Do MRI-detected erosions in the RA-risk phase of arthralgia reflect current or imminent radiographic erosions? A large longitudinal imaging study

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Clinical science

Do MRI-detected erosions in the RA-risk phase of arthralgia reflect current or imminent radiographic erosions? A large longitudinal imaging study

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Abstract

Objectives: Radiographic erosions of hands and feet are a hallmark of rheumatoid arthritis (RA) and treatment aims to prevent radiographic progression. In the at-risk phase of clinically suspect arthralgia (CSA), erosions on radiographs are rare but can be visible on MRI, which is a more sensitive imaging technique. However, the value of these MRI erosions and especially the relation with radiographic erosions is unknown. Therefore, we aimed to study if MRI-detected erosions in CSA (i) correspond with simultaneous radiographic erosions and (ii) associate with local radiographic progression.

Methods: Patients included in the Leiden CSA cohort (2012–2021) were followed until RA development or for 2 years. Unilateral hand-and-foot baseline MRIs were scored for erosions (RAMRIS score ≥ 1) and subclinical inflammation (synovitis/tenosynovitis/osteitis). Serial hand and foot radiographs (baseline, 12 and 24 months) were scored for erosions [Sharp-van-der-Heijde erosion-score (SHS) ≥ 1] and progression (delta-SHS ≥ 1). Generalized estimating equation evaluated if MRI erosions associated with radiographic erosions or progression in the same bone. Additionally, analyses were repeated considering concomitant MRI-detected subclinical inflammation.

Results: A total of 190/405 CSA patients (47%) had MRI-detected erosions at one or more of the 23 studied bone locations. An MRI-detected erosion associated with a local radiographic erosion [OR 5.23 (95%CI2.78–9.86)]; but in 96.5% of locations with an MRI-detected erosion a radiographic erosion was absent. MRI erosions with concomitant local subclinical inflammation revealed a stronger association [OR 6.29(2.94–13.48)]. Local radiographic progression was rare (0.4%). MRI erosions at baseline did not predict radiographic progression [OR 1.75(0.52–5.85)].

Conclusion: The majority of MRI-detected erosions in CSA patients does not correspond with radiographic erosive disease or progression. Therefore, MRI-detected erosions in this risk phase, especially without inflammation, should be regarded with caution to avoid overinterpretation.

Keywords: MRI-detected erosions, clinically suspect arthralgia, radiography.

Rheumatology key messages

- In clinically suspect arthralgia (CSA) patients, the majority of MRI-detected erosions does not correspond with radiographic erosive disease or progression.
- MRI-detected erosions in CSA patients should be regarded with caution to avoid overinterpretation.

Introduction

Erosive disease depicted on radiographs of hands is a hallmark of rheumatoid arthritis (RA). Traditionally, treatment is aimed at preventing erosive progression and its associated physical impairments. Due to improved treat-to-target strategies and novel treatments of the last decennia, prevalence of erosive progression has diminished and severe joint damage can largely be prevented [1, 2]. Nevertheless, even in early RA, erosions are still present and relevant for treatment decisions [3]. Also in patients with arthralgia suspicious for progression to RA (that is, clinically suspect arthralgia, CSA), radiographic erosions can occur [4].

Although conventional radiography is generally used to depict erosions in RA, erosions are also visible with more advanced imaging techniques such as magnetic resonance imaging (MRI). MRI has shown its value by visualizing (subclinical) joint inflammation and thereby identifying patients at high risk of progression to RA [5, 6]. Despite its use for detecting

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subclinical inflammation, MRI is also a sensitive imaging technique to detect erosions [7]. Thus far, the feasibility of MRI is limited by time and cost issues, but the development of short scanning protocols (such as the modified Dixon sequence) and using artificial intelligence to read the MRIs may increase the use of MRI for clinical practice in the nearby future [8]. Moreover, MRI-detected joint inflammation is also a component of the EULAR/ACR risk stratification criteria for RA development [9]. When MRI of small joints will be more often conducted to assess inflammation, MRI-detected erosions will become more frequently detected. However, to date, the relevance of MRI-detected erosions in arthralgia patients at risk for RA but without clinically apparent arthritis is unclear.

As it can be expected that MRIs of the small joints will be increasingly used, it is relevant to comprehend the value of MRI erosions in CSA patients. Its relation with 'true erosive disease' as depicted by radiographs, in particular, remains to be elucidated. Therefore, we performed a study in CSA patients on bone level to determine whether MRI-detected erosions depict simultaneous radiographic erosions or indicate local radiographic progression.

Methods

Patients and follow-up

Patients were consecutively included in the Leiden Clinically Suspect Arthralgia cohort (Leiden CSA) between April 2012 and May 2021. All included patients had recent-onset (<1 year) arthralgia of the small joints considered clinically suspect for progression to RA according to the clinical expertise of the rheumatologist. Exclusion criteria were presence of clinically apparent arthritis or if another explanation for the arthralgia was more likely than evolving RA (e.g. osteoarthritis or fibromyalgia). Patients were included regardless of ACPA status, which was determined after inclusion and considered positive as anti-CCP2 ≥ 7 U/ml (EliA CCP, Phadia, the Netherlands). The cohort is previously described more extensively and in Supplementary File 1, available at *Rheumatology* online [10]. All patients provided written informed consent. Patients were followed for two years or until development of inflammatory arthritis, whichever occurred firstly. Development of clinically apparent inflammatory arthritis was determined via physical examination at the outpatient clinic. Patients with CSA did not use disease-modifying antirheumatic drugs (DMARDs) during follow-up.

Imaging with MRI

Within two weeks after the inclusion baseline visit, a unilateral contrast-enhanced 1.5 T MRI of the wrist, second to fifth metacarpophalangeal (MCP) and first to fifth metatarsophalangeal (MTP) joints was conducted of the most painful side (or the dominant side in case of equally severe symptoms on both sides) (Supplementary File 2, available at *Rheumatology* online for MRI protocol). MRIs were scored according to the RA MRI scoring system (RAMRIS) for erosions, synovitis and osteitis, and for tenosynovitis according to Haavardsholm [11, 12]. Two independent trained readers scored all MRIs with high inter-reader intraclass correlation coefficients (≥0.91) and were blinded for clinical data.

Imaging with radiographs

At baseline and during follow-up visits at 12 and 24 months, or upon development of inflammatory arthritis, bilateral radiographs of hands and feet were made. Some patients underwent additional radiographs at 4 months follow-up. Radiographs were scored via the Sharp van der Heijde Scoring method (SHS). One trained reader [with high intrareader intraclass correlation coefficient (0.98)] scored all serial radiographs with known time order and was blinded for clinical data [13].

A detailed explanation of the locations scored via RAMRIS and SHS is provided in Supplementary File 3, available at *Rheumatology* online. For this study, we focused on bone-locations that were scored via both scoring methods: the proximal and distal bones of the second to fifth MCP joints, of the first to fifth MTP joints and the trapezium, scaphoid, lunate, distal radius and distal ulna bone. Thus, we studied 23 bones per patient.

Definitions of MRI-detected and radiographic erosions

A baseline MRI-detected erosion was defined as present if the mean RAMRIS erosion score of two readers was ≥1 (indicating 1–10% of the bone eroded). Additionally, we determined which erosions were accompanied by local subclinical inflammation. For the MCP and MTP joints, local subclinical inflammation was considered present if the mean RAMRIS synovitis/tenosynovitis/osteitis score of two readers was ≥1 in the similar joint, tendon sheath or bone as the equivalent MRI-detected erosion. For wrist-bone locations, mean osteitis score of two readers had to be ≥1 in the equivalent bone, or synovitis had to be ≥1 in the approximating wrist joints (radiocarpal or intercarpal joints for trapezium/scaphoid, radiocarpal or radio-ulnar for lunate/distal radius/distal ulna).

A radiographic erosion was defined as present if the SHS erosion score was ≥1. Radiographic erosive progression was defined as the change in SHS erosion score of ≥1 between the baseline radiograph and the last radiograph.

Statistical analyses

Analyses were done at bone level. The unilateral MRI was matched to the hand and foot radiographs of the ipsilateral side; the radiographs of the contralateral side were not used for this study.

The prevalence of MRI-detected and radiographic erosions was described at bone level and concordance was evaluated. The association of an MRI-detected erosion and a radiographic erosion or radiographic progression at the same location was studied via binomial generalized estimating equations (GEEs) with exchangeable correlation structure. By using GEE, intra-patient similarities between the 23 bone locations could be corrected for. GEEs with radiographic erosive progression as outcome were adjusted for age. Group-level test characteristics (sensitivity and specificity) and the likelihood ratio for a positive test (LR+) were calculated. The latter calculates the probability of abnormality (radiographic erosion) given the presence of an MRI-detected erosion [by formula 'sensitivity/(100-specificity)'] [14]. As the a priori probability of radiographic erosions in CSA is low, positive predictive values were not calculated as they are per definition low and thus not informative (Bayesian statistics) [15].

Because subclinical inflammation may be present prior to erosion development, hypothetically an erosion with local inflammation could be of different value than an erosion without local inflammation [16]. To study this, all analyses were repeated by evaluating MRI-detected erosions with accompanying subclinical inflammation at the same location.

Furthermore, as a sub analysis, patients were stratified for ACPA-status because of pathophysiological differences between the disease course of ACPA-positive and ACPA-negative RA [17, 18].

Analyses were conducted using SPSS (v29) and STATA (v16). *P*-values of <0.05 were considered significant.

Results

Patients

A total of 772 patients were consecutively included in the Leiden CSA cohort and 405 patients with a baseline MRI and ≥2 serial radiographs were included in present study (Supplementary File 4, available at *Rheumatology* online). Patients who were excluded due to missing imaging [baseline MRI ($n=49$), serial radiographs ($n=261$)] or due to DMARD treatment in a trial setting ($n=57$) had similar baseline characteristics as included patients (Supplementary File 5, available at *Rheumatology* online). The majority of patients was female (76%), mean age was 45 years, 13% was ACPA-positive and 21% was rheumatoid factor (RF)-positive (Table 1). During median 25 months follow-up, 67 (17%) patients developed inflammatory arthritis.

Presence of MRI-detected and radiographic erosions

On the patient level, 190 of 405 patients (47%) had MRI-detected erosions at one or more of the 23 studied bone locations. Mostly, these were present in the proximal bones of MCP-2 and -3, in the wrist and in the proximal bones of MTP-1 and -5 (Fig. 1). In total, 62 of 405 patients (15%) had any radiographic erosion. At bone level, 341 (3.7%) of the 9277 studied bones showed an MRI-detected erosion and 73 (0.8%) a radiographic erosion. Thus, MRI erosions were more prevalent than radiographic erosions.

MRI-detected erosions in relation to radiographic erosions

Then, concordance and discordance between MRI-detected and radiographic erosions were studied on bone level. Of the 341 locations with an MRI-detected erosion, 3.5% showed and 96.5% did not show a radiographic erosion. Consequently, a bone with an MRI erosion had higher odds of having a local radiographic erosion (OR 5.23, 95% CI 2.78–9.86) (Table 2A). Fig. 2 shows an example of concordance (both modalities show similar features) between an MRI and radiographic erosion (Fig. 2A) and discordance (modalities show something different) between the two imaging modalities (Fig. 2B).

Then, accompanying subclinical inflammation was taken into account. Of 179 locations with MRI-detected erosions with accompanying subclinical inflammation, 4.5% showed a radiographic erosion. The presence of local subclinical inflammation accompanying the MRI-detected erosion increased the association with a radiographic erosion (OR 6.29, 95% CI 2.94–13.48) (Table 2B).

When stratifying for ACPA status, in ACPA-negative CSA patients, 4.5% of bone locations with an MRI-detected erosion also showed a radiographic erosion and 95.5% did not show a radiographic erosion. Within the ACPA-positive CSA patients, none of the bone locations with an MRI erosion also showed a radiographic erosion. Thus, a radiographic erosion in the case of an MRI-detected erosion was rare in both ACPA-negative and ACPA-positive CSA.

Test characteristics of MRI-detected erosions for radiographic erosions

The specificity of MRI-detected erosions for radiographic erosions was 96%, and 98% when accompanying subclinical inflammation was present. This indicated that MRI can accurately identify the bones without a radiographic erosion. On the contrary, the sensitivity (the ability to identify those with a radiographic erosion) was 16%. The positive likelihood (LR+) of an MRI-detected erosion was 4.6 (Supplementary File 6, available at *Rheumatology* online). The LR+ increased to 5.9 after accounting for local concomitant MRI-detected subclinical inflammation.

After stratification for ACPA status, an MRI-detected erosion increased the probability of a local radiographic erosion in ACPA-negative CSA patients (LR+ 5.1). Numbers were too low for ACPA-positive CSA patients.

MRI erosions in relation to radiographic erosive progression

Of all bone locations, 35 (0.4%) locations showed radiographic progression during follow-up. Presence of a local MRI erosion at baseline did not associate with radiographic progression in the same bone (OR 1.75, 95% CI 0.52–5.85) (Table 2A). Also, no association was observed when accompanying subclinical inflammation was taken into account, although the OR increased (OR 3.23, 95% CI 0.95–10.95) (Table 2B). When studying ACPA-positive and -negative patients separately, results were similar. Thus, regardless of ACPA status, MRI-detected erosions were not associated with radiographic progression.

Table 1. Baseline characteristics of study population

	CSA patients ($n=405$)
Female sex	308 (76)
Age, years	44 ± 13
Symptom duration, weeks	20 (10–43)
TJC-68	5 (2–10)
VAS pain	50 (30–65)
ACPA-positive	51 (13)
RF-positive	85 (21)
CRP, mg/L	3 (3–5)
MRI-detected subclinical features	
Synovitis	1.0 (0–2.8)
Tenosynovitis	0 (0–1.5)
Osteitis	1.0 (0–1.5)
Erosion	1.5 (0.5–2.5)

Data are depicted in n (%), mean ± standard deviation or median (interquartile range) as applicable. ACPA is positive if anti-CCP2 ≥ 7 U/mL. RF is positive if ≥ 3.5 IU/mL. MRI-detected subclinical inflammatory features are depicted as RAMRIS scores.
ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; RAMRIS: RA MRI scoring system; RF: rheumatoid factor; TJC-68: tender joint count including 68 joints; VAS: visual analogue scale.

Discussion

In this large observational study including two imaging modalities, the value of MRI-detected erosions in symptomatic arthralgia patients at risk of RA was studied. Although MRI-detected erosions were statistically significant associated with local radiographic erosions, in the large majority of the bone locations with an MRI-detected erosion, a radiographic

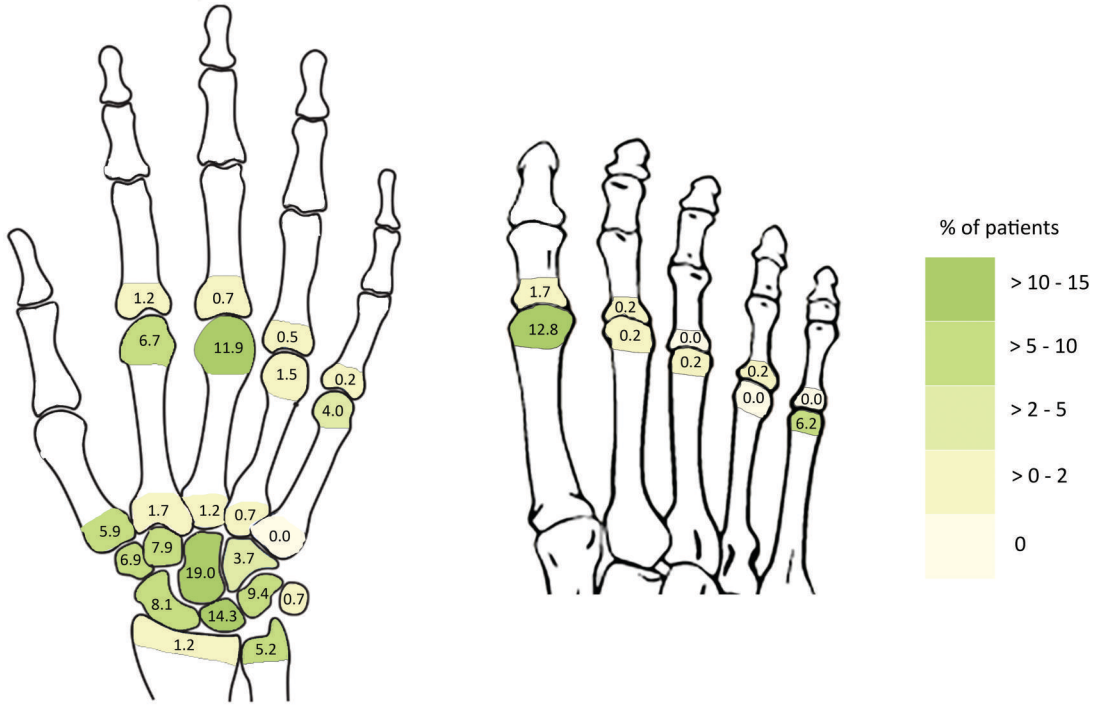

Figure 1. Prevalence of MRI-detected erosions of MCP, wrist and MTP joints in CSA patients at bone level. Percentages of patients with MRI-detected erosion (RAMRIS score ≥1) at specific bone locations. In total, 190 (47%) of 405 patients had at least one MRI-detected erosion. As examples, 6.7% of the total study population (27/405) had an MRI-detected erosion in the proximal bone of MCP2, and 0% of patients had an erosion in the distal bone of MTP3. This figure shows all bone locations that were scored by RAMRIS. For the statistical analyses, only bone locations that are scored with both the RAMRIS and SHS were included: the proximal and distal bones of the second to fifth MCP joints, first to fifth MTP joints and the trapezium, scaphoid, lunate, distal radius and distal ulna bone (23 locations in total). CSA: clinically suspect arthralgia; MCP: metacarpophalangeal; MRI: magnetic resonance imaging; MTP: metatarsophalangeal; RAMRIS: RA MRI scoring system

Table 2. Association between baseline MRI erosion and radiographic erosion or erosive progression

	Radiographic erosion at baseline		OR (95% CI)	Radiographic progression during follow-up		OR (95% CI)
A. MRI-detected erosion						
	Yes	No		Yes	No	
Total cohort						
Yes	12 (3.5%)	329 (96.5%)	5.23 (2.78–9.86)	3 (0.9%)	338 (99.1%)	1.75 (0.52–5.85)
No	61 (0.7%)	8875 (99.3%)		32 (0.4%)	8924 (99.6%)	
ACPA-positive						
Yes	0 (0%)	47 (100%)	—	1 (2.1%)	46 (97.9%)	3.19 (0.38–26.49)
No	6 (0.5%)	1110 (99.5%)		7 (0.6%)	1119 (99.4%)	
ACPA-negative						
Yes	12 (4.1%)	281 (95.9%)	5.92 (3.12–11.25)	2 (0.7%)	291 (99.3%)	1.44 (0.33–6.23)
No	55 (0.7%)	7743 (99.3%)		25 (0.3%)	7783 (99.7%)	
B. MRI-detected erosion + subclinical inflammation						
Total cohort						
Yes	8 (4.5%)	171 (95.5%)	6.29 (2.94–13.48)	3 (1.7%)	176 (98.3%)	3.23 (0.95–10.95)
No	65 (0.7%)	9033 (99.3%)		32 (0.4%)	9086 (99.6%)	
ACPA-positive						
Yes	0 (0%)	26 (100%)	—	1 (3.8%)	25 (96.2%)	5.73 (0.65–50.15)
No	6 (0.5%)	1131 (99.5%)		7 (0.6%)	1140 (99.4%)	
ACPA-negative						
Yes	8 (5.3%)	144 (94.7%)	7.20 (3.34–15.51)	2 (1.3%)	150 (98.7%)	2.62 (0.59–11.61)
No	59 (0.7%)	7880 (99.3%)		25 (0.3%)	7924 (99.7%)	

Numbers represent all studied bone locations. Odds ratios are obtained by GEEs analysing the association between a baseline MRI erosion (yes/no) and a baseline radiographic erosion (yes/no) or radiographic progression (yes/no). For example, an OR of >1 indicates a greater chance of presence of a radiographic erosion in the case of an MRI erosion in the same bone. Analyses with radiographic progression as outcome are adjusted for age. Results are depicted as OR (95% CI). MRI erosion + subclinical inflammation indicates that an MRI erosion is accompanied by local synovitis, tenosynovitis or osteitis. ACPA: anti-citrullinated protein antibody; CI: confidence interval; GEE: generalized estimating equations; OR: odds ratio.

erosion or radiographic progression was absent. MRI-detected erosions in patients with arthralgia at-risk for RA should therefore be considered with caution in order to avoid overinterpretation.

MRI-detected erosions were not associated with radiographic progression, also not in ACPA-positive arthralgia patients. This finding underlines for the clinician that an MRI-detected erosion on its own is not reason enough to

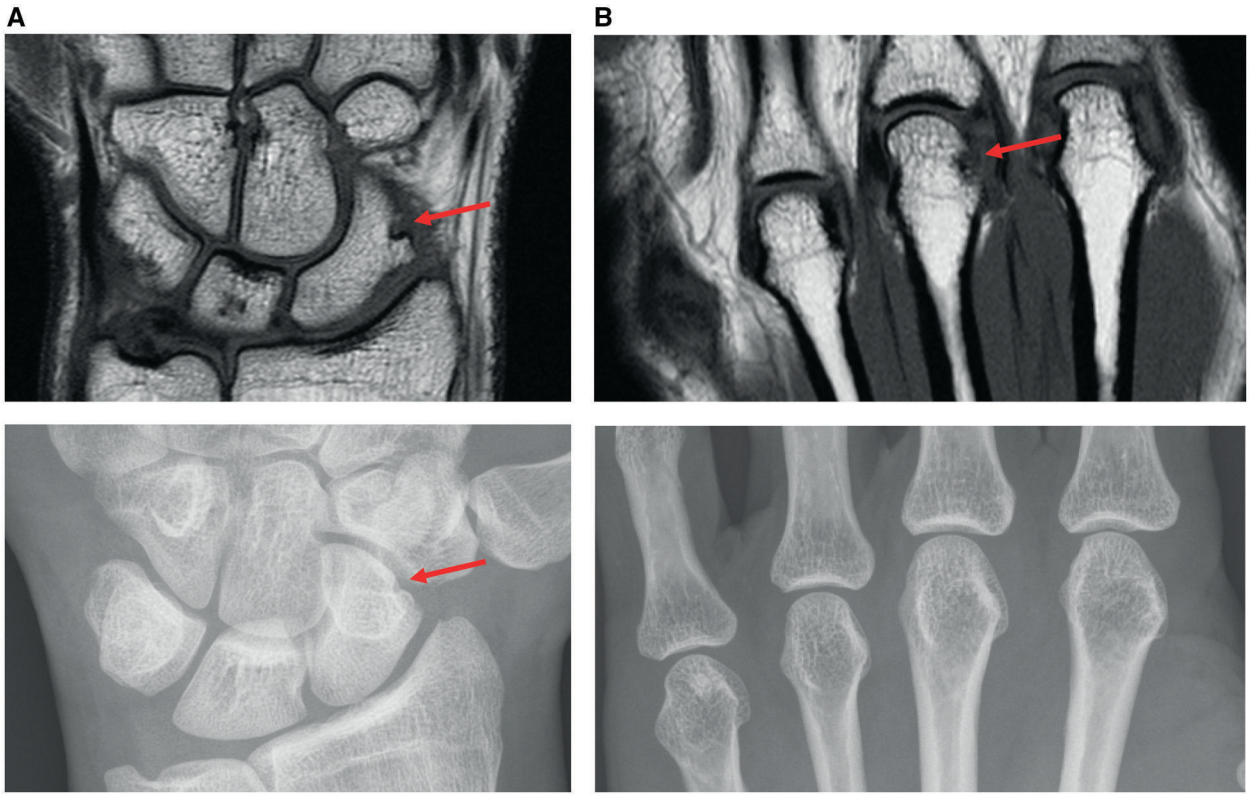

Figure 2. Two examples of an MRI-detected erosion with (**A**) a radiograph of the same location at the same time point with a radiographic erosion and (**B**) without a radiographic erosion. Two examples of CSA patients with an MRI erosion: the MRI and radiographs are performed at the same moment in time. (**A**) T1-weighted MRI of the left hand showing erosion of the scaphoid bone, with a minor cortex break at that location on the radiograph. (**B**) T1-weighted MRI of the left hand showing erosion of the third proximal metacarpophalangeal bone, with a normal radiograph from the same hand

suspect imminent RA. Moreover, little radiographic progression can be expected in the CSA population and a previously conducted study in active RA patients showed that one SHS point progression barely changes physical functioning [19]. Thus, erosive progression of this magnitude during CSA may not be of clinical importance.

In total, 341/9277 (3.7%) of the studied bones of CSA patients showed an MRI-detected erosion; of these only 12 also showed a radiographic erosion. These data underline the difference in sensitivity of MRI and conventional radiography; an erosion becomes detectable on a radiograph only when its volume is substantially larger compared with when it is visible on MRI [7, 20]. In an early disease stage such as CSA, it is therefore expected that the majority of erosions are too small for detection via radiography, but not via MRI. In this study, the majority (>90%) of erosions in CSA patients were only visible on the 3D MRI, but not on the 2D radiograph. Interestingly, some bone locations showed evidently more MRI-detected erosions (Fig. 1); proximal bones of the MCP and MTP joints depict more MRI erosions than the distal bone of the same joint. Also, erosions of the first and fifth MTP joint were more prevalent; erosions in these joints have previously been described as RA-specific [3]. Nevertheless, a previous study has studied symptom-free individuals and showed that MRI-detected erosions are also prevalent in persons aged 40–59 years [21]. Because the percentages of MRI erosions of CSA patients from our study were broadly similar to those found in the symptom-free population, this similarity highlights the non-specific nature of MRI erosions in the CSA population.

The value of erosions in CSA patients has been questioned earlier; MRI-detected erosions do not have predictive value for the development of RA [22]. In the present study, results were similar in patients who did and did not develop inflammatory arthritis during follow-up (data not shown). Also in early RA patients, radiographic erosive disease was no longer included in the scoring system of the 2010 RA classification criteria because it does not align with the goal to detect and treat a patient in an early disease stage [23]. These findings and developments, in combination with the data shown here, make the conclusion robust that MRI-detected erosive disease is not of clinical value.

We studied if the presence of a combination of an MRI-detected erosion and local subclinical inflammation increased the association with a radiographic erosion or progression. If this would reveal a strong relation it could be considered that the combination of an erosion and inflammation is more specific and that these erosions may be more closely involved in the pathological pathway of RA. We indeed observed that the presence of local subclinical inflammation increased the association between an MRI erosion and a radiographic erosion but still, the large majority of these erosions on MRI (95.5%) did not show a radiographic erosion or progression. This interplay of subclinical inflammation and bone erosion formation has been earlier described. Via a direct pathway, osteitis is strongly associated with formation of bone erosions and with local erosive progression [24, 25]. Also via an indirect pathway, subclinical inflammation has been described to induce osteoclast genesis that as a next step may lead to bone loss [26]. Specifically in ACPA-positive patients, both of these

pathways may lead to more extensive erosive disease. More severe inflammation of ACPA-positive CSA patients may lead to more erosion formation [17], or ACPAs may affect the bone homeostasis resulting in increased osteoclast activation [27]. Regardless of which of these hypotheses may be true, our data showed a tendency that subclinical inflammation initiated a stronger relation between MRI erosions and radiographic erosive progression in ACPA-positive patients compared with ACPA-negative patients. Nevertheless, numbers of events were too small to strongly conclude on this.

Presence of an MRI-detected erosion without a radiographic erosion was very high (96.5%). Nevertheless, there was also a minority of bones that was scored as radiographic erosion but not as MRI erosion. This could be the consequence of differences in the scoring of 2D/3D images, differences between scoring agreements of RAMRIS and SHS, or comprises of false-positive scores. However, because this entails a minority of the studied bones (<1%), this will not have majorly influenced the results.

The follow-up duration could be considered a limitation of this study. This relatively short period of two years might have been too brief to capture radiographic progression. Also, radiographs were only scored by one reader, though with an excellent intra-reader reliability (ICC = 0.98). Finally, despite the large sample size of this imaging study, the number of events in some subgroups was too low to perform statistical tests. Larger cohort studies or other study designs may be necessary to conclude on associations in these patients.

A strength of this study is that this is the first large observational study that included both MRI and conventional radiography in CSA patients and analysed the findings at bone level. This ensured a more thorough understanding of erosive disease within the symptomatic at risk phase of RA. Also, this study included the large sample size that is necessary for the expected low numbers of the outcome.

These data are consistent with the known relevance of MRI-detected subclinical inflammation in CSA. Previous research has already confirmed the importance of tenosynovitis, synovitis and osteitis in the disease course of RA, and that treatment of CSA patients with subclinical inflammation may be beneficial [28]. Treatment effects on erosions of CSA patients are unknown and MRI-detected erosions are not predictive for RA development [22]. MRI-detected erosions should therefore be valued separately from subclinical inflammation in future research.

In conclusion, in this large bone-level study in patients at risk of RA development, the majority of MRI-detected erosions did not depict radiographic erosive disease or radiographic progression. Therefore, treatment decisions should not be guided solely by the finding of MRI-detected erosions and overinterpretation should be avoided.

Patient partners were involved in the design of the CSA cohort.

All participants provided written informed consent before inclusion according to the Declaration of Helsinki. The research protocol for the Leiden CSA cohort (P11.210) was approved by the medical ethical committee of the Leiden University Medical Center (LUMC).

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data can be obtained from the corresponding author upon reasonable request.

Contribution statement

Q.A.D., A.H.M.v.d.H.-v.M. and H.W.v.S. designed the study. Q.A.D. collected the data. Q.A.D. and H.W.v.S. analysed the data. All authors contributed to the interpretation of the data and the writing of the manuscript. All authors approved the final version of the manuscript.

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