

## Characteristics of fracture and related factors in patients with rheumatoid arthritis

Akihide Nampei · Jun Hashimoto · Junichiro Koyanagi · Takeshi Ono ·  
Hideo Hashimoto · Noriyuki Tsumaki · Tetsuya Tomita · Kazuomi Sugamoto ·  
Norihiro Nishimoto · Takahiro Ochi · Hideki Yoshikawa

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**Abstract** To examine the clinical features of vertebral and non-vertebral fractures in patients with rheumatoid arthritis (RA), including insufficiency fractures, and to assess the risk factors for fracture, we prospectively studied 209 outpatients with rheumatoid arthritis for 1 year. The age, gender, Steinbrocker's functional class, glucocorticoid use, history of lower limb surgery, serum C-reactive protein (CRP), and use of bisphosphonates were evaluated. Examination for fractures was performed by radiography, computed tomography (CT), magnetic resonance imaging (MRI), and bone scanning. Thirty-three fractures occurred in 24 patients over the 1-year study period, and the incidence was 15.8 fractures per 100 patient-years. Fractures occurred at various sites. The majority (70%) was insufficiency fracture, and more than 50% caused ambulatory dysfunction. Radiographic findings were absent in 39% of the fractures at the onset of pain. The functional class and glucocorticoid dose were significantly associated with fracture development. This prospective study showed that the incidence of fractures, especially insufficiency fractures, was very high in patients with rheumatoid arthritis

and that most of their fractures caused gait disturbance. Early intervention to prevent secondary osteoporosis is recommended to maintain the quality of life in patients with rheumatoid arthritis, especially those with functional impairment or undergoing glucocorticoid therapy.

**Keywords** Fracture · Incidence · Insufficiency fracture · Rheumatoid arthritis · Risk factor

### Introduction

Patients with rheumatoid arthritis (RA) have a greater risk of osteoporosis and fracture than the general population, because of impaired walking ability, inflammation due to their disease, and glucocorticoid use. Fractures influence the morbidity and mortality of patients with primary osteoporosis, and some reports have demonstrated that the risk of vertebral or hip fractures is higher in patients with RA than in those with primary osteoporosis [1–5]. Several previous studies have revealed that many osteoporotic fractures occur at sites other than the spine and proximal femur in patients with RA [6–10]. Although those studies assessed the incidence of fractures, including fractures other than those of the spine and hips, most of them were performed retrospectively. On the other hand, several reports have emphasized the occurrence of pelvic or juxta-articular insufficiency fractures in patients with RA [11–15], but no study has yet clarified the incidence of insufficiency fracture in this disease. Insufficiency fractures are difficult to detect clinically without careful examination and appropriate radiological investigation based on a suspected diagnosis [16], making a retrospective study design not adequate to evaluate the occurrence of such fractures. Recently, a large-scale, population-based, cohort study

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A. Nampei · J. Hashimoto (✉) · J. Koyanagi · T. Ono ·  
H. Hashimoto · N. Tsumaki · T. Tomita · K. Sugamoto ·  
H. Yoshikawa  
Department of Orthopaedics, Osaka University Graduate School  
of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan  
e-mail: junha@ort.med.osaka-u.ac.jp

N. Nishimoto  
Laboratory of Immune Regulation, Osaka University Graduate  
School of Frontier Bioscience, 1-3 Yamadaoka, Suita 565-0871,  
Japan

T. Ochi  
Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka  
543-0035, Japan

performed in the UK [9] and a large-scale, prospective, observational study performed in Japan [10] were reported, but those studies were based on medical records and self-reporting by questionnaire, in which insufficiency fractures might also have been overlooked. A prospective study design and detection of fractures through careful clinical assessment by orthopaedic surgeons are recommended to clarify the actual characteristics of fractures affecting RA patients.

Therefore, we conducted a prospective study to investigate the actual incidence of fracture for all skeletal sites, including insufficiency fractures, and to assess the clinical presentation and risk factors for fracture in RA patients.

## Materials and methods

### Patients and study protocol

This prospective study enrolled subjects undergoing regular outpatient review at intervals of less than 3 months to avoid missing fractures. A total of 209 outpatients (31 men and 178 women) with RA according to the American College of Rheumatology 1987 revised classification criteria [17] were entered into the study at Osaka University

Hospital. The prospective follow-up period was 1 year from October 2003 to September 2004. The baseline characteristics of the patients are shown in Table 1 and include age, gender, duration of RA, serum C-reactive protein (CRP) level for assessment of disease activity, functional class (Steinbrocker's criteria [18]), surgical treatment of gait disturbance, glucocorticoid use (daily dose and duration), and bisphosphonate therapy for more than 2 years. Surgery for gait disturbance included total hip arthroplasty in 28 patients (nine bilateral), total knee arthroplasty in 64 patients (41 bilateral), total ankle arthroplasty in eight patients (two bilateral), hindfoot surgery in 14 patients (five bilateral), and forefoot surgery in 34 patients (14 bilateral). Ninety-two patients underwent lower limb surgery, and 61 patients had more than two operations. The sites of fracture, incidence of fracture, circumstances under which fractures occurred, and radiographic findings were evaluated. When more than two vertebral fractures occurred on one occasion, they were counted as one fracture. Circumstances were classified as no trauma (insufficiency fracture), minor trauma (such as a fall), or major trauma (such as a traffic accident). Insufficiency fracture was defined as fracture occurring in abnormal bone already weakened by decreased mineralization and with insufficient elastic resistance [16, 19].

**Table 1** Baseline characteristics of 209 patients with RA

Variables	Value	Number of patients
Age (years) (mean $\pm$ SD)	60.4 $\pm$ 11.5	
Gender		
Male (%)	14.8	31
Female (%)	85.2	178
Disease duration (years) (mean $\pm$ SD)	14.5 $\pm$ 10.2	
Disease activity (CRP) (mean $\pm$ SD)	2.0 $\pm$ 2.4	
Functional class		
I (%)	43.5	91
II (%)	41.6	87
III (%)	14.8	31
IV (%)	0	0
Surgical treatment of lower legs (%)	45.9	96
Glucocorticoid use		
Current users (%)	74.2	155
Daily dose (mg/day) (mean $\pm$ SD)	5.94 $\pm$ 3.45	
Duration (years)		
None (%)	23.4	49
0–2 years (%)	14.8	31
2–5 years (%)	19.6	41
5–10 years (%)	29.2	61
10 years $\leq$ (%)	12.9	27
Bisphosphonate use		
None or $\leq$ 2 years (%)	77.5	162
> 2 years (%)	22.5	47

RA rheumatoid arthritis, CRP C-reactive protein  
Functional classes according to Steinbrocker criteria

Fractures that occurred during normal daily activities without any trauma were considered to be insufficiency fractures.

### Diagnosis of fracture

When patients presented to the hospital with pain, a single orthopaedic surgeon (J.H.) examined them for fractures. Detection of fractures was initially performed by careful clinical examination and plain radiography. In the absence of radiographic findings, magnetic resonance imaging (MRI), computed tomography (CT), bone scanning, and longitudinal radiographic changes were used for diagnosis.

### Statistical analysis

Risk factors associated with the occurrence of fracture were evaluated. Those shown in Table 1 were assessed by univariate analysis using SPSS version 11.5 J software (SPSS Inc., Chicago, IL, USA), and the odds ratios and 95% confidence intervals (CI) were calculated. Subsequently, multivariate logistic regression analysis was performed for the factors that were significant according to univariate analysis. The level of significance was set at  $P < 0.05$  for all tests.

## Results

### Incidence and characteristics of fractures

We detected 33 fractures in 24 patients during the 1 year follow-up period. The incidence of fractures was 15.8 per 100 patient-years, and the incidence of patients with new fractures was 11.5 per 100 patient-years. Fractures occurred at various sites, including the rib, vertebra, pelvis, humerus, elbow, femur, knee, and foot (Table 2). All fractures affecting the pelvis and lower extremities, as well as one of four fractures involving the lumbar spine, resulted in ambulatory dysfunction (54.5%). The fracture occurred with no trauma (insufficiency fracture) in 23 cases (69.7%), and with minor trauma (fall) in ten cases (30.3%). There were no fractures due to major trauma (Table 2). Twenty fractures (60.6%) could be diagnosed by plain radiography at the onset of pain, while 13 fractures (39.4%) could not be detected on plain radiographs at that time (Table 2). MRI, CT, bone scanning, and longitudinal radiography were able to detect these 13 fractures. Among the 24 patients suffering fractures, nine had not received any prior surgical treatment, 15 had undergone lower limb surgery (two had total hip arthroplasty, nine had total knee arthroplasty, one had total ankle arthroplasty, four had

**Table 2** Fracture sites, circumstances, and radiographic change at onset of pain

Fracture site	Total number	Circumstance		Radiographic change	
		Minor trauma	Insufficiency fracture	Present	Absent
Ribs	2	0	2	2	0
Shoulder	4	4	0	4	0
Elbow	1	1	0	1	0
Spine	9	1	8	7	2
Sacrum	3	0	3	0	3
Pubis	5	0	5	2	3
Ilium	1	1	0	0	1
Hip	1	1	0	0	1
Femur	2	2	0	2	0
Knee	3	0	3	0	3
Foot, ankle	2	0	2	2	0
Total	33	10	23	20	13

hindfoot surgery, and seven had forefoot surgery), and eight patients had undergone more than two lower limb operations.

### Risk factors for fracture

Univariate analysis comparing patients with and without fractures was performed as an aid to selecting variables for inclusion in subsequent multivariate analysis. Among the variables investigated, functional class and glucocorticoid use (daily dose and duration) showed a significant difference ( $P < 0.05$ ), while age and lower limb surgery showed borderline significance ( $P < 0.1$ ) (Table 3). Variables that showed  $P < 0.1$  on univariate analysis were included in the subsequent multivariate analysis. The results of multivariate logistic regression analysis showed that daily glucocorticoid use and functional class were significantly associated with the risk of fracture in RA patients (Table 3). Using the same process, we found that the only significant risk factor for vertebral fractures was the daily glucocorticoid dose according to multivariate analysis (Table 3). On the other hand, analysis of the risk factors for pelvis/lower limb fractures revealed that only functional class was a significant predictor by multivariate analysis (Table 3). No risk factor was significantly correlated with fracture of the upper limbs (data not shown). Figure 1 shows the incidence of fractures stratified according to functional impairment. The incidence of all fractures tended to increase as the functional status deteriorated. Fractures of the upper limbs occurred in only stage I and

**Table 3** Possible risk factors for fracture in RA patients

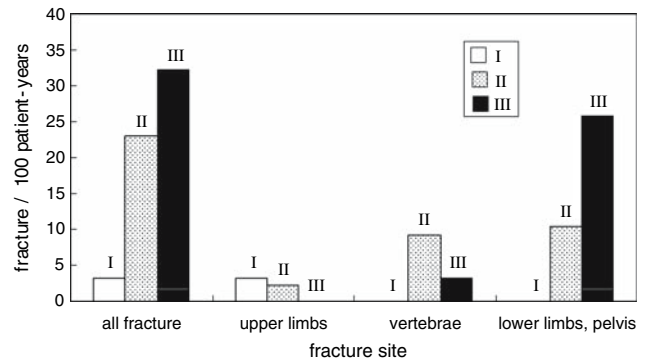
Variables	P	Odds ratio	95% CI
<b>All fractures</b>			
Univariate logistic regression			
Age	0.057	1.040/year	0.999–1.084
Functional class	0.001	2.963/ class	1.598–5.496
Glucocorticoid use			
Daily dose	0.003	1.174/mg	1.054–1.306
Duration	0.019	1.095/year	1.015–1.181
Surgical treatment of lower legs	0.089	2.140/site	0.891–5.138
Multivariate logistic regression			
Functional class	0.020	2.277/ class	1.136–4.562
Glucocorticoid use			
Daily dose	0.034	1.141/mg	1.010–1.290
<b>Vertebral fractures</b>			
Univariate logistic regression			
Age	0.056	1.084/year	0.998–1.177
Glucocorticoid use			
Daily use	0.034	1.212/mg	1.014–1.449
Multivariate logistic regression			
Glucocorticoid use			
Daily use	0.032	1.232/mg	1.018–1.492
<b>Fractures of pelvis and lower legs</b>			
Univariate logistic regression			
Functional class	0.001>	4.987/ class	2.032–12.237
Glucocorticoid use			
Daily use	0.010	1.195/mg	1.043–1.370
Duration	0.008	1.131/year	1.033–1.239
Surgical treatment of lower legs	0.093	2.819/site	0.840–9.463
Multivariate logistic regression			
Functional class	0.007	3.924/ class	1.462–10.535

CI confidence interval

stage II patients, while fractures of the pelvis/lower limbs and vertebra occurred in stage II and stage III patients. The incidence of pelvic/lower limb fractures increased along with functional deterioration.

**Discussion**

We performed our prospective study of 209 outpatients with RA to investigate the characteristics of fractures in this disease. We found that the incidence of fracture, including non-vertebral and insufficiency fractures, was very high in RA, being 15.8 fractures per 100 patient-years and 11.5 patients per 100 patient-years. These incidence



**Fig. 1** Fracture incidence stratified by functional impairment. The incidence of all fractures increased along with the severity of functional impairment. Upper limb fractures tended to occur in relatively mild RA, but the association was not significant, and vertebral fractures were not associated with functional status. On the other hand, fractures of the lower limbs and pelvis were significantly more common as the functional status deteriorated. I, II, and III refer to Steinbrocker’s functional classes

rates were higher than those reported previously, which were 1.57 fractures per 100 patient-years [7], 1.62 fractures per 100 patient-years (non-vertebral fractures) [8], 1.07 fractures per 100 patient-years [9], 1.68 fractures per 100 patient-years [10], and 3.59 fractures per 100 patient-years [20]. However, all of those previous studies were retrospective and depended on medical records, radiology reports, telephone interviews, or questionnaires. In our prospective study, fracture diagnosis was made by careful assessment of symptoms and signs by a single experienced rheumasurgeon along with adequate diagnostic imaging, because insufficiency fractures or juxta-articular fractures are difficult to detect in RA patients without careful examination and appropriate radiological investigation based on a high index of suspicion [16]. Thus, misdiagnosis and failure to detect insufficiency fractures or juxta-articular fractures were thought to be minimized in our study. This difference in methodology probably explains a large part of the difference in the incidence of fractures between our study and previous studies.

Another possible reason for the discrepancy may be differences in the background factors of the subjects. Our patients all had relatively severe RA and regularly attended a university hospital; 74.2% used oral corticosteroids, and approximately half of them had undergone major surgery on the lower limbs (total hip arthroplasty and/or total knee arthroplasty). Steroid use was varied in previous studies (58% [7], 47.8% [8], 25% [9], 61% [10]), but was lower than in our series, and it has been reported that 71% of patients who develop fractures have taken steroids [20]. In the most recent study [10], 22.5% of patients had a history of orthopedic surgery and 8.9% had a history of total knee arthroplasty, while 44% of our patients had received lower

limb surgery (excluding those with upper limb or spinal surgery) and 30.6% had undergone total knee replacement. Differences in the severity of RA, and different levels of corticosteroid use, might have influenced the incidence of fracture, making it inappropriate for our findings to be compared directly with those of other general cohort studies.

Our study showed four characteristic features of fractures occurring in patients with RA. The first was, as previously reported, that fractures may occur at various sites throughout the entire skeleton [6–10], including the ribs, upper and lower limbs, vertebrae, and pelvis, while hip and vertebral fractures predominate in patients with primary osteoporosis. This finding indicates that RA patients may suffer from both generalized osteoporosis and juxta-articular osteoporosis. The second point was that insufficiency fractures, which are caused by normal physiological stress, are the most common type of fracture (69.7%) in patients with RA. It has been reported that RA is one of the most common underlying diseases in patients with insufficiency fracture [11–15], and there have been many case reports of insufficiency fractures in RA patients [21–23], but the frequency of these fractures has been unclear. In our study, misdiagnosis and the overlooking of insufficiency fractures or juxta-articular fractures were presumably minimized. The third point was that fractures undetectable by plain radiography at the onset of pain are very common (39.4%). Among the insufficiency fractures, 47.8% could not be seen on the first plain radiograph obtained at the onset of pain (data not shown). Fractures of the upper extremity were caused by trauma and were radiologically apparent. Most of the vertebral and pelvic fractures were insufficiency fractures, but the former were relatively apparent on plain radiographs, and the latter were mostly undetectable by radiography. Long-bone fractures of the lower limbs were apparent on plain radiographs, but fractures of the knee and hip joints were frequently undetectable. According to previous reports, pelvic fractures are frequently insufficiency fractures [13, 24–26], with CT and MRI being more reliable methods for diagnosis than plain radiography [19, 26, 27]. Bone scanning is also useful for detection of sacral insufficiency fractures [28]. In our series, CT, MRI, and bone scanning were all useful, especially for pelvic fractures and peri-articular fractures. Thus, it is important to suspect the presence of an insufficiency fracture based on the results of meticulous physical examination, and such fractures will often be undetectable on plain radiographs in patients with RA. The fourth point was that the 54.5% of the fractures resulted in ambulatory dysfunction. This shows that prevention of fractures is important in patients with RA to maintain their mobility, just as prevention of joint destruction by anti-rheumatic therapy is important.

According to prior reports, the risk factors for fracture in RA patients are age, gender, low body mass index (BMI), ambulatory dysfunction, corticosteroid use [6, 7], bone mineral density [8], and joint deformity [15]. Our multivariate analysis showed that daily glucocorticoid use and functional class were significant overall risk factors for fracture in RA patients (Table 3). Analyzing the risk factors by site, we found that daily glucocorticoid use was a significant risk factor for vertebral fractures, but not for pelvic and lower limb fractures. This result is consistent with previous reports that vertebral fractures are significantly associated with daily glucocorticoid use [3, 29]. Our study also showed that functional class was a significant risk factor for pelvic and lower limb fractures, but not for vertebral fractures. Corticosteroid use, severe osteoporosis, and joint deformity have also been reported as risk factors of pelvic and lower limb fractures [15, 30]. Relationships between functional disturbance and hip fracture [31], wrist and hip fractures [32], and any type of fracture [33] have all been reported previously. Our findings did not contradict those previous reports and, additionally, showed that functional impairment is a stronger risk factor than glucocorticoid use for pelvic and lower limb fractures. Figure 1 shows the fracture incidence in relation to Steinbrocker's functional classification. The incidence of all fractures, as well as fractures of the pelvis and lower limbs, increased along with functional impairment. However, the incidence of upper limb and vertebral fractures was not correlated with the functional class. This suggests that greater mechanical stress due to weight bearing or ambulation is quite important to protect the pelvis and lower limbs from bone fragility.

Our study had several limitations. First, our subjects had relatively severe disease, with their physical function being worse than in others and half of them had undergone major lower limb surgery, and the rate of oral glucocorticoid use was high. Also, some possible risk factors for fracture were not evaluated in this study, such as bone mineral density, body mass index, fracture history, other medications for osteoporosis and RA, alcohol, and smoking. Third, we only evaluated painful fractures, without counting asymptomatic fractures (especially vertebral fractures). Since asymptomatic vertebral fractures and deformities are common in patients with primary osteoporosis [29, 34–37] as well as RA [38], our study would have underestimated the total fracture incidence by excluding painless vertebral fractures.

In conclusion, we prospectively investigated the characteristics of fractures, the overall fracture incidence, and risk factors for fracture (including insufficiency fracture) in RA patients over a 1-year period. The incidence of fracture was relatively high, and any site could be affected. In addition, 55% of the fractures caused gait impairment, 70%

were insufficiency fractures, and 39% were not detectable by plain radiography at the onset of pain. Significant risk factors for fracture were functional disability and glucocorticoid use. Early intervention to prevent secondary osteoporosis is important to avoid fractures and maintain the quality of life in patients with RA, especially those with functional impairment or glucocorticoid use.

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