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ORIGINAL ARTICLE

Is Femoral Fracture Healing Really Compromised in Patients with Rheumatoid Arthritis? Comparison Study Between Rheumatoid and Non-rheumatoid Arthritis Patients

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Abstract

Background In patients with rheumatoid arthritis (RA), some problems might occur in fracture healing; however, clinical evidence is limited. Therefore, we compared the time to union and complication rate of femoral fractures between RA and non-RA patients.

Materials and Methods This study included 42 RA patients who underwent osteosynthesis for femoral trochanter or shaft fracture. For comparison with the RA group, 126 non-RA patients were selected as a control group. The RA group was divided into the trochanteric (RA group I) and shaft fracture group (RA group II) for comparison with each control group (control groups I and II). We analyzed risk factors for nonunion or delayed union and divided patients according to whether atypical or ordinary fracture in shaft fracture.

Results Time to union ($p=0.823$) and complication rate ($p=0.440$) did not differ significantly between RA group I and control group I. A significantly longer time to union ($p=0.001$) and higher nonunion rate ($p=0.013$) were observed in RA group II compared with control group II. The presence of RA ($p=0.040$) and atypical femoral fracture ($p=0.006$) were significant risk factors for nonunion or delayed union.

Conclusions The high prevalence of atypical femoral fracture among the femur shaft fractures in the RA patients was considered a significant risk factor for nonunion and delayed union.

Keywords Femur fracture · Atypical femoral fracture · Rheumatoid arthritis · Delayed union · Nonunion

Introduction

Fractures in patients with rheumatoid arthritis (RA) are a challenge for orthopaedic surgeons. Bony abnormalities in RA patients are a focal and generalized disorder affecting cortical and cancellous bone, characterized by loss of bone volume and strength [1]. Compromised bony fixation resulting from osteoporotic bone may complicate fracture treatment. Femoral fractures may be more common in RA patients than in the general population, previous studies reported that femoral fracture in RA patients showed a high complication rate such as nonunion [2, 3]. The intertrochanteric femoral fracture in patients with RA also showed a high rate of nonunion compared to non-rheumatoid patients [2, 3]. These outcomes are supposed to be the result of imbalance between bone resorption and formation by various proinflammatory cytokines in rheumatoid patients, and RA can result in inhibition of the bone remodeling process and increased fracture healing time and the rate of complications, including nonunion [4]. However, other authors have reported that RA did not affect the fracture healing process in RA patients [5]. To date, clinical evidence of fracture healing potential in RA patients is inadequate.

Therefore, the aim of this study was to perform a comparative analysis of femoral fracture healing time and complication rate including delayed union and nonunion between rheumatoid and non-rheumatoid patients, as well as to

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determine the risk factors for delayed union and nonunion in the cohort of rheumatoid patients.

Materials and Methods

This study was conducted as a retrospective case-controlled study after receiving institutional review board approval at our University Hospital and all patients provided informed consent. A total of 33,687 patients were identified by searching for RA codes based on the codes of the International Classification of Diseases, 10th Revision, in the rheumatoid disease database of our institutional specialized rheumatoid center. Among these codes, the long bone fracture code of 255 patients was input at the same time. Of these patients, 120 cases underwent osteosynthesis for long bone fractures, in our institution between January 2004 and January 2013, and patients who underwent osteosynthesis for femur fracture (72 cases) were selected. The exclusion criteria included cases of second operation (6 cases) after first operation at another hospital, periprosthetic fracture (11 cases), and incomplete atypical femoral fracture that had prophylactic nailing (5 cases). In addition, osteosynthesis for femur neck fracture (5 cases) and distal metaphyseal fracture (3 cases) were excluded, because the comparison of these fracture types was considered less meaningful due to a small number of cases (Fig. 1).

Finally, 42 cases, including 20 cases of trochanteric fracture and 22 cases of shaft fracture (from just distal to the lesser trochanter to just proximal to the supracondylar flare), were included. Age, sex, injury mechanism, smoking/nonsmoking, preoperative ambulation status, medical comorbidities, and prescription history were assessed by reviewing the patients' medical records. Non-RA patients who were matched for age, sex, fracture site and type, injury mechanism, and medical comorbidity were matched as a control group for comparison with the RA group. None of the patients had open fractures.

Preoperative ambulation status could be categorized into independent ambulation, ambulation with aids and bedridden state. Independent ambulation was defined as patient not requiring any assistive devices. Ambulator with aids was defined as patient requiring assistive devices (ie, cane, walker). Bed-ridden state defined as patient couldn't mobilize, lying in bed all day [6]. The weight bearing protocol was equally applied to all patients. Non-weight bearing was done for 2 weeks postoperatively. Protective partial weight bearing was allowed from the 3rd week, and full-weight bearing was allowed at 4 weeks postoperatively.

Primary outcome measurement was performed for time to union, for which the sample number required for statistical analysis was calculated based on the preliminary study results performed for this study. The number of samples for the control group required to satisfy the 0.05 significance level and 80% statistical power based on the sample number of the limited experimental group was 3 times greater than that of the experimental group, so that the experimental and control groups required 40 and 120 cases, respectively. Accordingly, 126 non-RA patients were matched as a control group. Among these patients, 60 cases had trochanteric

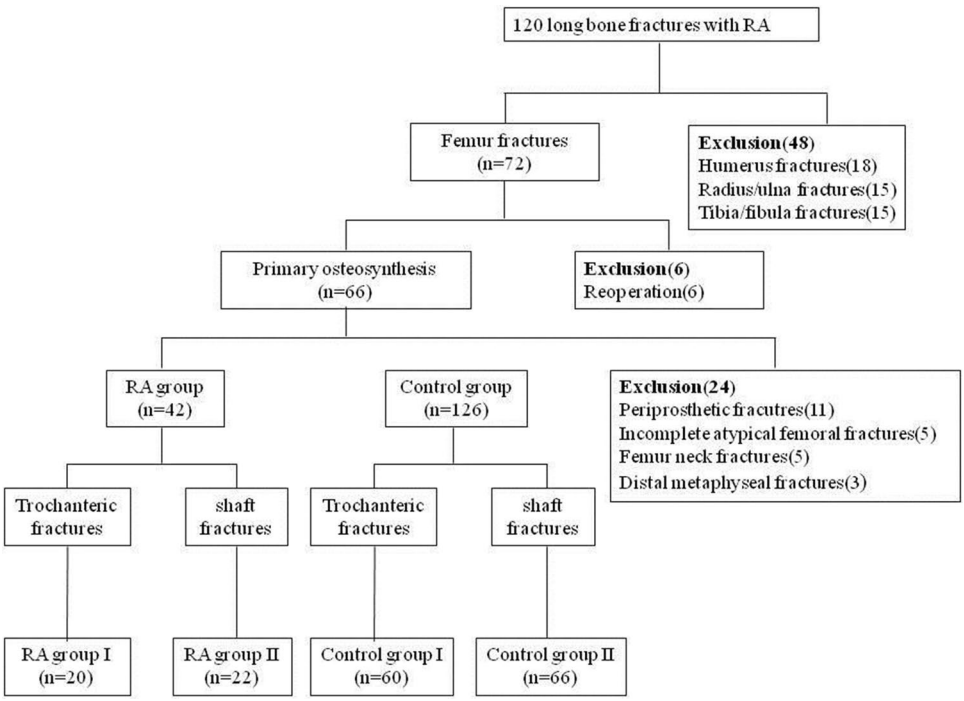

Fig. 1 Patient selection process

fractures and 66 cases had shaft fractures, respectively. The patients' demographic data is summarized in Table 1.

All operations were performed by three surgeons. The operations for trochanteric fracture were performed with closed reduction on a fracture table, with use of a compression hip screw (CHS) or proximal femoral nail. The operations for femoral shaft fracture mainly used an intramedullary nail (IM nail); however, a locking compression plate (LCP) with minimally invasive technique was used in some cases due to a narrow medullary canal. The types of implants used were CHS for 12 and 29 cases, IM nail for 21 and 75 cases, and LCP for 9 and 22 cases in the RA and control groups, respectively).

All patients underwent radiographic and physical examinations until bony union was achieved after the operation and every 6 months thereafter. Full weight bearing ambulation was allowed after visible callus formation was observed in anterolateral or lateral radiographs. The mean follow-up period was 18 months (range 12–46 months). None of the patients received an anti-resorptive agent for osteoporosis until fracture union. All rheumatoid arthritis patients took medication for rheumatoid arthritis 2 weeks after the operation.

On radiographic examination, the time to union after operation and presence of delayed or nonunion were evaluated. The radiographic evaluation was performed two times by two orthopedic surgeons who had not participated in the operation. The intraclass coefficient (ICC) and Kappa coefficient were used to verify the interobserver and intraobserver reliability of the radiographic evaluation. Bone union was defined by achievement of continuity of 3 cortexes in two vertical planes (anteroposterior and lateral view). The current study assumed that femur fracture patients with RA would have a relatively longer time to union. Among the generally accepted definitions of delayed union and nonunion, those that indicated the longest periods were selected [7]. Thus, delayed union was defined as a case in which union is not completed even after 8 postoperative months, and nonunion was defined as a case in which union is not completed even after 12 postoperative months [7]. In femoral shaft fracture, we determined whether atypical or ordinary femoral fracture. A shaft fracture was classified as an atypical femoral fracture (AFF) by the criteria established by the American Society for Bone and Mineral Research task force [8].

Table 1 Comparison of baseline data and radiographic outcomes between RA and control groups

	RA group ($n=42$)	Control group ($n=126$)	p value
Age, years	65.7 (7.3)	66.8 (8.9)	0.490
Sex (M/F)	3/38	8/118	1.000
Body mass index, kg/m^2	21.7 (3.5)	22.6 (3.0)	0.114
Bone mineral density, g/cm^2	0.508 (0.135)	0.548 (0.149)	0.173
Diabetes mellitus	5 (11.9%)	21 (16.7%)	0.460
Smoking	3 (7.1%)	14 (11.1%)	0.567
AO/OTA classification			
31A1	7 (16.7%)	22 (17.3%)	0.971
31A2	11 (26.2%)	33 (26.2%)	
31A3	2 (4.8%)	5 (4.2%)	
32A1	4 (9.5%)	18 (14.3%)	
32A2	7 (16.7%)	22 (17.5%)	
32A3	10 (23.8%)	22 (17.5%)	
32B1	1 (2.4%)	4 (3.2%)	
Operative techniques			
Implant			
CHS	12 (28.6%)	29 (23%)	0.558
IM nail	21 (50%)	75 (59.5%)	
Plate	9 (21.4%)	22 (17.5%)	
Bone union time, months	5.3 (2.6)	4.4 (1.7)	0.047*
Complication			
Nonunion	4 (9.5%)	1 (0.8%)	0.014*
Delayed union	5 (11.9%)	4 (3.2%)	0.044*

Data are presented as mean (SD) or as numbers (percentages)

RA Rheumatoid arthritis, *CHS* Compression hip screw, *IM* Intramedullary

*Significant difference

We compared radiographic outcome between the RA and control groups. Then, owing to the differences in time to union between metaphyseal and diaphyseal fractures, the RA group was divided into a trochanteric fracture group (RA group I) and a shaft fracture group (RA group II). A comparative analysis was then performed with each control group (control groups I and II). In addition, we analyzed risk factors for nonunion or delayed union including age, sex, diabetes mellitus (DM), smoking history, body mass index (BMI), bone mineral density (BMD), fracture type (AO/OTA classification), and type of implant.

Comparative analyses of variables with continuous data between the two groups were performed with either the Student *t* test or Mann–Whitney *U* test, depending on whether or not there was data distribution. Normality of data was evaluated using the Kolmogorov–Smirov test and Shapiro–Wilk test. Either the chi-square test or Fisher's exact test was used for the comparative analysis of variables with dichotomous data between the two groups. Multiple logistic regression analysis was performed to evaluate risk of nonunion or delayed union using variables that showed a significance level of $p < 0.2$ in the univariate analysis, considering confounding effects between the variables. A $p < 0.05$ was considered statistically significant. SPSS version 25.0 (Chicago, Illinois) was used for statistical analyses.

Results

Intraobserver and interobserver reliabilities for radiographic union were excellent, with ICCs of 0.86 [95% confidence interval (CI) 0.82–0.90] and 0.76 (0.69–0.81), respectively. For AFF, the intraobserver and interobserver reliabilities of the radiological evaluation were also excellent, with Kappa coefficients 0.92 (95% CI 0.86–0.98) and 0.88 (0.82–0.94), respectively.

In overall comparison of RA and control group, no statistically significant differences according to age, sex, DM, smoking history, body mass index (BMI), bone mineral density (BMD), fracture type (AO/OTA classification), and type of implant were observed between the RA and control groups (Table 1). In the RA group, the usage of glucocorticoid, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs) were 80.9% (34/42), 45.2% (19/42), and 69.0% (29/42), respectively. For preoperative ambulation status in RA group, 36 patients were able to perform independent ambulation, while 5 patents required aids and 1 patient was bed ridden. In non-RA group, 114 patients were able to perform independent ambulation, while 11 patents required aids and 1 patient was bed ridden. Preoperative ambulation status was no statistically difference between two groups ($p = 1.000$). The mean time to union was 5.3 months in the RA group and 4.4 months in the control group, indicating that the time was significantly longer in the RA group ($p = 0.047$) than in the control group. Nonunion and delayed union were observed in 4 and 5 cases in the RA group, and 1 and 4 cases in the control group, respectively, indicating that the prevalence of nonunion and delayed union were significantly higher in the RA group than in the control group ($p = 0.014$, $p = 0.044$). Infection was detected in 1 case in the RA group and 4 cases in the control group, all of which were superficial wound infections, which improved after administration of intravenous antibiotics.

For analysis of differences in outcomes according to fracture site in the RA patients, the RA group was divided into the trochanteric and shaft fracture groups and comparative analysis was performed with each control group. To control for factors other than the fracture site that affected the analysis results, the baseline characteristics of RA groups I and II were compared. No significant differences according to age, sex, BMI, BMD, DM, and smoking were observed between the two groups (Table 2), and there were no significant differences in medication and duration of RA.

Subgroup I Analysis: Trochanteric Fracture

There were no significant differences according to age, sex, BMI, BMD, DM, smoking, fracture type, and type of implant between RA group I and the control group I (Table 3). The mean time to union was 3.8 months (range 2–10 months) in RA group I and 3.7 months (range 2–10 months) in control group I, showing no significant difference between the two groups ($p = 0.823$). Regarding complications, one case (5.0%) showed delayed union (time to union: 10 months) in RA group I, and one case (1.7%) showed delayed union (10 months) in control group I. There was no statistically significant difference between the two groups ($p = 0.440$). Fortunately, both groups had no nonunion.

Subgroup Analysis II: Femoral Shaft Fracture

No significant differences according to age, sex, BMI, BMD, DM, smoking, fracture type, and type of implant were observed between RA group II and control group II (Table 4). The mean time to union was 6.9 months (range 3–12 months) in RA group II and 5.0 months (range 3–12 months) in control group II, indicating a significantly longer period in RA group II than in the control group ($p = 0.001$). Regarding complications, there were four cases of nonunion (18.1%) and four delayed union (18.1%) in RA group II, and one case of nonunion (1.5%) and three delayed union (4.5%) in the control group II. Based on these outcomes, the incidence of nonunion was significantly higher in RA group II than in control group II ($p = 0.013$). In RA group II, all cases of nonunion underwent

Table 2 Comparison of baseline data between RA groups I and II

	RA group I ($n=20$)	RA group II ($n=22$)	p value
Age, years	67.2 (7.5)	64.4 (7.0)	0.227
Sex (M/F)	2/18	1/21	0.598
Body mass index, kg/m^2	21.8 (4.2)	21.7 (2.8)	0.932
Bone mineral density, g/cm^2	0.468 (0.103)	0.542 (0.151)	0.107
Diabetes mellitus	3 (15%)	2 (9.1%)	0.656
Smoking	1 (5%)	2 (9.1%)	1.000
Medication			
Steroid	8 (40%)	9 (40.9%)	0.952
DMARDs	16 (80%)	17 (77.3%)	1.000
Biologic agent	3 (15%)	4 (18.2%)	1.000
Prior bisphosphonate therapy	14 (70%)	17 (77.3%)	0.592
Duration of Rheumatoid Arthritis, years	14.8 (8.6)	16.1 (6.0)	0.570

Data are presented as mean (SD) or as numbers (percentages)

DMARDs disease-modifying anti-rheumatic drugs

Table 3 Comparison of baseline data and radiographic outcomes between RA and control Group I

	RA group I ($n=20$)	Control group I ($n=60$)	p value
Age, years	67.2 (7.5)	67.5 (4.6)	0.830
Sex, M/F	2/18	2/58	0.259
Body mass index, kg/m^2	21.8 (4.2)	23.3 (3.3)	0.107
Bone mineral density, g/cm^2	0.468 (0.103)	0.530 (0.142)	0.113
Diabetes mellitus	3 (15%)	11 (18.3%)	1.000
Smoking	1 (5%)	3 (5%)	1.000
AO/OTA classification			
31A1	7 (35%)	22 (36.7%)	0.972
31A2	11 (55%)	33 (55%)	
31A3	2 (10%)	5 (8.3%)	
Operative techniques			
Implant			
CHS	12 (60%)	29 (48.3%)	0.366
IM nail	8 (40%)	31 (51.7%)	
Bone union time, months	3.8 (2.0)	3.7 (1.5)	0.823
Complication			
Nonunion	0	0	
Delayed union	1 (5%)	1 (1.7%)	0.440

Data are presented as mean (SD) or as numbers (percentages)

reoperation and union was achieved after reoperation with autogenous iliac bone graft. The case of nonunion in control group II was confirmed to have achieved union at 10 months after reoperation.

AFF was detected in 16 (72.7%) of 22 cases in RA group II and in 10 (15.2%) of 66 cases in control group II, so that the prevalence of AFF was higher in RA group II than in control group II ($p = 0.001$). Of the 16 AFF cases in RA group II, there were three nonunion and three delayed union (Fig. 2), and of the 10 AFF cases in control group II, there were 1 nonunion and 1 delayed union during the follow up period.

There were 17 cases of taking bisphosphonate before the occurrence of fracture in RA group II (77.3%) and 16 cases in control group II (24.2%), showing a significantly high frequency of taking bisphosphonate in RA group II ($p = 0.001$). All cases of AFF were taking alendronate 70 mg/week, for a mean medication period of 7.2 (2–15) years.

Analysis of Risk Factors for Nonunion and Delayed Union

Risk factors were analyzed for 14 cases (5 non-unions, 9 delayed unions). Variables that showed a significance level

Table 4 Comparison of baseline data and radiographic outcomes between RA group II and control group II

	RA group II ($n=22$)	Control group II ($n=66$)	p value
Age, years	64.4 (7.0)	67.7 (11.1)	0.385
Sex (M/F)	1/21	6/60	0.675
Body mass index, kg/m^2	21.7 (2.8)	22.0 (2.7)	0.355
Bone mineral density, g/cm^2	0.542 (0.151)	0.571 (0.156)	0.511
Diabetes mellitus	2 (9.1%)	10 (15.2%)	0.722
Smoking	2 (9.1%)	11 (16.7%)	0.504
AO/OTA classification			
32A1	4 (18.2%)	18 (27.3%)	0.771
32A2	7 (31.8%)	22 (33.3%)	
32A3	10 (45.5%)	22 (33.3%)	
32B1	1 (4.5%)	4 (6.1%)	
Operative techniques			
Implant			
Plate	9 (40.9%)	22 (33.3%)	0.519
IM nail	13 (59.1%)	44 (66.7%)	
Bone union time, months	6.9 (2.4)	5.0 (1.7)	0.001*
Complication			
Nonunion	4 (18.2%)	1 (1.5%)	0.013*
Delayed union	4 (18.2%)	3 (4.5%)	0.062
Atypical femoral fracture	16 (72.7%)	10 (15.2%)	0.001*
Prior bisphosphonate therapy	17 (77.3%)	16 (24.2%)	0.001*

Data are presented as mean (SD) or as numbers (percentages)

*Significant difference

of $p < 0.2$ in the univariate analysis were age, BMD, steroid use, taking bisphosphonate, RA, fracture site, and AFF. DM and smoking did not show a significance level of $p < 0.2$, but were included in the variables for risk factor analysis, as important factors affecting fracture union. In the risk factor analysis, RA ($p = 0.040$), and AFF ($p = 0.006$) showed statistically significant difference (Table 5), whereas other factors, including age ($p = 0.082$), BMD ($p = 0.237$), steroid use ($p = 0.680$), taking bisphosphonate ($p = 0.694$), fracture site (0.113), DM ($p = 0.220$), and smoking ($p = 0.680$) did not show significant differences.

Discussion

In patients with rheumatoid arthritis, excessive activation of osteoclastogenesis by the overexpression of various pro-inflammatory cytokines can inhibit bone remodeling, and changes in callus composition by systemic inflammation can interfere with fracture healing [4, 9, 10]. However, there are limited clinical data on fracture healing in RA patients. In our study, the overall outcomes in RA patients with femur fracture showed significant differences in terms of time to union and occurrence of nonunion or delayed union. However, the comparison of the trochanteric fracture group showed no significant differences in time to union and nonunion or delayed union. On the other hand, the comparison of shaft fracture in RA patients showed significantly long time to union and high rate of nonunion or delayed union compared to non-RA patients.

In intertrochanteric fracture analysis, unlike results of the previous studies which showed high rate of nonunion in intertrochanteric femoral fracture in RA patients [2, 3], no significant differences in complication rate of trochanteric fractures were observed between the RA and non-RA groups in the current study. In the previous studies, cases of nonunion resulted from mechanical instability unrelated to fracture healing potential of the RA patients in the studies. No mechanical failure was detected in this study. This may be due to improved osteosynthesis techniques and implant designs in recent years [11–13]. In addition, cancellous bone of metaphysis has a high regenerating capacity, including a large surface area, high bone formation and mineralization rates, better blood supply, and thicker periosteum with greater cellularity [4]. Van Wunnik et al. [14] reported that for fracture repair, bone regenerating capacity was more important than bone matrix quality. Thus, RA did not affect the repair of trochanteric fracture if there is no mechanical instability.

In femoral shaft fracture analysis, AFF was the important factor resulting in a higher complication rate. Of 22 cases of femur shaft fracture in RA patients, 16 cases had AFFs,

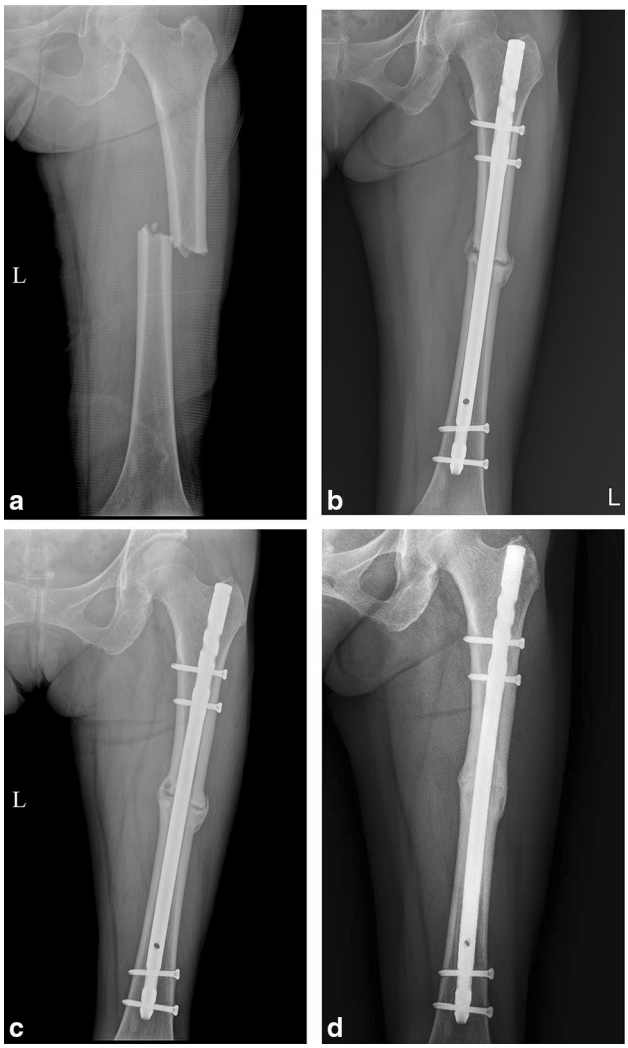

Fig. 2 Sixty-seven-year-old female with RA who had been taking alendronate for 5 years fell from a standing height. **a** Her radiographs showed complete fractures extend through both cortices with a medial spike at the midshaft area. **b** A radiograph obtained 9 months postoperatively shows nonunion of the fracture. **c** After 12 month postoperation, bridging callus was visible, but fracture did not heal completely. **d** A final radiograph shows bony union at 21 months postoperatively

Table 5 Odds ratio for occurrence of nonunion or delayed union

Variable	Odds ratio	95% CI		*p* value
		Lower	Upper	
Rheumatoid arthritis	3.76	1.06	13.33	0.040*
Atypical femoral fracture	5.83	1.66	20.43	0.006*

*Significant difference

showing a higher prevalence of AFF in the RA patients compared with the non-RA patients, which in turn resulted in higher incidences of nonunion or delayed union. Bone turnover over suppression is thought to be the pathophysiological mechanism of AFF, with accumulation of microcracks due to the adynamic bone that has lost the ability to repair. These microcracks propagate and weaken the bony area, leading to eventual complete fracture [15]. Some studies reported prevalence rates of AFF among subtrochanteric and diaphyseal fractures, excluding fractures caused by high-energy trauma and periprosthetic fracture, from 17 to 29% [16, 17]. Compared to previous reports, our study reports a significantly higher prevalence of AFF among shaft fractures in RA patients. Most RA patients have osteoporosis due to systemic inflammation, long-term use of corticosteroid, and immobility by joint destruction, and are commonly prescribed bisphosphonate (BP) [18–20]. Many studies reported close relation of long-term use of BP with the occurrence of atypical femoral fracture [17, 21]. In the current study, more patients took BP in the RA group than in the non-RA group. RA patients usually visited the clinics for rheumatoid medication [22, 23], and rheumatoid medications, as well as BP for osteoporosis were prescribed [1]. Kamatari el al [24] reported that BP compliance of rheumatoid patients was significantly higher compared with non-RA patients. We thought that higher prescription and compliance of BP resulted in the increase in the rate of AFF in RA patients.

Many authors reported a higher prevalence of delayed healing and nonunion in AFFs than in ordinary subtrochanteric or diaphyseal osteoporotic fractures [15]. Edwards et al [25] reported delayed union or nonunion in 26% of cases of AFFs, and Weil et al reported that 46% of AFF patients required a second operation [26]. Odvina et al. who performed a histomorphometric analysis in patients with spontaneous fracture after undergoing alendronate treatment, identified marked bone turnover suppression, which was explained as a result of suppressed bone turnover caused by long-term use of BP [15]. The suppressed bone turnover reportedly lasted from several months to several years, even after discontinuation of BP medication. In our study, we thought that high nonunion or delayed union rate in the RA femoral shaft fracture group was induced by the effects of complex factors, including long-term BP use, corticosteroid, and RA disease activity [34, 35].

The current study had the following limitations. First, the study was conducted in a retrospective nature, and therefore, other factors including disease activity and exact medication status of RA patients which might have affected the outcome could not be evaluated. Second, the number of patients was small. Third, different implants were used according to the preference of the surgeon and this might have affected the outcomes. Fourth, there is the possibility of selection bias in which patients with non-AFF might be selected during the selection of the control group; however, in this study, the prevalence of AFF in the control group was similar to those in previous reports [16, 17].

In conclusion, femoral trochanteric fracture in RA patients showed favorable outcome compared to non-RA patients; however, the femoral shaft fracture showed high incidence of delayed union or nonunion in RA patients compared to non-RA patients. The high incidence of AFF in RA patients is an important reason for these outcomes. Therefore, we suggest that careful operation, regular follow up, and finally a proper plan, such as second operation, are necessary in RA patients with femoral shaft fracture.

Conclusions

The high prevalence of atypical femoral fracture among the femur shaft fractures in the RA patients was considered a significant risk factor for nonunion and delayed union.

Funding None.

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest.

Ethical standard statement Ethical approval was obtained from Institutional Review Board of the university hospital prior to conducting this study.

Informed consent We certify that we have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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