High prevalence of foot insufficiency fractures in patients with inflammatory rheumatic musculoskeletal diseases

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Summary

The prevalence of osteoporotic vertebral fractures in rheumatic and musculoskeletal diseases (RMD) is well known but not of insufficiency fractures (IF).

This study shows that IF of the feet occur rather frequently in RMD. Conventional radiography is not sufficient to make a diagnosis. Magnetic resonance imaging is essential for a diagnosis of IF in the feet.

Thus, IF are an important differential diagnosis in RMD patients with foot pain - they have to be excluded before therapeutic decisions are made.

Abstract

Background. Foot pain occurs frequently in rheumatic musculoskeletal diseases (RMD) such as rheumatoid arthritis (RA) with > 90% reporting symptoms. Osteoporosis is common comorbidity leading to vertebral fractures detected by conventional radiography (CR) and magnetic resonance imaging (MRI). The prevalence of insufficiency fractures (IF) in RMD is not well known.

Objective. To assess the prevalence of foot IF in RMD patients with foot pain.

Methods. In a retrospective design, 1,752 MRIs of consecutive patients presenting with foot pain in two time periods between 2016 - 2018 were evaluated. The group with IF was matched with controls with foot pain without IF. Bone mineral density (BMD) was assessed by DXA. Multivariate analyses were performed.

Results. A total of 1,145 MRIs of patients (mean age 59 years, 83% female) with inflammatory (65.4%) or non-inflammatory RMD (34.6%) was available. Most patients had RA (42.6%), psoriatic arthritis (22.4%), axial spondyloarthritis (11.1%) or connective tissue disease (7.6%). Foot IF were found in 129 MRI 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 non-inflammatory RMD had IF: 9.1% vs 4.1%, respectively ($p<0.001$). Using CR, IF were only detected in 25%. Low BMD and a history of fractures were more frequent in patients with IF: 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 of RMD patients, many without osteoporosis. MRI was more sensitive than X-rays to detect IF.

Introduction

Rheumatoid arthritis (RA) is a frequent chronic inflammatory rheumatic musculoskeletal disease (RMD) predominantly affecting small joints by inflammation which is often associated with joint damage and functional loss and premature mortality (1-3). There are many other inflammatory RMD such as psoriatic arthritis (PsA), but also non-inflammatory 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 – 93% (7,8). Foot problems mainly starting in the metatarsophalangeal (MTP) joints in nearly 90% of cases (9) are the first symptom in 15% of RA patients (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 – 60% of the patients, while 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 form of bursitis, tendinitis, tenosynovitis, fasciitis, neuropathy, skin ulceration and rheumatoid nodules may occur (10). A high body mass index (BMI) 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 > 50 years worldwide are expected to be at high-risk of a fragility fracture (15). This has prompted EULAR and EFORT to develop recommendations to promote a more effective management and prevention of such fractures (16,17).

Low bone mineral density (BMD) and falls are major risk factors for fractures. Early recognition is important because fractures tend to recur (18), and their prevention is possible by using validated fracture risk assessment tools such as FRAX (19) and devices to assess BMD such as dual X-ray absorptiometry (DXA) to determine osteoporosis as defined by WHO (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 involves also 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).

While conventional radiography is still recognized as the method of choice to assess fractures diagnostic imaging to assess IF seems better with 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, X-rays and MRI, and to determine risk factors.

Patients and 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 magnetic resonance imaging (Siemens Aera 1.5 Tesla) of the foot or the ankle. From this data set, the frequency of insufficiency fractures (IF) as confirmed by the radiologist (MF) was determined. Due to the retrospective study design no written consent of patients was obtained. The study was approved by the ethical committee of the Ruhr University Bochum, nr. 20-7068-BR.

In a next step, patients with IF were matched and compared to patients with the same demographic data such as gender, age, 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 06/30/2016 - 07/01/2018.

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 active yes or no according to the records.

Patients with IF were compared with patients without IF who had the same or similar demographic data. One patient with IF was assigned to two control patients based on the following criteria: gender, age +/- 10 years, disease (diagnosis) and disease duration about 5 years.

The primary endpoint was the number of patients with IF in foot MRIs within the study observation periods (06/30/2016 to 07/01/2018).

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 two steps. First, the ratio, median, mean, interquartile range and standard deviation of each aspect examined were calculated in Excel. This was followed by an examination in SPSS for statistical correlation and

relevance. Then the two time periods were compared to check whether the numbers and percentages were similar.

Then, 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 insufficiency fractures. Chi-square test and Fischer test allowed conclusions about the independence of the variables. Assessment of the metric in correlation with the nominal data set was based on Spearman's rank correlation coefficient for nonnormally distributed data and Pearson's correlation coefficient for normal distribution. 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.

Results

A total of 1,752 MRIs was identified. There were more foot than ankle MRIs: 1,430 MRI scans of the foot (81.6%) and 322 of the ankle (18.4%). These MRIs were from 1,145 patients with an inflammatory rheumatic disease (65.4%) and from 607 with no inflammatory rheumatic disease (34.6%).

Most patients (n= 483) with an inflammatory rheumatic disease (IRD) had RA (42.2%), 256 PsA (22.4%), 127 axSpA (11.1%), and 279 had other inflammatory rheumatic diseases (24.4%). Among these there were 87 patients with connective tissue diseases (7.6% of IRD patients) including lupus, Sjoegren’s syndrome, scleroderma 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 (14.0%).

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

A total of 129 MRIs of patients had an IF (7.48%). The prevalence of IF was higher in foot MRIs (n=116, 8.11%) than in ankle MRIs (n=13, 4.04%), respectively. In Figures

1-3 several examples of IF are given, and in addition, for comparison, one example of a patient with dactylitis who had no fracture.

A total of 104 patients with an inflammatory rheumatic disease had an IF (9.1%).
A total of 25 patients with non-inflammatory rheumatic diseases had an IF (4.1%).

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

- between 2016-2017, 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 foot, 8 ankle).
- between 2017-2018, 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 foot, 5 ankle).

Among the 104 patients with an inflammatory rheumatic disease and IF, there were 55 patients with RA (52.9%), 21 with PsA (20.2%), 20 with connective tissue diseases (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 one bone (44%). In these patients, a total of 159 fractures was 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 one fracture or with more than one fracture (data not shown).

Patients' 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 (i.e. women were 4.8 times more often affected than men). In the IF group the median age was 59, the mean disease duration was 8,4 years. Patients with RA (mean age 62) and Vasculitis/PMR (mean age 71.5) were significantly older than the other groups of inflammatory diseases (mean age 53-56) or patients with non-inflammatory diseases (mean age 52). All patients with IF and the controls reported foot pain but no history

of trauma. Fewer patients in both groups had foot swelling: 32.6% with IF and 34.1% of controls.

Among the patients with IF, RA was the most common inflammatory RMD (n=55), followed by PsA (n=21) and connective tissue diseases (n=20).

- 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 connective tissue diseases, 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, an X-ray was taken before the MRI examination. By X-ray, fractures were only detected in 25% of cases. MRIs were requested in 40.3% of patients with IF 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. While 37.2% of patients with IF reported current smoking this was less frequent in the controls (23.1%), p=0.005. The median BMI was 28.52 kg/m^2 (IQR 7.90) in the controls and 27.31 kg/m^2 (IQR 7.55) in the IF patients (p=0.018).

Patients with IF were more likely to have an abnormal bone mineral density (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, while osteopenia was found in 24.0% of IF and 18.8% of controls. One third of the IF patients and two thirds of the controls had a normal BMD. A previous fracture was more likely to have occurred in patients with IF, where 34.9% of patients with IF and only 8.9% of controls had a history of fracture (p<0.001).

Patients with IF and osteoporosis (63.0 years, IQR 15.0) or osteopenia (63.0 years, IQR 16.0) were older than those with normal BMD (53.0 years, IQR 16.0), p<0.001. This was similar in the control group, where patients with osteoporosis and osteopenia had a median age of 61.0 (IQR 13.5) and 63.0 (IQR 15.0), respectively.

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% osteopenia. In this group, only 18.4% of women had osteoporosis, 21.1% osteopenia and 60.5% a normal BMD (p=0.013).

Patients with low BMD were more likely to receive anti-osteoporotic therapy. Thus, a proportion of 89.1% with IF and osteoporosis received such therapy, 35.5% of

patients with osteopenia and 14.0% of patients with normal BMD (p<0.001). In the control group, 78.4% of patients with osteoporosis received anti-osteoporotic therapy, 14.0% of patients with osteopenia and 0.7% of patients with normal BMD (p<0.001).

The main anti-osteoporotic agents used were bisphosphonates (almost 40%) and denosumab (about 10%). The median vitamin D level was higher in the IF than in the control group: 31.0 (IQR 21.0) and 25.0 ng/ml (IQR 15.0), respectively (p=0.032).

In patients with IF, MTX therapy was associated with low BMD. In patients with IF and osteoporosis, more than half (58.2%) took MTX, 41.9% with osteopenia and only 23.3% of patients with a normal BMD (p=0.002). In the control group, 27.0% of patients with osteoporosis took MTX, 27.9% with osteopenia and 28.2% of patients with normal BMD (p=0.990). In the IF group, 66.7% of patients with a history of fractures took MTX (p<0.001) as compared to the control group with 40.0% (p=0.18). The median MTX dose was 15.0 mg/week (IQR 5.0) in both groups, p=0.18.

Biologics were taken by 21.7% of patients with IF compared to 17.0% of controls (p=0.28).

Most patients were obese: 63.3% in the IF 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, osteoporosis therapy, bone mineral density, MTX and biologic exposure.

Discussion

This retrospective study clearly shows that insufficiency fractures (IF) are a frequent problem in patients with RMDs such as connective tissue diseases (CTD), rheumatoid arthritis (RA) and psoriatic arthritis (PsA) with 8-23% of patients affected.

The cohort studied is unique in the way that we took the MRIs of patients with foot pain performed in our center in two different time periods. This aspect, however, can be considered as an important strength of this retrospective study, since the prevalence of IF found in these two 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 didn't 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 non-inflammatory 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 non-inflammatory musculoskeletal diseases – in around 5%.

This study has 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 is not possible to determine the prevalence of IF in all patients with RMD but only in those who presented to our tertiary care hospital with foot pain. As such, it is possible that IF 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 non-academic hospitals or ambulatory clinics.

Our study also clearly confirms that MRI rather than conventional X-rays 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 X-rays. 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% osteoporosis - significantly different to the matched control group; and 35% 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.

Insufficiency fractures, in 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 quantitatively (reduced BMD) compromised bone. This is in contrast to the so called stress fractures which are defined as fractures that occur due to inappropriate and possibly repeated stress on a healthy bone – 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 should be better considered as stress fractures due to altered biomechanics because of foot deformities or inappropriate loads. Nevertheless, this, in our experience, will only 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 for 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, we don't have standardized disease activity assessments such as DAS28 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 parameter to differentiate patients with pain due to IF from those with active arthritis in that region.

The fact that anti-osteoporotic therapy showed an association with IF is probably explained by the greater risk of fracture of patients with IF obviously had already

before the current fracture occurred. In any case, anti-resorptive therapy with bisphosphonates did obviously not prevent IF. This may be different with other anti-osteoporotic 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 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 of MTX with low BMD, osteoporosis and fractures (41-43). In a recent meta-analysis, 80 RMD patients were described who had IF or stress fractures due to an osteopathy presumably caused by MTX (44). However, whether the use of MTX or rather increased disease activity and/or influence of other factors is responsible for these observations remains to be solved.

Treatment with biologics, especially with TNF 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 rather due to the severity and persistent activity of the disease rather than a negative direct effect of these drugs (36).

Conclusions

In conclusion, this study shows and confirms that IF are 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 DMARDs such as MTX are a relevant risk factor for IF.

Tables and Figures: see extra files

Conficts of interest: Bjoern Buehring, Nadine Al-Azem, Uta Kiltz, Martin Fruth, Ioana Andreica, David Kiefer, Stella Tsiami, Xenofon Baraliakos und Jürgen Braun declare that they have no conflict of interest.

Contributorship: Study design by B. Buehring, N. Al-Azem and J.Braun. Data extraction from files: N. Al-Azem and S.Tsiami. Information on patient data: I.Andreica and D.Kiefer. Images including interpretation: M.Fruth, X.Baraliakos, J.Braun. Data analysis: B.Buehring, N.Al-Azem, U.Kiltz, X.Baraliakos and J.Braun.

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Figure 1. Magnetic resonance images (MRI) of the forefoot and the corresponding X-ray in 2 patients with an insufficiency fracture.

Figure 1a. MRI of a **r**adiographically occult subcapital fracture of 3rd metatarsal head in a 56-year-old female patient with rheumatoid arthritis, 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 (yellow arrows).

Figure 1b. MRI of a **r**adiographically not detected fracture of the basis of the 3rd metatarsal right foot (yellow arrow) of a 61-year-old male patient with psoriatic arthritis, disease duration 6 years. Due to the complex anatomy in this area radiographic the detection of fractures can be challenging. 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.

Figure 2 a and b. Sagittal contrast enhanced T1weighted fat saturated magnetic resonance images (MRI) of the forefoot and the corresponding X-rays in 2 patients.

Figure 2a. MRI of a 66-year-old female patient admitted with foot pain and suspicion of arthritis showing a subchondral fracture of the 2nd 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).

Figure 2b. MRI of a 51-year-old male patient with long standing axial spondyloarthritis with peripheral involvement showing dactylitis of the 4th toe with dominant arthritis of the metatarsophalangeal joint, no fracture .

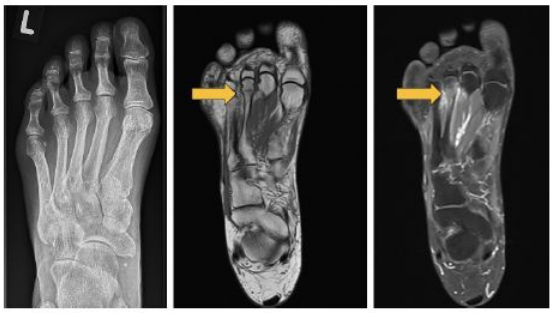
The radiograph shows a mineralized periostal reaction of the proximal basophalangeal metadiaphysis (white arrows), no fracture.

Figure 3a and b. Magnetic resonance images (MRI) and the corresponding radiographs of 2 patients.

Figure 3a. Coronar MRI proton density weighted (Pdw) turbo spin echo (TSE) fat saturated (FS) and the corresponding radiograph of a 57-year-old female patient with an osteodestructive course of rheumatoid arthritis presenting with lateral ankle pain for about 6 weeks.

Both, MRI and X-ray, show a juxtasyndesmal insufficiency fracture of the fibula with reactive periostal thickening and mineralization due to callus formation (yellow arrows).

Figure 3b. MRI T1weighted and STIR of a 42-year-old female patient with Psoriatic Arthritis for approx. 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.



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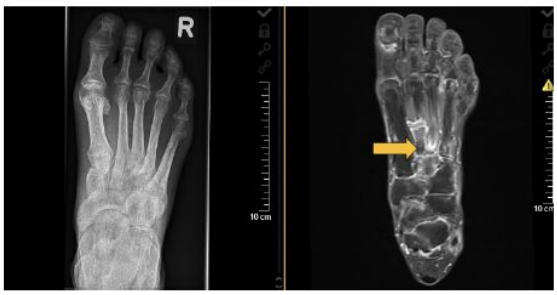

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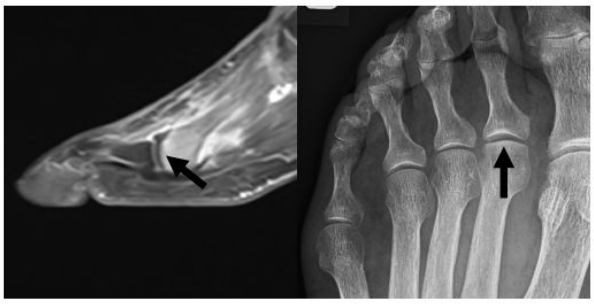

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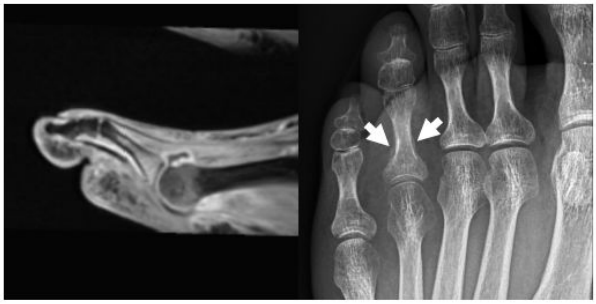

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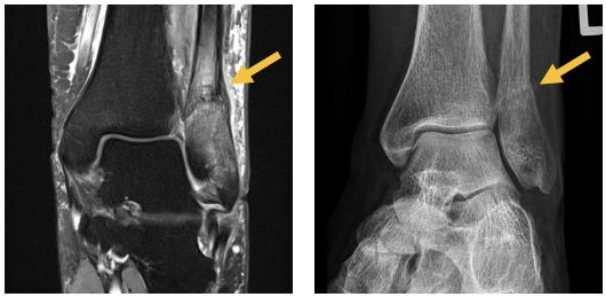

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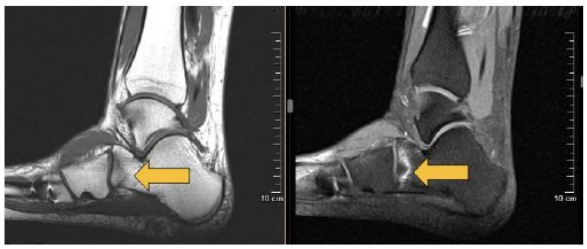

Figure 3b. MRI T1weighted and STIR of a 64-year-old male patient with gout. The T1w MRI shows a blurred zigzag-shaped hypointense fracture line at the anterior calcaneum with surrounding bone marrow edema depicted by STIR imaging.

Table 1 Demographics of patients with IF and controls without IF

Variable	Patients with IF n = 129	Controls without IF n = 229
Females, n (%)	107 (82.9)	185 (80.8)
Median age in years (IQR)	59 (15.5)	58 (15.0)
Age range (in years)	17-85	20-84
Mean disease duration (years)	8.4 (10.3)	7.3 (8.0)
Rheumatoid arthritis, n=483 (% of patients with or without IF)	55 (42.6)	106 (46.3)
Psoriatic arthritis, n=256 (%) (% of patients with or without IF)	21 (8.2)	43 (18.8)
Connective tissue diseases, n=87 (%) (% of patients with or without IF)	20 (15.5)	38 (17%)
NIRD, n=607 (%)	25 (19.4)	35 (15.3)

IF = insufficiency fracture; IRD = inflammatory rheumatic disease;
NIRD = non-inflammatory rheumatic diseases

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

Variable	IF (%)	Controls without IF (%)	P value
Current smoking, n (%)	48 (37.2)	53 (23.1)	**0.005**
BMI (kg/m^2)	27.3 (7.6)	28.5 (7.9)	**0.018**
Lowest T-score	- 2.000 (1.6)	- 1.600 (1.9)	**0.002**
Osteoporosis, n (%)	55 (42.6)	37 (16.2)	**< 0.001**
Osteopenia, n (%)	31 (24.0)	43 (18.8)	
Normal BMD, n (%)	43 (33.3)	149 (65.1)	
History of fractures, n (%)	45 (34.9)	20 (8.6)	**< 0.001**
Anti-osteoporotic therapy, n (%)	66 (51.2)	36 (15.7)	**< 0.001**
Glucocorticoid intake, n (%)	62 (48.1)	102 (44.5)	0.521
Methotrexate, n (%)	55 (42.5)	64 (27.9)	**0.005**
Biologics, n (%)	28 (21.7)	39 (17)	0.276

BMI = body mass index (BMI); BMD = bone mineral density; IF = insufficiency fracture

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

Variable	Regression coefficient B	Standard error (SD)	Binary regression	df	p value	OR	95% CI low	95% CI high
Sex	-0.803	0.49	2.71	1	0.1	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	-0.016	0.02	0.61	1	0.44	1.0	0.95	1.02
Disease activity	-0.95	0.37	6.76	1	**0.009**	0.39	0.19	0.79
Elevated APP	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	**0.037**	2.17	1.05	4.49
Anti-osteoporotic therapy	1.37	0.52	6.89	1	**0.009**	3.93	1.42	10.9
Vitamin D level	0.02	0.01	3.42	1	0.065	1.02	1.0	1.04
BMD			7.04	2	**0.030**			
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	**0.013**	2.36	1.2	4.66
Biologics	0.91	0.41	5.03	1	**0.025**	2.48	1.12	5.5

IF = insufficiency fractures; IRD = inflammatory rheumatic diseases; RA = rheumatoid arthritis; PsA = psoriatic arthritis; BMD = bone mineral density; APP = acute phase proteins. MTX = methotrexate. Df = degree of freedom; CI = confidence interval; OR = odds ratio. Significant p values are in bold letters.