ORIGINAL ARTICLE

Vertebral fractures affect functional status in postmenopausal rheumatoid arthritis patients

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Abstract Functional disability is a major concern in patients with rheumatoid arthritis (RA). This retrospective study investigated the risk factors for vertebral fractures (VFs) in postmenopausal RA patients and determined the impact of VFs on functional status. Data from a cohort of 200 postmenopausal RA patients in a single hospital registry were analyzed. Demographic and clinical data, imaging data from spine radiographs, and bone mineral density (BMD) data were collected from the patients at baseline and at the final visit (a mean of 2.9 years after the first visit). Risk factors for incident VFs and their impact on the modified health assessment questionnaire (mHAQ) were analyzed. Twenty-eight patients (14 %) developed new VFs (NVFs). Logistic regression analysis adjusted for age, BMI, and disease duration revealed that daily dose of prednisolone, femoral neck BMD, use of active vitamin D_3, and use of a bisphosphonate at baseline were factors associated with NVF, with odds ratios (95 % confidence interval) of 1.27 (1.05–1.54), 0.94 (0.91–0.97), 0.34 (0.13–0.89), and 0.31 (0.12–0.82), respectively. Patients with NVF exhibited worse mHAQ scores and a greater increase in mHAQ scores from baseline compared with those without NVF. In conclusion, incident VFs were associated with reduced functional status in postmenopausal patients with RA. It is important to prevent VFs to maintain the functional status of RA patients.

Keywords Osteoporosis · Prednisolone · Quality of life · Rheumatoid arthritis · Vertebral fracture

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Introduction

Rheumatoid arthritis (RA) is defined as a chronic systemic disease characterized by proliferative synovitis, and it results in severe joint destruction. The prevalence of RA in Japan is estimated at 1 % of the population, which is almost the same as in Western populations (0.5–1.0 %) [1, 2]. Inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), as well as proteinases such as matrix metalloproteinases, are abundantly expressed in synovial tissues of RA patients and are involved in joint destruction [3]. In severe RA, persistent inflammation leads to generalized osteoporosis as well as local osteoporosis, which increases the risk of fragility fractures.

In RA, functional disability is a major concern because it not only restricts a patient's activities of daily living but also reduces work capability, resulting in a substantial economic burden [4–6]. There are several studies concerning risk factors associated with the functional status of RA patients [7–11]. However, there are few studies assessing the relationship

between fractures and functional status of RA patients. We investigated the influence of vertebral fractures (VFs) on the functional status of postmenopausal RA patients, and determined the risk factors for occurrence of VF.

Materials and methods

Patients

The subjects were selected from a single hospital registry of RA patients (National Hospital Organization Sagamihara Hospital). Two hundred postmenopausal RA patients who had complete records of demographic characteristics, clinical data such as disease activity score in 28 joints (DAS-28) and modified health assessment questionnaire (mHAQ), bone mineral density (BMD), and spine radiographs were eligible for this study. All patients fulfilled the American College of Rheumatology 1987 revised classification criteria for RA. The data were collected at baseline and at the final visit (a mean of 2.9 years after the first visit). All patients gave written informed consent, and the study was approved by the local ethics committee of Sagamihara Hospital.

Assessment of VFs in thoracic and lumbar spine

Lateral view radiographs of thoracic and lumbar spine were obtained from all the patients. VFs were diagnosed using the criteria of the Japanese Society for Bone and Mineral Research: the ratio of vertebral height at the mid and the anterior (or posterior) region was less than 0.8, and/or the ratio of the vertebral height at the anterior and posterior region was less than 0.75. New VFs (NVFs) were defined as follows: the vertebral height at the final assessment decreased by over 15 % or 4 mm compared with baseline. The films were independently investigated and assessed by three expert clinicians (H.F., J.T., and N.J.).

Information on the existence of back pain was also obtained from all patients. Clinical (symptomatic) VF was defined as VF with back pain, and asymptomatic VF as VF without back pain.

Measurements of bone mineral density

BMD measurements of the hip (femoral neck) and the lumbar spine (L1–4, anterior–posterior) were performed by trained technicians using dual-energy x-ray absorptiometry (QDR-4500, Hologic Co., Japan).

Data collection

Data were collected twice at a mean ± standard deviation (SD) interval of 2.9 ± 0.52 years. Baseline data were obtained from 2002 to 2005, and the final assessment was performed from 2005 to 2008. Clinical data included disease duration, age at menopause, length of time after the menopause, prescribed daily dose of prednisolone (PSL), use of bisphosphonates (etidronate disodium, alendronate or risedronate), calcium, and active vitamin D_3 (alfacalcidol or calcitriol). Rheumatology experts examined the tender joint count (28 joints), the swollen joint count (28 joints), and existence of joint replacement (total hip or knee joint replacement), and the patient's and investigator's global assessments of disease activity were measured on a 100-mm visual analog scale. DAS was computed using the 28-joint count. Self-reported physical disability was assessed by mHAQ score.

Statistical analysis

Demographic characteristics, clinical data, and BMD measurements were compared between NVF(−) and NVF(+) groups at baseline using 2-sided t-tests for continuous variables and chi-squared tests for categorical variables. The possible predictors of NVF were subsequently entered into a logistic regression analysis. The inclusion criteria for independent variables in the logistic regression analysis were those variables with a p value <0.10 in the univariate analysis to identify the variables that might be associated with NVF. Statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). To assess which factor was statistically significant, the residuals which represented the difference between the observed value of the variables and the predicted value were analyzed.

Results

Baseline characteristics

Table 1 presents the demographic and clinical characteristics of 200 patients at baseline. The mean age of the patients was 61.5 ± 6.5 years, disease duration was 15.0 ± 10.1 years, and postmenopausal period was 12.1 ± 7.3 years. The proportion of rheumatoid factor-positive patients was 73.0 %. The classification and the stage of RA were as follows: Steinbrocker's classification, class 1, 60 patients (30.0 %); class 2, 117 patients (58.5 %); class 3, 23 patients (11.5 %), and class 4, no patient (0.0 %); Steinbrocker's stage 1, 37 patients (18.5 %); stage 2, 38 patients (19.0 %); stage 3, 37 patients (18.5 %), and stage 4, 88 patients (44 %). Mean mHAQ score was 0.55 ± 0.53 and mean DAS-28 score was 3.82 ± 1.08. Fifty-three patients (26.5 %) had low disease activity (DAS-28 ≤3.2), 124 patients (62.0 %) had

Table 1 Demographic and clinical variables of 200 postmenopausal rheumatoid arthritis patients

Baseline variables	All patients ($N = 200$)	NVF(−) ($N = 172$)	NVF(+) ($N = 28$)	p
Age (years)	61.5 ± 6.5	61.3 ± 6.6	62.4 ± 5.9	0.397
Height (cm)	151.8 ± 5.6	152.1 ± 5.5	150.2 ± 6.3	0.100
Weight (kg)	51.9 ± 8.1	51.7 ± 7.8	53.0 ± 10.0	0.429
BMI (kg/m^2)	22.5 ± 3.5	22.4 ± 3.4	23.5 ± 4.1	0.123
Disease duration (years)	15.0 ± 10.1	14.5 ± 9.9	18.0 ± 11.2	0.090
Postmenopausal duration (years)	12.1 ± 7.3	11.9 ± 7.3	13.4 ± 7.6	0.315
Rheumatoid factor positive (%)	73.0	71.5	82.1	0.240
Corticosteroid user (%)	70.5	68.0	85.7	0.057
Corticosteroid dose (mg/day)[a]	3.1 ± 2.5	2.9 ± 2.5	4.2 ± 2.5	0.011
Bisphosphonate user (%)	51.0	53.5	35.7	0.081
Calcium user (%)	60.0	62.8	42.9	0.059
Active vitamin D$_3$ user (%)	63.5	66.3	47.4	0.061
Modified HAQ score	0.55 ± 0.53	0.52 ± 0.53	0.73 ± 0.53	0.049
DAS-28[b]	3.82 ± 1.08	3.75 ± 1.09	4.23 ± 0.96	0.029
Global assessment score	3.5 ± 2.4	3.4 ± 2.4	4.2 ± 2.4	0.124
Tender joint count, 28 joints	2.6 ± 3.7	2.5 ± 3.4	3.5 ± 5.0	0.185
Swollen joint count, 28 joints	2.0 ± 2.5	1.8 ± 2.2	3.1 ± 3.8	0.091
CRP (mg/dl)	0.87 ± 1.14	0.83 ± 1.07	1.15 ± 1.48	0.165
ESR (mm/h)	39.6 ± 21.1	39.1 ± 20.3	42.8 ± 25.6	0.396
Serum BAP (U/l)	26.5 ± 10.5	26.2 ± 10.7	28.2 ± 8.7	0.350
Urine NTx (nmol BCE/mmol Cr)	49.0 ± 26.1	48.5 ± 26.7	52.1 ± 22.2	0.490
Joint replacement (%)[c]	16.0	14.5	25.0	0.166
Baseline vertebral fracture (%)	18.0	15.7	32.1	0.036
BMD at lumbar spine (g/cm^2)	0.787 ± 0.152	0.795 ± 0.147	0.737 ± 0.175	0.065
BMD at femoral neck (g/cm^2)	0.576 ± 0.137	0.583 ± 0.137	0.529 ± 0.129	0.050
PR at lumbar spine (%)	77.8 ± 15.1	78.6 ± 14.6	72.9 ± 17.3	0.066
PR at femoral neck (%)	73.1 ± 17.4	74.1 ± 17.4	67.3 ± 16.4	0.053
T-score at lumbar spine	-2.02 ± 1.38	-1.95 ± 1.33	-2.46 ± 1.58	0.070
T-score at femoral neck	-1.95 ± 1.23	-1.89 ± 1.23	-2.37 ± 1.18	0.055

Data of patients with ($N = 28$) and without ($N = 172$) new vertebral fractures (NVF) were compared

Data are expressed as mean $\pm$ standard deviation, N (%)

BMI body mass index, *HAQ* health assessment questionnaire, *DAS* disease activity score, *CRP* C reactive protein, *ESR* erythrocyte sedimentation rate, *BAP* bone alkaline phosphatase, *NTx* type I collagen cross-linked N-telopeptides, *BMD* bone mineral density, *PR* peak reference

[a] Doses are equivalent to prednisolone

[b] DAS computed using 28-joint counts

[c] Proportion of patients who underwent total knee or hip replacement surgery

moderate disease activity ($3.2 < $ DAS-28 ≤ 5.1), and 23 patients (11.5 %) had high disease activity (DAS-28 >5.1). The number of patients who had joint replacement surgery in the lower extremities (total hip or knee joint replacement) was 32 (16.0 %).

Mean BMD was 0.787 ± 0.152 g/cm^2 at the lumbar spine, and 0.576 ± 0.137 g/cm^2 at the femoral neck. Osteoporosis, defined as a T-score ≤ -2.5 SD, was identified at the lumbar spine in 40.5 % of patients and at the femoral neck in 32.5 %. A previous VF was detected in 36 patients (18.0 %) at baseline.

New vertebral fractures

Twenty-eight patients (14 %) had NVFs during the observation period, and the prevalence of VF at the final visit was 27.5 % (55 patients) (Table 1). Of the 28 patients with NVF, 17 patients had one fracture, and 11 patients had two or more fractures. In total, 47 of 3,400 vertebrae (1.4 %) were fractured, 16 (34.0 %) being thoracic fractures and 31 (66.0 %) lumbar fractures. The annual incidence of NVF was 4.8 per 100 patients. Thirteen of 28 (46.4 %) NVF patients had asymptomatic NVF, while 15
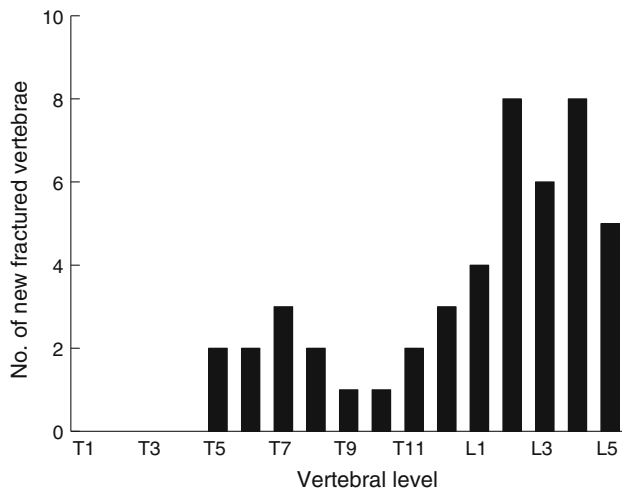
Fig. 1 Distribution of new vertebral fractures identified by lateral radiography in postmenopausal rheumatoid arthritis patients

patients (53.6 %) had clinical (symptomatic) NVF. Thirty-nine of 55 (70.9 %) VF patients at the final assessment had asymptomatic VF, while 16 patients (29.1 %) had clinical VF ($p < 0.001$). In patients treated with PSL ≥ 5 mg/day, the prevalence of asymptomatic VF was significantly higher than in those with symptomatic VF (30.7 and 8.0 %, respectively, $p < 0.001$). Fractures were most commonly identified in the mid-thoracic and the thoracolumbar regions, and the distribution of fractured vertebrae was similar to that reported in osteoporosis patients (Fig. 1).

The baseline characteristics were compared between NVF(−) and (+) groups (Table 1). There were no statistically significant differences in age, height, weight, BMI, disease duration, postmenopausal duration, rheumatoid factor positivity, proportion of PSL users, proportion of bisphosphonate users, calcium users, active vitamin D_3 (alphacalcidol) users, C-reactive protein level, erythrocyte sedimentation rate, serum bone alkaline phosphatase, urine type I collagen cross-linked N-telopeptides, and the proportion of patients who underwent joint replacement surgery. Significant differences were observed in the daily dose of PSL, mHAQ scores, DAS-28 scores, and prevalent VF. The mean daily doses of PSL were 2.9 ± 2.5 and 4.2 ± 2.5 mg/day, mHAQ scores were 0.52 ± 0.53 and 0.73 ± 0.53, and DAS-28 scores were 3.75 ± 1.09 and 4.23 ± 0.96 in the NVF(−) and (+) groups, respectively. The prevalence of VF at baseline was 15.7 and 32.1 %, respectively. Mean final DAS-28 score was 3.6 ± 1.1 and 4.2 ± 1.2 ($p < 0.05$), and final BMD at the femoral neck was 0.573 ± 0.124 and 0.500 ± 0.111 ($p < 0.01$) in the NVF(−) and (+) groups, respectively.

Logistic regression analysis adjusted for age, BMI, and disease duration using variables whose p-value was less than 0.10 by univariate analysis revealed that dose of PSL

Table 2 Logistic regression analysis of risk factors for new vertebral fractures

Variables	Regression coefficient	SE	OR	95 % CI	p
PSL (mg/day)	0.24	0.10	1.27	1.05–1.54*	0.013
DAS-28[a]	0.37	0.21	1.45	0.96–2.18	0.075
BMD, PR at femoral neck (%)	−0.06	0.02	0.94	0.91–0.97*	0.001
Active vitamin D_3 use	−1.07	0.49	0.34	0.13–0.89*	0.028
Bisphosphonate use	−1.18	0.50	0.31	0.12–0.82*	0.019

Multivariate adjusted odds ratio and 95 % confidence intervals and p values for the association are shown

Logistic regression (stepwise) analysis ($N = 200$). Statistical analysis was performed using the variables whose p value was <0.10 in the univariate analysis, and adjusted for age, BMI, and disease duration. * at 95 % CI means $p < 0.05$ in the logistic analysis

*SE* standard error, *OR* odds ratio, *CI* confidence interval, *PSL* prednisolone

[a] DAS computed using 28-joint counts

(mg/day), femoral neck BMD, use of vitamin D_3, and use of a bisphosphonate at baseline were factors associated with NVF, with odds ratios (95 % confidence interval) of 1.27 (1.05–1.54), 0.94 (0.91–0.97), 0.34 (0.13–0.89), and 0.31 (0.12–0.82), respectively (Table 2). Patients with higher DAS-28 score had a greater tendency to suffer NVF, with no statistical significance (odds ratio 1.45, $p = 0.075$).

When the patients were subdivided into four groups based on the use of PSL and on DAS-28, the incidence of NVF was lowest in patients with low disease activity (DAS-28 <4.0) and receiving lower doses of PSL (<5 mg/day) ($p < 0.01$), while the incidence in patients with lower disease activity (DAS-28 <4.0) receiving higher doses of PSL (≥ 5 mg/day) was the highest of all the groups ($p < 0.05$). There was no significant difference in the incidence of NVF between patients with high disease activity (DAS-28 ≥ 4.0) receiving higher doses of PSL (≥ 5 mg/day) and those receiving lower doses of PSL (<5 mg/day) ($p = 0.426$) (Fig. 2).

Influence of NVFs on functional status

Mean mHAQ scores of NVF(−) and NVF(+) groups at the final assessment were 0.54 ± 0.56 and 0.88 ± 0.56, respectively, with a significant difference ($p = 0.003$). Patients with NVF at L3–5 exhibited significantly poorer final mHAQ scores than NVF(−) patients ($p < 0.05$) (Fig. 3a). Patients with NVF also exhibited a greater increase in mHAQ score from baseline compared with those without NVF ($p < 0.05$) (Fig. 3b). We also examined
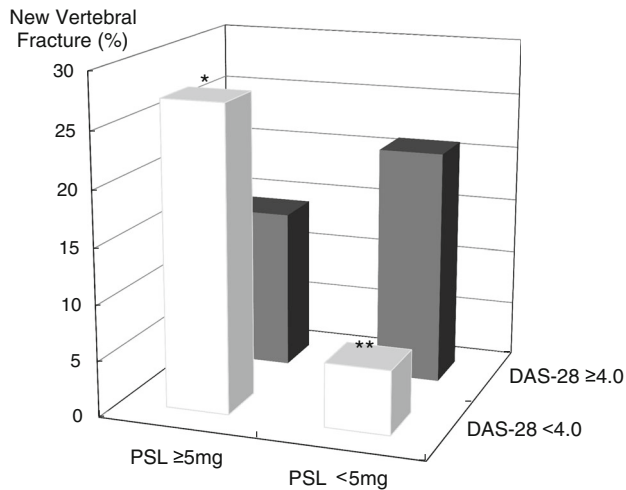
Fig. 2 Comparison of the incidence of new vertebral fractures between subgroups divided by the baseline dose of prednisolone (≥5.0 and <5.0 mg/day) and the DAS-28 score (≥4.0 and <4.0). * and **, significantly different between all groups (residual analysis); *$p < 0.05$, **$p < 0.01$

the influence of NVF in patients without baseline VF, and found that the mHAQ scores in these patients were significantly higher than in NVF(−) patients with no baseline VF (0.86 ± 0.63 and 0.48 ± 0.53, respectively, $p < 0.01$).

The mean mHAQ score in the group with NVF at the L3–5 level (without baseline VF) was significantly higher than in the group with no NVF (0.90 ± 0.69 and 0.48 ± 0.53, respectively, $p < 0.05$). The mean final mHAQ score in the clinical NVF(+) group was significantly higher than in the NVF(−) group (0.91 ± 0.69 and 0.54 ± 0.56, respectively, $p < 0.05$), while the mean mHAQ score (0.79 ± 0.42) in patients with asymptomatic NVF(+) was higher than in the NVF(−) group, with no significant difference (Fig. 3c).

Discussion

Several studies have reported that the risk of VF in RA patients is higher than that in primary osteoporosis patients. The prevalence of VF was reported as 15–36 %, and the annual incidence of NVF was around 4.0 per 100 patients [12–19]. Spector et al. [20] reported that the rate of VF in women with RA was over twice that of controls. Arai et al. [21] reported that the prevalence of VF in Japanese RA patients was 21 %, while that in age-matched healthy women was 5 %. We found that 14 % of the postmenopausal RA patients in our study developed NVF during 2.9 years (mean) of observation, and the prevalence of VFs was 27.5 % in total, which confirmed the high risk of VFs in RA patients, although we did not compare the prevalence with control patients.
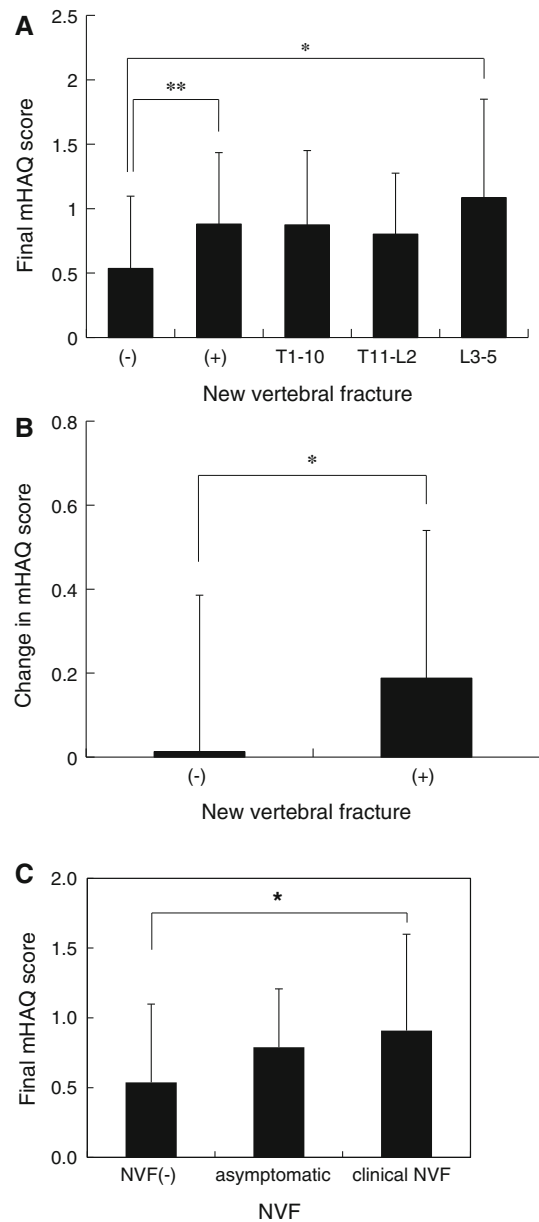
Fig. 3 Impact of vertebral fractures on mHAQ scores. **a** Effect of a new vertebral fracture on final mHAQ score. **b** Effect of a new vertebral fracture on the change in mHAQ score from baseline. **c** Effect of asymptomatic and clinical new vertebral fractures on mHAQ score. * and **, significantly different; *$p < 0.05$, **$p < 0.01$

Although a statistically significant difference was not found for disease activity in the logistic regression analysis, there was a tendency for DAS-28 to be higher in the NVF(+) group, and this also affected the incidence of NVF associated with BMD (existence of osteoporosis). El Maghraoui et al. [13] also reported that the prevalence of VF was increased in patients with higher DAS score. Dirven et al. [12] reported that disease activity over time was higher in patients with VFs. This may be because high levels of proinflammatory cytokines such as TNF-α and IL-6 in RA patients with high

disease activity may lead to deleterious bone quality, resulting in greater susceptibility to VF.

In contrast to previous studies, age was not significantly associated with NVF incidence. When patients were categorized into three age groups (≤ 59, 60–69, and ≥ 70 years old), the percentage of bisphosphonate users was highest in the ≥ 70-year-old group (46.9, 56.8, and 70.8 %, respectively), which may affect the incidence of NVF.

Although PSL use is a risk factor for NVF, the occurrence of NVF in patients with high disease activity (DAS-28 ≥ 4.0) was lower in PSL ≥ 5 mg treatment group than in PSL <5 mg treatment group, although there was no significant difference (Fig. 2). We speculated that, in spite of its deleterious effects on bone, PSL use has some beneficial effects on preventing VFs in these patients by controlling disease activity. Consistent with our results, Ghazi et al. reported that the prevalence of VF was inversely related to the use of steroids, and Dirven et al. reported that there was no association between VFs and steroid use [12, 17, 21–23].

The efficacy of drug treatment against VF has been well established in osteoporosis patients [24–29]. Although we did not find a significant difference in the occurrence of NVF between the groups with or without bisphosphonate treatment in our study (9.8 and 18.4 %, respectively, $p = 0.08$), there was a tendency for patients using bisphosphonates, in particular alendronate and risedronate, to suffer NVF less frequently than those without bisphosphonate treatment (data not shown). However, the sample size in each category was too small to draw a definite conclusion. In addition, the duration of bisphosphonate treatment was not recorded.

Importantly, the patients with NVF exhibited significantly worse final mHAQ scores and a greater increase in mHAQ compared with those without NVF, indicating that NVFs decrease the functional status of RA patients. Furthermore, we found that a NVF without a baseline VF affected patient functional status similar to a NVF with a previous VF.

There are few studies that have investigated the relationship between VF and functional status of RA patients. Dirven et al. reported that functional ability over time was worse in patients with VFs than in patients without VFs, but they did not examine VFs at baseline. Furuya et al. [30] demonstrated that the risk of VF increased by 2.42 for each 1-point increase in Japanese HAQ scores, which is consistent with our results. These results clearly demonstrate the importance of VF prevention in maintaining good functional status in RA patients. Our data also suggest that fracture of the lower lumbar spine had a greater impact on health-related quality of life (QOL). Previous studies in the general population which investigated the association between the site of vertebral deformity and QOL reported similar results [31–33].

The incidence of asymptomatic VF was significantly higher than that of clinical, symptomatic VF in patients treated with PSL. This result is consistent with a previous study [14]. Functional status was poorer in patients with clinical VF or asymptomatic VF than in patients without VF, but clinical VF affected the mHAQ score more than asymptomatic VF. Because the difference was found in the analysis of both NVF and total VF, it is likely that the clinical symptom itself also contributes to a decrease in functional status.

There are several limitations to our study. First, this was a retrospective cohort study performed in one hospital. In addition, only 200 patients in the registry were eligible for the study, mainly because of the incompleteness of the data. In this study we analyzed NVF regardless of the existence of baseline VF because we thought it clinically essential to include data of previous VF in the investigation of incidental NVF. In addition, a larger number of patients is needed to perform additional sub-analysis. Furthermore, the duration of bisphosphonate treatment was not recorded, as mentioned above. Future prospective studies with more systematic data collection are required to draw definite conclusions.

In conclusion, we demonstrated that the incidence of NVF was a risk factor for worsening functional status in postmenopausal patients with RA. In addition, the dose of PSL, BMD, active vitamin D_3 use, and bisphosphonate use were strongly associated with the occurrence of NVF. Disease activity was also an important factor. To maintain a good QOL in RA patients, it is essential to prevent VFs by treating osteoporosis as well as reducing RA disease activity.

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