relatively preserved [28]. In another report, cortical porosity and thinning of the subtrochanteric area were confirmed in the patients with proximal femoral fracture, whose PTH value was higher than control [29]. The thickness of the cortex in the intertrochanteric femur was thinner in patients with trochanteric fractures than those with neck fractures in another report [30]. From these reports, a high PTH value might weaken the intertrochanteric to the subtrochanteric area and increase fracture risk. Furthermore, elevated PTH values and lower 25(OH)D values are related to recurrent falls [27]. From these previous reports, it is suggested that in the patients with higher PTH value, there had been cortical porosity and a history of frequent falls.

There are several limitations in this study. First, this work involved a retrospective cross-sectional study. The changes in the 25(OH)D value, iPTH, and BMD were not evaluated before falls and during the follow-up period. Furthermore, duration of osteoporosis treatment was not clear. Second, the subjects were the patients with fragility hip fractures only. We did not have a control group composed of age-and gender-matched patients without fragility hip fracture. Third, the background of the patients was not uniform, and activity before the fall was not assessed.

5. Conclusion

This study indicated that the 25(OH)D value was 11.2 ng/ml in Japanese patients with fragility hip fracture, which is very low. The

25(OH)D value was significantly related to the number of moderate and severe VFs and iPTH values. In the patients with trochanteric fractures, 25(OH)D value was significantly lower, and iPTH value was higher than in patients with neck fractures. There was a significant negative correlation between 25(OH)D and iPTH value only in the patients with trochanteric fractures. Further research is necessary to clarify the PTH response to vitamin D deficiency.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

The authors thank Mikako Kaneko (Iwaki Medical Center) for patient recruitment and Ayumi Sawada and Masami Ohwada (Iwaki Medical Center) for assistance with the input of biochemical and imaging examination orders.

References

- [1] Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, et al. The clinical diagnosis of osteoporosis: a position statement from the national bone health alliance working group. Osteoporos Int 2014 May;25(5): 1439–43.
- [2] Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ 2000 Feb 5;320(7231):341–6.
- [3] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Hassan Murad HM, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011 Jul;96(7):1911–30.
- [4] Julian C, Lentjes MA, Huybrechts I, Luben R, Wareham N, Moreno LA, et al. Fracture risk in relation to serum 25-hydroxyvitamin D and physical activity: results from the EPIC-Norfolk cohort study. PLoS One 2016 Oct;11(10): e0164160.
- [5] Tamaki J, Iki M, Sato Y, Kajita E, Nishino H, Akiba T, et al. Total 25-hydroxyvitamin D levels predict fracture risk: results from the 15-year follow-up of the Japanese population-based osteoporosis (JPOS) cohort study. Osteoporos Int 2017 Jun;28(6):1903—13.
- [6] Yoshimura N, Muraki S, Oka H, Morita M, Yamada H, Tanaka S, et al. Profiles of vitamin D insufficiency and deficiency in Japanese men and women: association with biological, environmental, and nutritional factors and coexisting disorders: the ROAD study. Osteoporos Int 2013 Nov;24(11):2775–87.
- [7] Man RE, Li LJ, Cheng CY, Wong TY, Lamoureux E, Sabanayagam C. Prevalence and determinants of suboptimal vitamin D levels in a multiethnic Asian population. Nutrients 2017;9(3):313.
- [8] Saito H, Kishimoto KN, Mori Y, Okuno H, Tanaka M, Itoi E. A vitamin D analogue, eldecalcitol, enhances expression of fast myosin heavy chain subtypes in differentiated C2C12 myoblasts. J Orthop Res 2017 Mar;22(2): 345–50
- [9] Saito T, Mori Y, Irei O, Baba K, Nakajo S, Itoi E. Effect of eldecalcitol on muscle function and fall prevention in Japanese postmenopausal women: a randomized controlled trial. J Orthop Res 2021 Jan;26(1):173–8.
- [10] Sakuma M, Endo N, Oinuma T, Hayami T, Endo E, Yazawa T, et al. Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int 2006;17(11):1608–14.

- [11] Nakano T, Tsugawa N, Kuwabara A, Kamao M, Tanaka K, Okano T. High prevalence of hypovitaminosis D and K in patients with hip fracture. Asia Pac J Clin Nutr 2011;20(1):56–61.
- [12] Fisher A, Srikusalanukul W, Davis M, Smith P. Hip fracture type: important role of parathyroid hormone (PTH) response to hypovitaminosis D. Bone 2010 Aug;47(2):400-7.
- [13] Soen S, Fukunaga M, Sugimito T, Sone T, Fujiwara S, Endo N, et al., Japanese Society for Bone and Mineral Research and Japanese Osteoporosis Society Joint Review Committee for the Revision of the Diagnostic Criteria for Primary Osteoporosis. Diagnostic Criteria for primary osteoporosis: year 2012 revision. I Bone Miner Metab 2013 May:31(3):247–57.
- [14] Fink HA, Milavetz DL, Palermo L, Nevitt MC, Cauley JA, Genant HK, et al. What proportion of incident radiographic vertebral deformities is clinical diagnosed and vice versa? I Bone Miner Res 2005 Jul;20(7):1216—22.
- [15] Japanese Society of Nephrology eds. Evidence-based clinical practice guideline for CKD 2018. Tokyo-lgakusha, Tokyo, Japan (in Japanese) p.2.
- [16] Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993 Sep;8(9):1137–48.
- [17] Nuti R, Martini G, Valenti R, Gambera D, Gennari L, Salcadori S, et al. Vitamin D status and bone turnover in women with acute hip fracture. Clin Orthop Relat Res 2004 May:422:208–13.
- [18] El Maghraoui A, Ouzzif Z, Mounach A, Rezqi A, Achemlal L, Bezza A, et al. Hypovitaminosis D and prevalent asymptomatic vertebral fractures in Moroccan postmenopausal women. BMC Woman's Health 2012 Apr 24:12:11.
- [19] Jiajue R, Jiang Y, Qi X, Wang Q, Wang W, Pei Y, et al. Calciotropic hormones and the prevalence of vertebral fractures in Chinese postmenopausal women with vitamin D insufficiency: peking vertebral fracture study. Calcif Tissue Int 2019 Jun; 104(6):622–30.
- [20] Lentle BC, Berger C, Probyn L, Brown JP, Langsetmo L, Fine B, et al. Comparative analysis of the radiology of osteoporotic vertebral fractures in women and men: cross-sectional and longitudinal observations from the Canadian Multicentre Osteoporosis Study (CaMos). J Bone Miner Res 2018 Apr;33(4): 569–79.
- [21] van Ballegooigen AJ, Robinson-Cohen C, Katz R, Criqui M, Budoff M, Siscovick D, et al. Vitamin D metabolites and bone mineral density: the multiethnic study of atherosclerosis. Bone 2015 Sep;78:186–93.
- [22] Di Monaco M, Castiglioni C, Tappero R. Parathyroid hormone response to severe vitamin D deficiency is associated with femoral neck bone mineral density: an observational study of 405 women with hip fracture. Hormones (Basel) 2016;15(4):527–33.
- [23] Gonnelli S, Caffarelli C, Maggi S, Rossi S, Siviero P, Gandolini G, et al., BREAK Study Group. The assessment of vertebral fractures in elderly women with recent hip fractures: the BREAK study. Osteoporos Int 2013 Apr;24(4): 1151—9.
- [24] Cho Y, Lee I, Ha SH, Park JH, Park JH. Comparison of hip subregion bone mineral density to the type of proximal femur fracture. Arch Osteoporos 2020 Aug 5;15(1):122.
- [25] Zhao J, Cai Q, Jiang D, Wang L, Chen S, Jia W. The associations of serum vitamin D and bone turnover markers with the type and severity of hip fracture in older women. Clin Interv Aging 2020;15:1971–8.
- [26] Zhang L, Chan C, Yang Y, Liu B, Zhu Y, Chen R, et al. Vitamin D deficiency/ insufficiency is associated with risk of osteoporotic thoracolumbar junction vertebral fractures. Med Sci Monit 2019;25:8260–8.
- [27] Dretakis K, Igoumenou VG. The role of parathyroid hormone (PTH) and vitamin D in falls and hip fracture type. Aging Clin Exp Res 2019 Oct;31(10): 1501—7.
- [28] Rejnmark L, Ejlsmark-Svensson H. Effects of PTH and PTH hypersecretion on bone: a clinical perspective. Curr Osteoporos 2020 Jun;18(3):103–14.
- [29] Osima M, Borgen TT, Lukic M, Grimnes G, Joakimsen RM, Eriksen EF, et al. Serum parathyroid hormone is associated with increased cortical porosity of the inner transitional zone at the proximal femur in postmenopausal women: the Tromsø study. Osteoporos Int 2018 Feb;29(2):421–31.
- [30] Zhuang H, Li Y, Lin J, Cai D, Yan L, Yao X. Cortical thickness in the intertrochanteric region may be relevant to hip fracture type. BMC Muscoskelet Disord 2017 Jul 18;18(1):305.