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# High Prevalence of Foot Insufficiency Fractures in Patients With Inflammatory Rheumatic Musculoskeletal Diseases

Bjoern Buehring[1], Nadine Al-Azem[1], Uta Kiltz[1], Martin Fruth[2], Ioana Andreica[1], David Kiefer[1], Styliani Tsiami[1], Xenofon Baraliakos[1], and Jürgen Braun[1]

*ABSTRACT.* ***Objective.*** To assess the prevalence of foot insufficiency fractures (IF) in patients with rheumatic musculoskeletal disease (RMD) with foot pain.

***Methods.*** In a retrospective design, 1752 magnetic resonance imaging (MRI) scans of consecutive patients presenting with foot pain in 2 time periods between 2016 and 2018 were evaluated. The group with IF was matched with controls with foot pain without IF. Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry. Multivariate analyses were performed.

***Results.*** A total of 1145 MRI scans of patients (median age 59 yrs, 82.9% female) with an inflammatory (65.4%) and of 607 with no inflammatory (34.6%) RMD (median age 58 yrs, 80.8% female) were available. Most patients had rheumatoid arthritis (RA; 42.2%), and others had psoriatic arthritis (22.4%), axial spondyloarthritis (11.1%), or connective tissue disease (CTD; 7.6%). Foot IF were found in 129 MRI scans of patients (7.5%). There was no difference between time periods. The prevalence of IF was highest in CTD (23%) and RA (11.4%). More patients with an inflammatory than a noninflammatory RMD had IF (9.1% vs 4.1%, respectively; $P < 0.001$). Using conventional radiography, IF were only detected in 25%. Low BMD and a history of fractures were more frequent in patients with IF than without (42.6% vs 16.2% and 34.9% vs 8.6%, respectively; $P < 0.001$).

***Conclusion.*** A high prevalence of foot fractures was found in MRI scans of patients with RMD, many without osteoporosis. MRI was more sensitive than radiographs to detect IF.

*Key Indexing Terms:* bone mineral density, fragility fractures, osteoporosis, rheumatoid arthritis

Rheumatoid arthritis (RA) is a frequent chronic inflammatory rheumatic musculoskeletal disease (RMD) predominantly affecting small joints by inflammation, and is often associated with joint damage, functional loss, and premature mortality.[1-3] There are many other inflammatory RMDs, such as psoriatic arthritis (PsA), but there are also noninflammatory RMDs possibly causing similar symptoms.

Foot symptoms in patients with RA are rather prevalent, and they may derive from inflammation, altered foot mechanics, deformity, secondary skin lesions, and combinations.[4-6] Current foot problems in RA were reported by > 90% of patients, and the incidence of foot impairment was estimated between 85% and 93%.[7,8] Foot problems, starting in the metatarsophalangeal (MTP) joints in nearly 90% of cases,[9] are the first symptom in 15% of patients with RA.[4,5] Chronic synovial inflammation may result in capsular distension, attrition of collateral ligaments, and plantar fascia laxity, leading to subluxation and dislocation of MTP joints and the characteristic deformities seen in advanced RA such as hallux valgus, hammertoe, claw toe, mallet toe, and plantar and dorsal hyperkeratosis.[9,10] RA also involves ankle and hindfoot joints in 30% to 60% of patients, whereas the midfoot seems to be less frequently affected.[4,5,9,10] However, the first metatarsal joint is often affected, which often causes instability of the midfoot.[4,5,9,10] Forefoot joint damage in RA is related to increased pressure underneath the forefoot, especially pressure under the first and fourth MTP joints.[11] In severe RA, foot problems in the form of bursitis, tendinitis, tenosynovitis, fasciitis, neuropathy, skin ulceration, and rheumatoid nodules may occur.[10] A high BMI (calculated as weight in kilograms divided by height in meters squared) may additionally affect foot health in RA.[12]

The differential diagnosis of foot pain in RA includes not only disease activity, structural damage, and deformities due to RA but also insufficiency fractures (IF). However, their prevalence has not been studied much in cohorts with inflammatory RMDs to date.[13,14] Fractures are a major health problem. By 2040, over 300 million adults aged > 50 years worldwide are expected to be at high risk of a fragility fracture.[15] This has prompted the European Alliance of Associations for Rheumatology and the European Federation of National Associations of Orthopaedics and Traumatology to develop recommendations to promote a more effective management and prevention of such fractures.[16,17]

[1]*B. Buehring, MD, N. Al-Azem, MD, U. Kiltz, MD, I. Andreica, MD, D. Kiefer, MD, S. Tsiami, MD, X. Baraliakos, MD, J. Braun, MD, Rheumazentrum Ruhrgebiet, Herne, and Ruhr-Universität Bochum, Bochum;* [2]*M. Fruth, MD, Radiologie Herne, Herne, Germany.*

*B. Buehring and N. Al-Azem contributed equally to this work.*

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*Address correspondence to Prof. J. Braun, Rheumazentrum Ruhrgebiet, Claudiusstr.45, 44649 Herne, Germany.*
*Email: juebraun@gmx.de.*

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Low bone mineral density (BMD) and falls are major risk factors for fractures. Early recognition is important because fractures tend to recur.[18] Their prevention is possible by using validated fracture risk assessment tools such as the Fracture Risk Assessment Tool[19] and devices to assess BMD, such as dual x-ray absorptiometry, to determine osteoporosis as defined by the World Health Organization.[20]

Risk factors for osteoporosis include age, postmenopausal state, glucocorticoid use, low body weight, low calcium, low vitamin D, immobility, and chronic inflammation as in RA.[21] In RA, general bone loss and local peripheral bone loss at the site of inflammation occurs and the risk for fractures is doubled[22-24]; this also applies to male patients.[25] Indeed, osteoporosis is a common comorbidity of patients with RA.[21] This can be partly explained by the high proportion of postmenopausal females affected, the use of glucocorticoids, and the decreased mobility of patients. The prevalence of osteoporosis and fractures in RA is high in all age groups.[21]

Although conventional radiography is still recognized as the method of choice to assess fractures, diagnostic imaging to assess IF seems better with magnetic resonance imaging (MRI).[26-28] There is increasing evidence that this is also true for the detection of arthritis by MRI in the feet of patients with RA.[29-32]

The major aim of this study was to assess the prevalence of IF of the feet in patients with RMD including RA using both radiographs and MRI, and to determine risk factors.

## METHODS

This is a retrospective study based on the analysis of documented data of patients presenting to a specialized tertiary rheumatologic care center, the Rheumazentrum Ruhrgebiet, in Herne, Germany. All patients had foot pain (defined as pain in the foot and/or ankle region), but no trauma, and had received MRI (Siemens Aera 1.5T) of the foot or the ankle. From this dataset, the frequency of IF as confirmed by the radiologist (MF) was determined. Due to the retrospective study design, no written consent of the patients was obtained. The study was approved by the ethical committee of the Ruhr University Bochum (no. 20-7068-BR).

In a next step, patients with IF were matched and compared to patients with the same demographic data, such as sex, age, and underlying rheumatic disease, but without fracture. The electronic database of the radiology department at the hospital was searched for MRI scans of the foot and ankle during the period June 30, 2016, to July 1, 2018.

Disease activity was determined based on the records, which means by discretion of the rheumatologist in charge of the patient according to the records. This could only be qualitatively done, which means the patient was judged to be an active yes or no according to the records.

Patients with IF were compared to patients without IF who had the same or similar demographic data. One patient with IF was assigned to 2 control patients based on the following criteria: sex, age ± 10 years, disease (diagnosis), and disease duration of approximately 5 years.

The primary endpoint was the number of patients with IF in foot MRI within the study observation periods (June 30, 2016, to July 1, 2018).

Secondary endpoints were the difference between the number of foot IF diagnosed on foot MRI and fractures diagnosed on conventional radiography, as well as risk factors for IF and factors that may have influenced fracture healing.

The statistical analysis was performed in 2 steps. First, the ratio, median, mean, IQR, and SD of each aspect examined were calculated in Microsoft Excel. This was followed by an examination in SPSS (IBM Corp.) for statistical correlation and relevance. Then the 2 time periods were compared to check whether the numbers and percentages were similar.

Following this, patients with IF and controls were first grouped and then assessed separately. Among others, risk factors for the development of IF and osteoporosis as described in the literature were assessed and calculated.

Cross-tabulations were used to bivariately examine the relative frequency of the potential factors influencing the development of IF. Chi-square test and Fisher exact test allowed conclusions about the independence of the variables. Assessment of the metric in correlation with the nominal dataset was based on Spearman rank correlation coefficient for nonnormally distributed data and Pearson correlation coefficient for normally distributed data. Purely metric correlations were examined by the Wilcoxon-Mann-Whitney test. Multiple logistic regression analysis was used to assess the multifactorial influence to develop IF.

*Patient and public involvement.* Patients were involved since it was a major advantage for them to get the correct diagnosis of foot fracture.

## RESULTS

A total of 1752 MRI scans were identified. There were more foot than ankle MRI scans (1430 MRI scans of the foot [81.6%] and 322 of the ankle [18.4%]). These MRI scans were from 1145 patients with an inflammatory rheumatic disease (IRD; 65.4%) and from 607 patients with no IRD (34.6%).

Most patients (n = 483) with an IRD had RA (42.2%), PsA (n = 256, 22.4%), or axSpA (n = 127, 11.1%), and 279 had other inflammatory rheumatic diseases (24.4%). Among these, there were 87 patients with connective tissue diseases (CTD; 7.6% of patients with IRD) including systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, and dermatomyositis (31.2%); 64 with crystal arthropathies, mainly gout (22.9%); 40 with vasculitis or polymyalgia rheumatica (14.3%); 49 with undifferentiated arthritis (17.6%); and 39 with sarcoidosis (14%).

Among the subjects with no IRD, there were mainly patients with degenerative and/or mechanic musculoskeletal diseases (n = 379) and primary fibromyalgia (n = 228).

A total of 129 MRI scans of patients had an IF (7.5%). The prevalence of IF was higher in foot MRI scans (n = 116, 8.1%) than in ankle MRI scans (n = 13, 4%), respectively. In Figure 1, Figure 2, and Figure 3, several examples of IF are given; for comparison, 1 example of a patient with dactylitis who had no fracture is given.

Further, a total of 104 patients with an IRD had an IF (9.1%), and a total of 25 patients with non-IRD had an IF (4.1%).

Importantly, there was no difference in the prevalence of IF between both time periods studied:

- Between 2016 and 2017, there were 716 MRI scans of the foot and 157 of the ankle (n = 873). Among them, 67 patients (7.7%) had an IF (59 feet, 8 ankles).
- Between 2017 and 2018, there were 714 MRI scans of the foot and 165 of the ankle (n = 879). Among them, 62 patients (7.1%) had an IF (57 feet, 5 ankles).

Among the 104 patients with an IRD and IF, there were 55 patients with RA (52.9%), 21 with PsA (20.2%), 20 with CTD (19.2%), 6 with polymyalgia rheumatica or vasculitis (5.8%), and 2 with gout (1.9%).

Many patients with IF (n = 57) had fractures in more than 1 bone (44%). In these patients, a total of 159 fractures were



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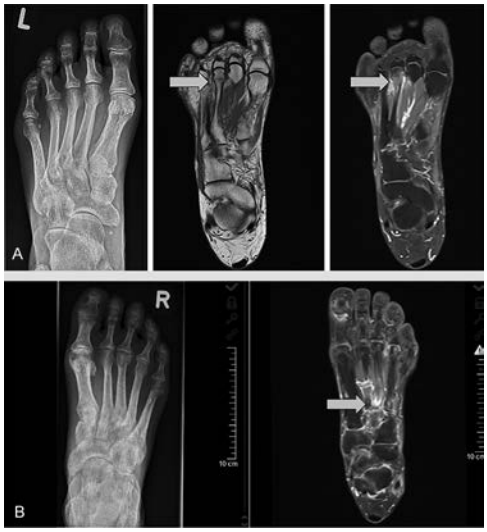


*Figure 1.* MRI of the forefoot and the corresponding radiograph in 2 patients with an IF. (A) MRI of a radiographically occult subcapital fracture of the third metatarsal head in a 56-year-old female patient with RA, disease duration 2.5 years. T1w-MRI reveals the fracture as a hypointense line (middle figure), whereas contrast-enhanced fat saturated T1w-MRI delineates the periostal reaction and activation of the surrounding bone marrow mimicking periostitis and ostitis (gray arrows). (B) MRI of a radiographically not-detected fracture of the basis of the third metatarsal right foot (gray arrow) of a 61-year-old male patient with PsA (disease duration 6 yrs). Due to the complex anatomy in this area, the detection of fractures can be challenging radiographically. That is why MRI is the method of choice for the evaluation of fractures. Contrast-enhanced fat saturated T1w-MRI delineates the fracture as a hypointense line and shows reactive periostal and bone marrow activation. IF: insufficiency fracture; MRI: magnetic resonance imaging; PsA: psoriatic arthritis; RA: rheumatoid arthritis; T1w: T1-weighted.

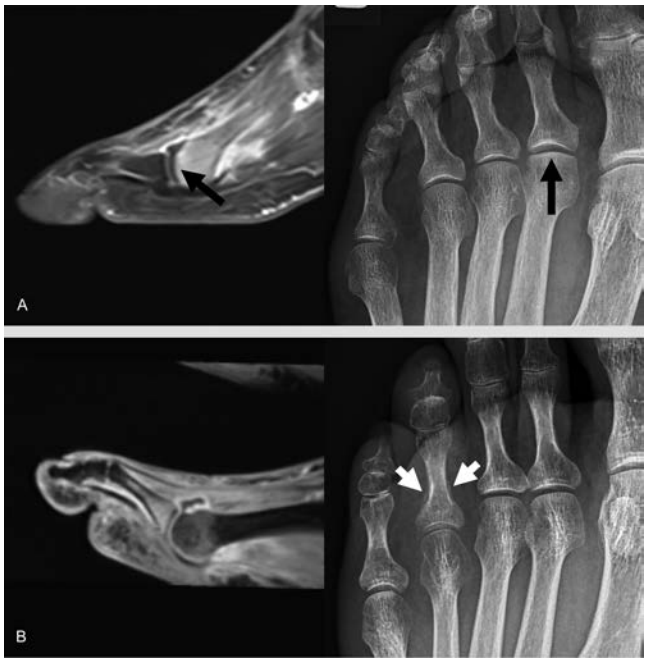


*Figure 2.* Sagittal contrast-enhanced T1w fat-saturated MRI of the forefoot and the corresponding radiographs in 2 patients. (A) MRI of a 66-year-old female patient admitted with foot pain and suspicion of arthritis showing a subchondral fracture of the second metatarsal head. Both the radiograph and the MRI demonstrate minor linear subchondral sclerosis and lost sphericity of articular surface due to an infraction (black arrows). (B) MRI of a 51-year-old male patient with long standing axSpA with peripheral involvement showing dactylitis of the fourth toe with dominant arthritis of the metatarsophalangeal joint, no fracture. The radiograph shows a mineralized periostal reaction of the proximal basophalangeal metadiaphysis (white arrows), no fracture. AxSpA: axial spondyloarthritis; MRI: magnetic resonance imaging; T1w: T1-weighted.

reported. The localization of fractures concentrated on the metatarsal bones (n = 60), which were most frequently affected (51.7% of foot IF). Other commonly affected sites were the calcaneus, the talus, the cuneiforme bones, and the cuboid. No statistically significant differences were seen between individuals with 1 fracture and those with more than 1 fracture (data not shown).

Patient demographics of patients with IF and controls are shown in Table 1. There were no major differences in patient demographics between these groups. Among the 129 patients with foot IF, there were 82.9% women and 17.1% men (ie, women were 4.8 times more often affected than men). In the IF group, the median age was 59 years and the mean disease duration was 8.4 years. Patients with RA (mean age 62 yrs) and vasculitis/polymyalgia rheumatica (mean age 71.5 yrs) were significantly older than the other groups of inflammatory diseases (mean age 54.8 yrs) or patients with noninflammatory diseases (mean age 52 yrs). All patients with IF and the controls reported foot pain but no history of trauma. Few patients in both groups had foot swelling (32.6% of patients with IF and 34.1% of the controls).

Among patients with IF, the most common RMD was RA (n = 55/483, 11.4%), followed by PsA (n = 21/256, 8.2%), and CTD (n = 20/87, 23%).

- Out of 483 patients with RA, 55 had an IF (11.4%).
- Out of 256 patients with PsA, 21 had an IF (8.2 %).
- Out of 87 patients with CTDs, 20 had an IF (23%).
- Out of 607 patients with no inflammatory RMD, 25 had an IF (4.1%).

In 74.4% of patients with IF, a radiograph was taken before the MRI examination. By radiograph, fractures were only detected in 25% of cases. MRI scans were requested in 40.3% of patients with IFs to exclude a fracture and in the remainder to detect inflammation.

Table 2 shows the general risk factors, which are presented in more detail below. Although 37.2% of patients with IF reported current smoking, this was less frequent in the controls (23.1%; $P = 0.01$). The median BMI was 28.5 (IQR 25.4-33.1) in the controls and 27.3 (IQR 23.7-45.9) in the patients with IF ($P = 0.02$).

Patients with IF were more likely to have an abnormal BMD measurement compared to the control group (Table 2). Osteoporosis was present in 42.6% of patients with IF and in only 16.2% of controls, whereas osteopenia was found in 24% of patients with IF and 18.8% of controls. One-third of the patients with IF and two-thirds of the controls had a normal BMD. A previous fracture was more likely to have occurred in



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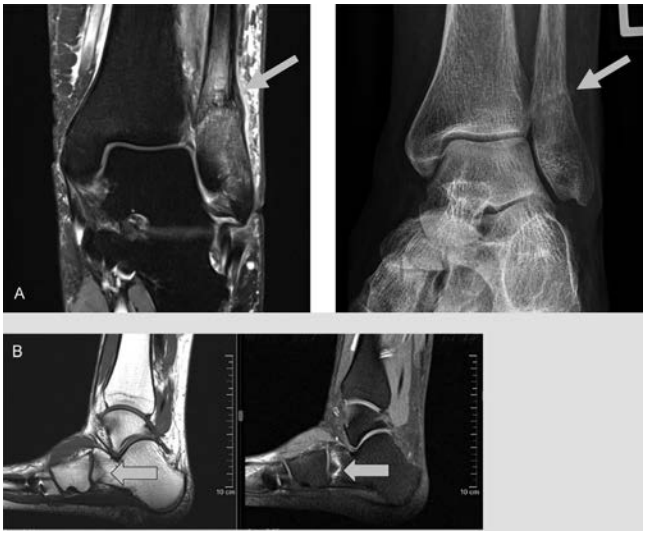


*Figure 3.* MRI and the corresponding radiographs of 2 patients. (A) Coronal proton density–weighted turbo spin-echo fat-saturated MRI and the corresponding radiograph of a 57-year-old female patient with an osteodestructive course of RA presenting with lateral ankle pain for about 6 weeks. Both MRI and radiograph show a juxtasyndesmal IF of the fibula with reactive periostal thickening and mineralization due to callus formation (gray arrows). (B) T1w-MRI and STIR of a 42-year-old female patient with PsA for approximately 10 years treated with chronic glucocorticoids and multiple csDMARDs, bDMARDs, and tsDMARDs. The T1w-MRI shows a blurred zigzag-shaped hypointense fracture line at the anterior calcaneum with surrounding bone marrow edema depicted by STIR imaging. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic DMARD; IF: insufficiency fractures; MRI: magnetic resonance imaging; STIR: short tau inversion recovery; T1w: T1-weighted; tsDMARD: targeted synthetic DMARD.

*Table 1.* Demographics of patients with IF and controls without IF.

| | Patients With IF, n = 129 | Controls Without IF, n = 229 |
|---|---|---|
| Female, n (%) | 107 (82.9) | 185 (80.8) |
| Age, yrs, median (IQR) | 59.0 (52.0-67.0) | 59.0 (51.0-66.0) |
| Age range, yrs | 17-85 | 20-84 |
| Mean disease duration, yrs (IQR) | 6.0 (2.0-12.0) | 5.0 (2.0-10.0) |
| RA, n (%) of patients with or without IF (n = 483) | 55 (42.6) | 106 (46.3) |
| PsA, n (%) of patients with or without IF (n = 256) | 21 (8.2) | 43 (18.8) |
| CTD, n (%) of patients with or without IF (n = 87) | 20 (15.5) | 38 (17) |
| NIRD, n (%) (n = 607) | 25 (19.4) | 35 (15.3) |

CTD: connective tissue disease; IF: insufficiency fracture; NIRD: noninflammatory rheumatic diseases; PsA: psoriatic arthritis; RA: rheumatoid arthritis.

patients with IF, where 34.9% of patients with IF and only 8.6% of controls had a history of fracture ($P < 0.001$).

Patients with IF and osteoporosis (63.0 yrs, IQR 56.5-71.5) or osteopenia (63.0 yrs, IQR 53.0-68.0) were older than those with normal BMD (53.0 yrs, IQR 45.5-61.0; $P < 0.001$). This was similar in the control group, where patients with osteoporosis and osteopenia had a median age of 61.0 (IQR 59.0-71.0) and 63.0 (IQR 57.5-72.0), respectively.

*Table 2.* Patient demographics and risk factors for IF (univariate analysis).

| | IF | Controls Without IF | *P* |
|---|---|---|---|
| Current smoking | 48 (37.2) | 53 (23.1) | **0.01** |
| BMI[a], median (IQR) | 27.3 (23.7 to 45.9) | 28.5 (25.4 to 33.1) | **0.02** |
| Lowest *t*-score, median (IQR) | −2.0 (−2.6 to −1.1) | −1.6 (− 2.2 to −0.3) | **0.002** |
| Osteoporosis | 37 (42.6) | 55 (16.2) | **< 0.001** |
| Osteopenia | 31 (24) | 43 (18.8) | **< 0.001** |
| Normal BMD | 43 (33.3) | 149 (65.1) | **< 0.001** |
| History of fractures | 45 (34.9) | 20 (8.6) | **< 0.001** |
| Antiosteoporotic therapy | 66 (51.2) | 36 (15.7) | **< 0.001** |
| Glucocorticoid intake | 62 (48.1) | 102 (44.5) | 0.52 |
| MTX | 55 (42.5) | 64 (27.9) | **0.01** |
| Biologics | 28 (21.7) | 39 (17) | 0.28 |

Values are expressed as n (%) unless otherwise indicated. Significant *P* values are in bold. [a] BMI calculated as weight in kilograms divided by height in meters squared. BMD: bone mineral density; IF: insufficiency fracture; MTX: methotrexate.

Female sex was a risk factor for abnormal BMD only in the control group; 44.9% of women with IF had osteoporosis and 25.2% had osteopenia. In the control group, only 18.4% of women had osteoporosis, 21.1% had osteopenia, and 60.5% had a normal BMD ($P = 0.01$).

Patients with low BMD were more likely to receive antiosteoporotic therapy. Thus, a proportion of 89.1% of patients with IF and osteoporosis received such therapy, as did 35.5% of patients with osteopenia and 14% of patients with normal BMD ($P < 0.001$). In the control group, 78.4% of patients with osteoporosis received antiosteoporotic therapy, as did 14% of patients with osteopenia, and 0.7% of patients with normal BMD ($P < 0.001$).

The main antiosteoporotic agents used were bisphosphonates (almost 40%) and denosumab (approximately 10%). The median vitamin D level was higher in the IF than in the control group (31.0 ng/mL [IQR 20.0-41.0] and 25.0 ng/mL [IQR 18.0-36.0], respectively; $P = 0.03$).

In patients with IF, methotrexate (MTX) therapy was associated with low BMD. In patients with IF and osteoporosis, more than half (58.2%) took MTX, as did 41.9% with osteopenia, but only 23.3% of patients with a normal BMD took MTX ($P = 0.002$). In the control group, 27.0% of patients with osteoporosis took MTX, as did 27.9% with osteopenia and 28.2% of patients with normal BMD ($P = 0.99$). In the IF group, 66.7% of patients with a history of fractures took MTX ($P < 0.001$), as compared to 40% ($P = 0.18$) of the control group. The median MTX dose was 15.0 mg/week (IQR 10.0-15.0) in both groups ($P = 0.18$).

Biologics were taken by 21.7% of patients with IF compared to 17% of controls ($P = 0.28$).



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*Table 3.* Patient demographics and risk factors for IF (multivariate analysis).

| | Regression Coefficient, B | Standard Error | Binary Regression | df | *P* | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| Sex | –0.80 | 0.49 | 2.71 | 1 | 0.10 | 0.45 | 0.17-1.16 |
| RA | 1.53 | 1.14 | 1.8 | 1 | 0.18 | 4.62 | 0.49-43.31 |
| PsA | 2.08 | 1.2 | 3.03 | 1 | 0.08 | 8.0 | 0.77-83.23 |
| Other IRD | 1.87 | 1.16 | 2.6 | 1 | 0.11 | 6.5 | 0.67-63.28 |
| No IRD | | | 4.11 | 3 | 0.25 | | |
| Disease duration | –0.02 | 0.02 | 0.61 | 1 | 0.44 | 1.0 | 0.95-1.02 |
| Disease activity | –0.95 | 0.37 | 6.76 | 1 | **0.01** | 0.39 | 0.19-0.79 |
| Elevated APR | 0.52 | 0.35 | 2.22 | 1 | 0.14 | 1.68 | 0.85-3.3 |
| Previous fractures | 0.59 | 0.44 | 1.81 | 1 | 0.18 | 1.8 | 0.77-4.22 |
| Smoking | 0.77 | 0.37 | 4.35 | 1 | **0.04** | 2.17 | 1.05-4.49 |
| Antiosteoporotic therapy | 1.37 | 0.52 | 6.89 | 1 | **0.01** | 3.93 | 1.42-10.9 |
| Vitamin D level | 0.02 | 0.01 | 3.42 | 1 | 0.07 | 1.02 | 1.0-1.04 |
| BMD | | | 7.04 | 2 | **0.03** | | |
| Low BMD | 0.55 | 0.59 | 0.86 | 1 | 0.36 | 1.73 | 0.54-5.5 |
| MTX | 0.86 | 0.35 | 6.19 | 1 | **0.01** | 2.36 | 1.2-4.66 |
| Biologics | 0.91 | 0.41 | 5.03 | 1 | **0.03** | 2.48 | 1.12-5.5 |

Significant *P* values are in bold. APR: acute-phase reactant; BMD: bone mineral density; df: degree of freedom; IF: insufficiency fracture; IRD: inflammatory rheumatic diseases; MTX: methotrexate; OR: odds ratio; PsA: psoriatic arthritis; RA: rheumatoid arthritis.

Most patients were obese (63.3% in the IF group compared to 74.2% in the control group).

A multivariable analysis of the risk factors for the development of an IF was performed (Table 3). The model could explain 78.9% of the contributing factors. Factors with *P* values < 0.05 were disease activity, smoking, antiosteoporotic therapy, BMD, MTX, and biologic exposure.

## DISCUSSION

This retrospective study clearly shows that IFs are a frequent problem in patients with RMDs such as CTD, RA, and PsA, with 8% to 23% of patients affected.

The cohort studied is unique in the way that we took the MRI scans of patients with foot pain performed in our center in 2 different time periods. This aspect can be considered as an important strength of this retrospective study, since the prevalence of IF found in these 2 periods that were independently studied revealed almost the same results.

The high prevalence in CTD may be due to a higher intake of glucocorticoids in the past, but the present intake did not influence the occurrence of IF in this analysis. However, the cumulative dose of glucocorticoids was not assessed in this study. In that line, patients with an inflammatory RMD had a higher prevalence of IF than those with noninflammatory RMDs, but this needs further study.

Our results are in accordance with other studies published more recently[33,34] and earlier on.[35] In the latter study, fractures occurred most frequently in the second and third metatarsals. In our study, the forefoot and midfoot regions were more frequently involved than the ankle joints. Other rheumatic diseases were less frequently but also affected by IF, but in a similar range as in noninflammatory musculoskeletal diseases—approximately 5%.

This study focused on patients presenting with foot pain; thus, this is a clinically relevant problem, and, importantly, the pain was quite often due to fracture. Due to the retrospective design of this study, it was possible to determine the prevalence of IF only in those who presented to our tertiary care hospital with foot pain and not in all patients with RMD. As such, it is possible that IFs were missed in patients who did not experience pain, for example, in patients with polyneuropathy. On the other hand, the frequency of IF may well be lower in other clinical settings such as nonacademic hospitals or ambulatory clinics.

Our study also clearly confirms that MRI rather than conventional radiographs is the method of choice to assess IF. Since no validated scoring system for arthritis had been used, we cannot reliably comment on the relative frequency of inflammation vs fracture in the cohorts. Limitations of MRI include the higher costs and limited availability in some countries. However, the results of this study clearly suggest that the sensitivity of MRI to detect foot fractures is much higher than that of conventional radiographs. Therefore, MRI should be more frequently performed in unclear cases since conventional radiographs are often unable to detect IF. Even though this is associated with an increase in costs, it needs to be stressed that, clearly, treatment of an IF is much different than therapy of active arthritis.

The significance of risk factors was substantiated by univariate and multivariate analyses. However, the results were not identical. Expectedly, two-thirds of patients with IF had a low BMD and > 40% had osteoporosis, which was significantly different to the matched control group. Thirty-five percent of patients with an IF had even suffered a prior fracture. Among the traditional risk factors, age, sex, and smoking, the latter was most convincing, but the first two also have a role even if not decisive.

IF, to our understanding, occur when inadequate (or insufficient) forces lead to a fracture of bone that, under normal circumstances, should not occur. Thus, fractures under minor inappropriate loads are caused by a qualitatively and



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quantitatively (reduced BMD) compromised bone. This is in contrast to the so-called stress fractures, which are defined as fractures that occur as a result of inappropriate and possibly repeated stress on a healthy bone, such as in competitive sports.

The observation that risk factors for IF are similar to those for classic osteoporotic fractures potentially has important implications because IF of the feet are traditionally not included in the list of pathologic fractures due to osteoporosis. Therefore, they are also not included in fracture risk estimations and treatment decision algorithms. Future studies need to explore whether including IF in such algorithms does improve care by preventing IF and other fractures.

However, based on the retrospective study design and the sometimes-limited information obtained from patients' records, we cannot exclude that some of the observed fractures would be better considered as stress fractures due to altered biomechanics because of foot deformities or inappropriate loads. Nevertheless, this, in our experience, will be the case in only a few patients, since, based on this history, those patients will much more likely be referred to orthopedic surgeons.

That disease activity plays a role in the development of IF seems to make sense since inflammation is a trigger for bone loss.[21,36] However, this is a limitation of the study, as we do not have standardized disease activity assessments such as the Disease Activity Score in 28 joints because too many patients had no reliable scores in their records. Another limitation of our study is that the timing and onset of foot pain was not systematically recorded. Therefore, we cannot answer the question whether certain characteristics of foot pain could be used as a clinical variable to differentiate patients with pain due to IF from those with active arthritis in that region.

The fact that antiosteoporotic therapy showed an association with IF is probably explained by the greater risk of fracture that patients with IF likely already had before the current fracture occurred. In any case, antiresorptive therapy with bisphosphonates obviously did not prevent IF. This may be different with other antiosteoporotic agents acting on osteoblasts and bone formation. For example, the recombinant human parathyroid hormone is a bone anabolic drug able to increase BMD and reduce fractures[37]—better than the antiresorptive drug alendronate.[38] Recently, romosozumab, the first inhibitor of sclerostin, a glycoprotein that prevents bone formation and stimulates bone resorption, has been approved for the treatment of osteoporosis.[39] Finally, it has been recommended that patients at high risk of osteoporotic fractures should receive an osteoanabolic agent first.[40]

The anchor drug in RA, methotrexate (MTX), has already shown an association with low BMD, osteoporosis, and fractures.[41-43] In a recent metaanalysis, 80 patients with RMD were described as having IF or stress fractures due to an osteopathy, presumably caused by MTX.[44] However, whether the use of MTX, increased disease activity, and/or the influence of other factors is responsible for these observations remains to be solved.

Treatment with biologics, especially with tumor necrosis factor inhibitors, was not osteoprotective as expected, but was associated with an increased risk of IF in the multivariate analysis. Similar to what was discussed above, this is due to the severity and persistent activity of the disease rather than a negative direct effect of these drugs.[36]

In conclusion, this study shows and confirms that IF is an important differential diagnosis in patients with RA and foot pain with or without swelling. Since MRI is useful for both the detection of fractures and the detection of inflammation, our study clearly favors the use of MRI to differentiate and detect inflammation or fracture. This is important because therapy is different. Our data support the view that risk factors for IF in patients with RMD are similar to those for osteoporotic fractures. This raises the question whether IF should also be considered as osteoporotic fractures. This would encourage the early assessment of BMD in patients with inflammatory RMD to prevent fractures and to possibly initiate osteoprotective therapy in those with a high fracture risk, preferably with osteoanabolic agents. Finally, more research is needed to determine whether disease-modifying antirheumatic drugs such as MTX are a relevant risk factor for IF.

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## DATA SHARING STATEMENT

Data are on file in the hospital Rheumazentrum Ruhrgebiet.

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