The use of MRI in early inflammatory arthritis

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Older age is associated with more MRI-detected inflammation in hand and foot joints

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Abstract

Objectives

Although MRI is recommended for diagnostic use in detecting joint inflammation, its value in clinical practice has not been settled. Older symptom-free persons show more MRI-detected inflammation in their hands and feet. Within arthritis patients, a similar effect could be present (a general age effect). The association of age with MRI inflammation could also be enhanced by disease (disease-dependent age effect). Because both effects could have diagnostic consequences, we evaluated the association between age-at-onset and MRI-detected inflammation in early arthritis and RA.

Methods

Unilateral contrast-enhanced MRI of the MCP joint, wrist and MTP joints was performed in 589 newly presenting early arthritis patients, of whom 229 had RA. Bone marrow oedema, synovitis and tenosynovitis were summed, yielding the MRI inflammation score. MRI findings were associated with age and compared with those of 193 (previously reported) symptom-free controls.

Results

Early arthritis and RA-patients had, respectively, 2.6 (95% CI: 2.3, 3.0, P<0.001) and 3.7 times (95% CI: 3.2, 4.3, P<0.001) higher MRI inflammation scores than controls (adjusted for age). At higher age of onset, early arthritis and RA patients had higher MRI inflammation scores (1.03/year, P<0.001). A similar effect was observed in controls (1.03/year, P<0.001). The interaction term age*group (arthritis/RA vs controls) was non-significant (P = 0.80 and P = 0.23), suggesting that the age effect was not disease dependent. At the joint level, older RA patients had more extended MRI inflammation, but the preferential locations were similar.

Conclusion

Older age is associated with more MRI-detected inflammation, and the effect was similar in arthritis and controls. This age effect should be considered when interpreting hand and foot MRI for diagnostic purposes.

Introduction

MRI of hand and foot joints is a sensitive method for detecting inflammation. It has been recommended that MRI could be of use for diagnostic and prognostic purposes, and also for the monitoring of disease activity and disease progression.[1] Although MRI has been proven valuable for research purposes, the value of MRI-detected inflammation for clinical practice in patients with arthritis is not yet fully established. One of the unanswered questions is whether age should be considered when evaluating inflammation on hand and foot MRIs for diagnostic purposes. The results of several tests in medicine, for instance ESR and DXA, are always interpreted relative to the age. Whether age effects are present for MRI-detected inflammation is largely unknown.

Some previous studies in RA have revealed that patients that present at an older age have more severe joint destruction.[2–8] In addition, an explorative analysis on a small group of patients suggested that older patients also present with more severe MRI-detected inflammation.[2] A recent study in volunteers from the general population observed a positive correlation between age and the extent of inflammation on hand and foot MRI.[9] It is unclear if a similar association also exists in patients presenting with early arthritis or RA. If an effect of age exists within patients, this would be relevant in certain situations, for instance, when applying the 2010 criteria for RA, where MRI results may be used to establish the number of involved joints.[10] If older patients present with more inflamed joints, this implies that older patients will fulfill the criteria more easily than younger patients.

Hypothetically, the effect of age on MRI-detected inflammation in early arthritis or early RA could be similar to the effect in symptom-free persons. Then, although arthritis patients will have more severe inflammation than symptom-free persons, a general age effect independent of arthritis will be present. Also, in the case of arthritis, the association of age with the extent of MRI-detected inflammation may be enhanced (a disease-dependent age effect). Third, although less likely (based on observations in symptom-free volunteers), it is possible that arthritis patients presenting at an older age do not have more severe MRI-detected inflammation than younger arthritis patients. In addition, if an association between age and the extent of MRI-detected inflammation exists, it is relevant to explore whether the anatomic locations most frequently affected are similar for patients presenting at a younger age and at an older age. Therefore, this cross-sectional study aimed to determine: whether age of onset is associated with MRI-detected inflammation in early arthritis patients and in early RA patients; whether the effect of age on MRI-detected inflammatory findings differs between early arthritis, early RA and symptom-free controls, that is, whether there is a general effect of age or a disease- dependent effect of age; and whether the anatomical locations most frequently showing MRI-detected inflammation differ in patients presenting at different ages.

Methods

Patients

From August 2010 to October 2014 MRI was performed in 598 consecutively included patients of the Leiden Early Arthritis Clinic. The Early Arthritis Clinic is a prospective inception cohort including patients with clinically confirmed arthritis with a symptom duration of <2 years. At first visit, patients and rheumatologists completed questionnaires, joint counts (66/68 swollen/tender joint counts) were performed, serum samples obtained and an MRI made.[11] MRI was performed a median of 9 days [interquartile range (IQR): 516 days] after the first visit in all early arthritis patients and in RA patients a median of 8 days (IQR: 415) after the first visit. Two weeks after first presentation, when the results of the routine laboratory investigations were known (rheumatologists did not obtain MRI results), patients received their diagnosis and treatment was initiated. Nine patients were excluded from analyses, because no contrast agent was administered; hence, the scans of 589 patients were evaluated.

Results regarding the association between age and MRI-detected inflammation were compared with the association observed in symptom-free controls, as previously reported.[9] In short, the symptom-free controls were obtained by advertisements in local newspapers and websites. They had no history of inflammatory rheumatic diseases, no joint symptoms during the preceding month and no evidence of arthritis at physical examination. Approval was obtained from the Leiden University Medical Center medical ethics committee, and all patients and symptom-free controls signed informed consent forms.

MRI scanning and scoring

Unilateral MRIs were made of the 2nd5th MCP, wrist and 15th MTP joints of the most painful side or the dominant side in the case of equally severe symptoms on both sides. Contrast-enhanced MRI was performed on a MSK Extreme 1.5T extremity MRI system (General Electric) (see supplementary methods, available at Rheumatology Online, for a detailed description of the protocol). Briefly, before contrast enhancement, a T1-weighted sequence was acquired of the MCP and wrist joints in the coronal plane. Postcontrast, T1-weighted, fat-saturated sequences were acquired in the coronal and axial plane. Due to time constraints, the foot was scanned with a different protocol. In the first 371 patients, a T1-weighted sequence and a T2-weighted fat-saturated sequence were acquired in the axial plane (relative to the anatomical position) before contrast agent administration. In the remaining 218 patients postcontrast, T1-weighted, fatsaturated sequences were acquired in the axial and coronal plane. Bone marrow edema (BME) and synovitis were scored in line with the definitions of the RA MRI scoring system (also applied at the MTP joints).[12] Tenosynovitis was scored according to the Haavardsholm method (also applied at the flexor and extensor tendons of the 2-5th MCP joints).[13] All bones, joints and tendons were scored 03: the BME score is based on the affected volume of the bone (no BME,<33%, 33-66%,>66%), the synovitis score on the presumed volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe) and the tenosynovitis score on the thickness of peritendinous effusion or synovial proliferation with enhancement (normal,<2, 2-5,>5 mm).[12,13] BME, synovitis and tenosynovitis were

assessed at, respectively, 33 locations (range 0-99), 12 locations (range 0-36) and 18 locations (range 0-54). The total inflammation score per patient was calculated by summing the BME, synovitis and tenosynovitis scores (range 0-189). Each MRI was scored by two trained readers (W.P.N. and E.C.N.), blinded to all clinical data. The mean of the scores of both readers was used for analyses.

Intraclass correlation coefficients (ICCs) for the total inflammation scores were calculated to determine the reliability of the readers. The intra-reader ICCs were 0.98 and 0.93 (based on 40 scans scored twice) and the interreader ICC was 0.95 (based on all 598 scans). The ICCs of the two readers (L.M. and H.W.vS.) of the symptomfree controls are described in the reference.[9] The ICC for the mean scores of both pairs of readers was calculated on 30 scans scored by both pairs; this ICC was 0.93.

Individual BME, synovitis and tenosynovitis scores that could not be determined on MRI, mostly due to inhomogeneous fat suppression or movement artefacts, were imputed with the median value for that feature across all locations within the same patient of that scorer. In early arthritis patients in total, 946 (2.4% of 38 874) individual BME scores, 339 (2.4% of 14 136) synovitis scores and 169 (0.8% of 21 204) tenosynovitis scores were missing.

Analyses
To assess the association between age and total inflammation, linear regression was performed with the total inflammation score as the dependent variable and age as the independent variable. The total inflammation score was log10-transformed [log10(score + 1)], because, when using the untransformed inflammation scores in the regression analyses, the relationship between age and total inflammation appeared to be exponential when plotted and the residuals were not normally distributed. After log-transformation, the residuals were symmetrized.

To assess possible preferential locations of inflammation in RA patients, the prevalence of BME, synovitis and tenosynovitis per scored location was determined. MRI inflammation was considered present at a specific anatomic location when the mean score of both readers was51. Subanalyses were performed to determine the prevalence of severe inflammatory findings; here only mean scores of 52 were used. Statistical analyses were performed in IBM SPSS, v20.0. P-values of<0.05 were considered significant.

Results

Patient characteristics
Baseline characteristics are shown in Table 1. Of all the 589 early arthritis patients, 229 (39%) fulfilled the 2010 ACR/EULAR RA classification criteria at presentation. The mean age (S.D.) was 54.8 (15.5) years over all early arthritis patients, and 55.9 (14.4) in RA patients. The median total MRI inflammation scores in all early arthritis patients and the subgroup of RA patients were 7.0 (IQR: 2.0-15.0) and 13.5 (IQR: 6.5-26.0), respectively. The baseline characteristics of the symptom-free controls were reported previously: their mean (S.D.) age was 49.8 years (15.8) and their total MRI inflammation score was median 2.0 (IQR: 0.5-4.5).[9]

Table 1 Baseline characteristics of all early arthritis patients and patients presenting with RA

	All early arthritis patients	Patients presenting with RA	Controls
N	589	229	193
Age in years, mean (SD)	54.8 (15.5)	55.9 (14.4)	49.8 (15.8)
<40 years, n(%)	101 (17.1)	33 (14.4)	51 (26.4)
40-60 years, n(%)	242 (41.1)	95 (41.5)	90 (46.6)
>60 years, n(%)	246 (41.8)	101 (44.1)	52 (26.9)
Women, n (%)	363 (61.6)	155 (67.7)	
Symptom duration in weeks, median (IQR)	12.3 (4.8-26.3)	14.6 (8.3-28.1)	
66-Swollen joint count, median (IQR)	3 (2-7)	6 (2-11)	
68-Tender joint count, median (IQR)	6 (2-11)	9 (5-16)	
CRP in mg/L, median (IQR)	5.7 (3-17)	9 (3-21.4)	
RF positive, n (%)	186 (33.3)	146 (66.7)	
ACPA positive, n (%)	137 (24.0)	124 (54.1)	

Some serology data were missing as follows: in all early arthritis for RF, n = 30; for ACPA, n = 18. In RA: for RF, n = 10.

Association between age and MRI inflammation in early RA patients

First, the association between age and the total MRI inflammation score at presentation was assessed separately in all early arthritis patients and RA patients (Fig. 1A and B). In all early arthritis patients, the total MRI inflammation score was higher in patients that presented at older age; the total MRI inflammation score was 1.032 (95% CI: 1.028, 1.037) times higher per year difference in age. Within RA, the same was seen; the total inflammation score was 1.025 (95% CI: 1.018, 1.033) times higher per year difference in age (Table 2). The association between age and total MRI inflammation was also assessed in symptom-free controls (Fig. 1C); here the MRI inflammation score was 1.031 (95% CI: 1.026, 1.036) times higher per year increase in age (Table 2). An effect size of 1.03 indicates a 3% higher total MRI inflammation score per year older at presentation; this is 34% higher per 10 years (1.03^10).

These results, showing similar effect sizes in the three groups, supported the hypothesis of a general effect of age on MRI inflammation. To evaluate the hypotheses statistically, the total MRI inflammation scores of early arthritis patients (or the subgroup of RA patients) were compared with the inflammation scores of the symptomfree controls in one analysis (Fig. 2A and B). Although early arthritis (or RA patients) had higher inflammation scores than controls [adjusted for age, early arthritis patients had 2.6 (95% CI: 2.3, 3.0, P<0.001) times higher inflammation scores and RA patients had 3.7 (95% CI: 3.2, 4.2, P<0.001) times higher inflammation scores (Table 2)], interaction terms between the studied groups and age were not significant (1.001, 95% CI: 0.993, 1.009, P = 0.80 for the comparison of early arthritis patients with controls and 0.995, 95% CI: 0.986, 1.003, P = 0.23 for the comparison of RA patients with controls) (Table 2). This suggested that the association between age and MRI inflammation is not different for the different groups, thus that there was no disease-specific effect of age.

Table 2 Results of linear regression analyses of age at presentation in relation to the MRI inflammation score

	Early arthritis			Rheumatoid arthritis			Symptom-free controls[a]		
	Beta[b] (95%CI)		p	Beta[b] (95%CI)		p	Beta[b] (95%CI)		p
Univariable analyses									
Constant	1.6	(1.3-2.1)	<0.001	3.2	(2.1-4.8)	<0.001	0.7	(0.5-0.9)	0.002
Age (in years)	1.032	(1.028-1.037)	<0.001	1.025	(1.018-1.033)	<0.001	1.031	(1.026-1.036)	<0.001
	Control & Early arthritis			Control & Rheumatoid arthritis					
Multivariable analyses									
Constant	0.6	(0.5-0.8)	<0.001	0.7	(0.6-1.0)	0.018			
Age (in years)	1.032	(1.028-1.036)	<0.001	1.028	(1.024-1.033)	<0.001			
Group (control/patient)[c]	2.6	(2.3-3.0)	<0.001	3.7	(3.2-4.2)	<0.001			
Multivariable analyses									
Constant	0.7	(0.4-1.0)	0.026	0.7	(0.5-0.9)	0.011			
Age (in years)	1.031	(1.024-1.038)	<0.001	1.031	(1.025-1.038)	<0.001			
Group (control/patient)[c]	2.5	(1.6-3.9)	<0.001	4.9	(3.0-8.0)	<0.001			
Interaction Age*Group	1.001	(0.993-1.009)	0.80	0.995	(0.986-1.003)	0.23			

[a]The association between age and MRI-detected inflammation in the symptom-free controls has been described more extensively previously.[9] [b]The beta and 95% CI limits reported are 10^{beta} and $10^{confidence\ interval\ limits}$. [c]The variable group is the difference between symptom-free controls and early arthritis patients or RA patients, using symptom-free controls as the reference. The interaction term was introduced to test for a disease-specific (or group-specific) effect of age at presentation on MRI inflammation.

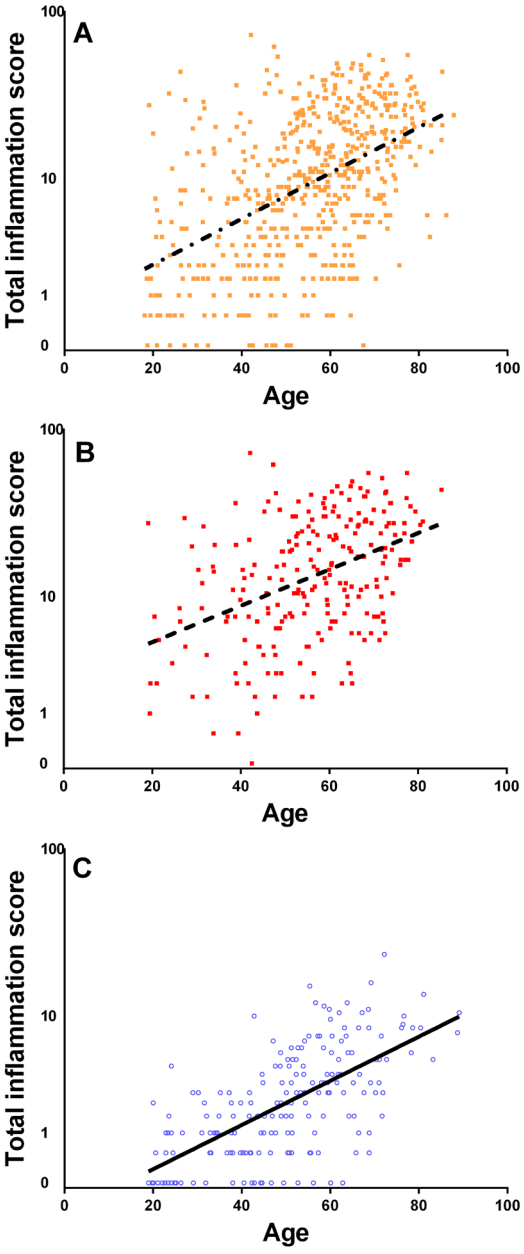


Figure 1 Total MRI inflammation score plotted against age at presentation

Total MRI inflammation plotted against age at presentation: in early arthritis patients (A), RA-patients (B) and symptom-free controls (C). The y axes are transformed to logarithmic scale. The results of linear regression are described in Table 2.

This is also visualized by the combination of the scatter plots of early arthritis and RA patients and symptom-free controls (Fig. 2A and B); the fitted univariable regression lines were near parallel, illustrative of similar effects of age. The vertical distance between the two regression lines is illustrative for the higher inflammation scores in patients than in controls. When the regression analyses were repeated using age as a categorical variable (<40, 40-60 and>60 years), this resulted in similar findings (Supplementary Table 1A and C, available at Rheumatology Online).

Localization of MRI-detected inflammation in RA patients presenting at different ages

Next it was assessed whether the localization of inflammation differed for RA patients who presented at different age categories (characteristics of subgroups in Supplementary Table 2, available at Rheumatology Online). The prevalence of inflammation at the MCP, wrist and MTP joints was assessed at all scored location (joints, bones and tendons) in three age categories:<40, 40-60 and>60 years (Fig. 3A and E). This revealed that at older age, more locations were affected; the median number of affected locations (joints, bones and tendons) in the age groups<40, 40-60 and>60 years were 3 (IQR: 1-9), 7 (3-14) and 12 (6-19), respectively (Kruskal-Wallis test: P<0.001). However, in general, locations that were most frequently inflamed at a young age also had the highest

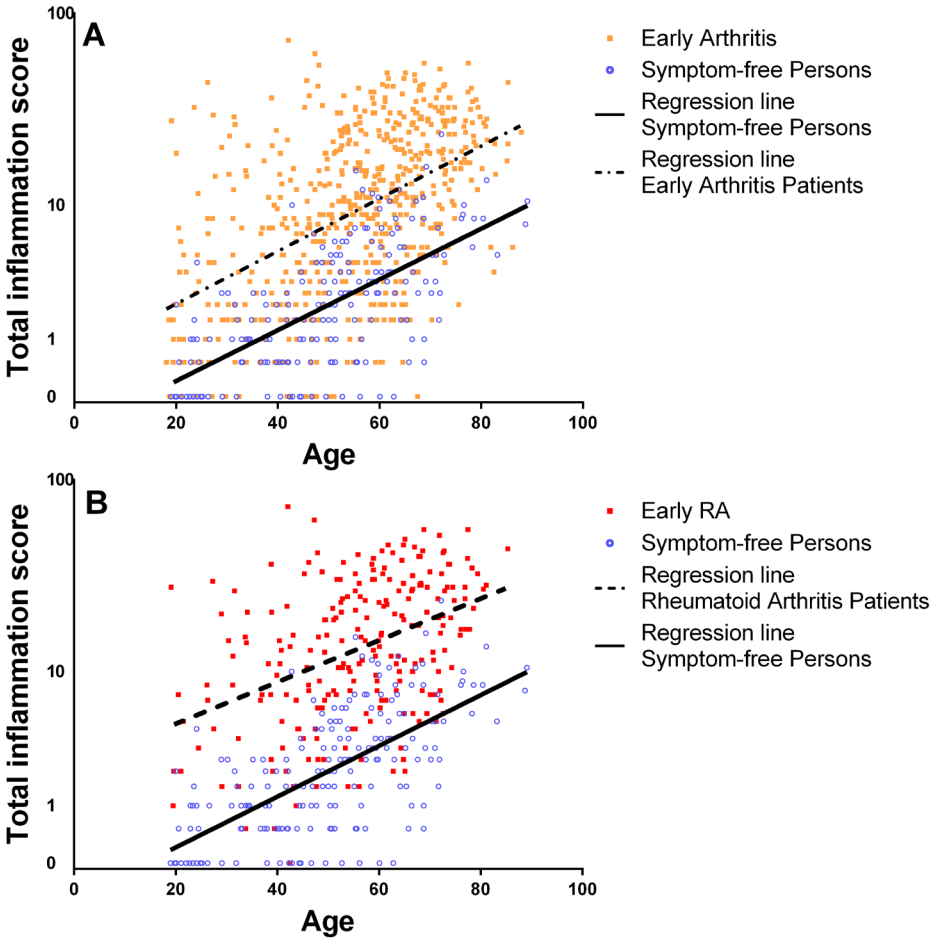


Figure 2 Comparing the relationship between age and total MRI inflammation with that for symptom-free controls

Comparing the relationship between age and total MRI inflammation in early arthritis patients (A) and RA patients (B) with symptom-free controls. The y axes are transformed to logarithmic scale. The results of linear regression are described in Table 2.

prevalence at older age. For instance, MCP2 not only had the highest prevalence of synovitis in the MCP joints (24%) in RA patients<40 years old, but also in patients aged 40-60 (35%) and>60 years old (62%) (Fig. 3A). In addition, BME in the wrist was predominantly present in the proximal row of carpal bones (scaphoid, lunate and triquetrum bone) and the capitate bone, with a prevalence ranging from 3 to 15% in RA patients<40 years; in patients 40-60 years, the prevalence ranged from 14 to 21%, and in patients>60 years, the prevalence ranged from 20 to 30% (Fig. 3B). Similarly, the locations of tendon involvement were the same at all age categories, and the prevalence was also higher in the older patient groups (Fig. 3C). In the foot joints, the increase in prevalence of inflammation with age was less clear, though MTP1 and MTP5 had the highest prevalence of inflammation in all age categories (Fig. 3D and E).

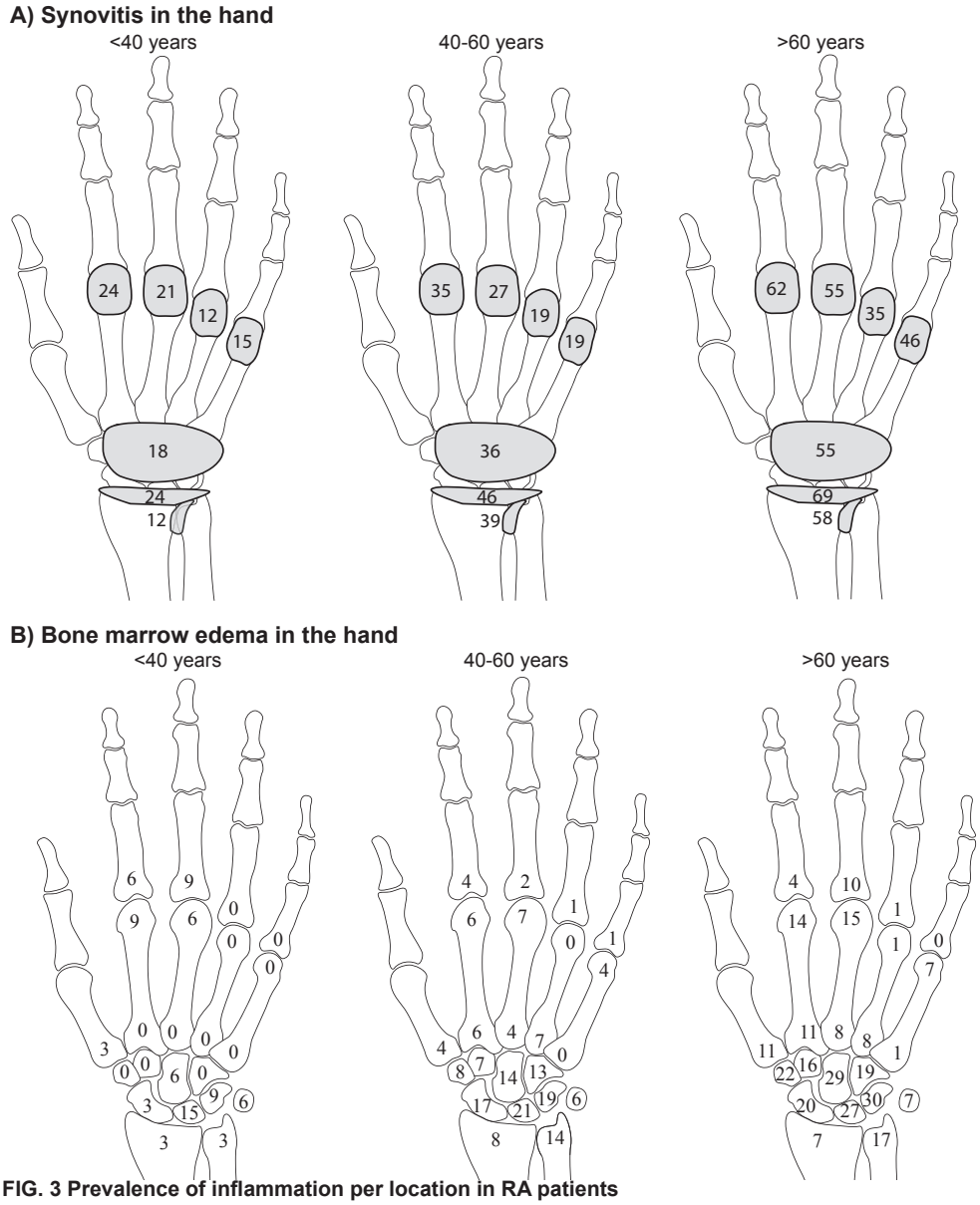
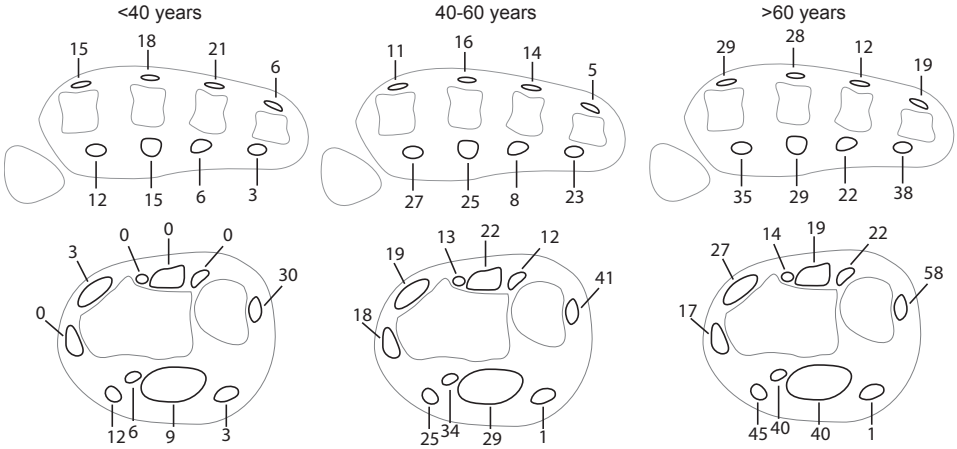


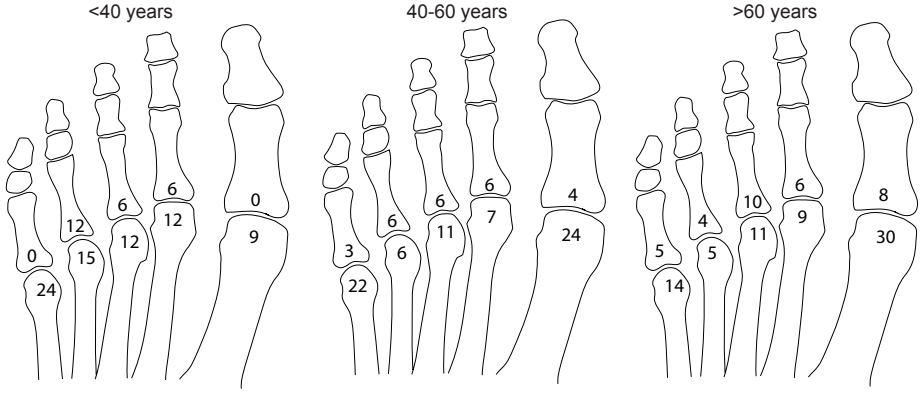
FIG. 3 Prevalence of inflammation per location in RA patients

Numbers shown are the prevalence of inflammation per scored location for three age categories (<40, 40-60,>60 years); that is, the percentage of patients in an age category with a mean score of ≥1 for the specific location. Scored anatomic locations are described in the Methods section.

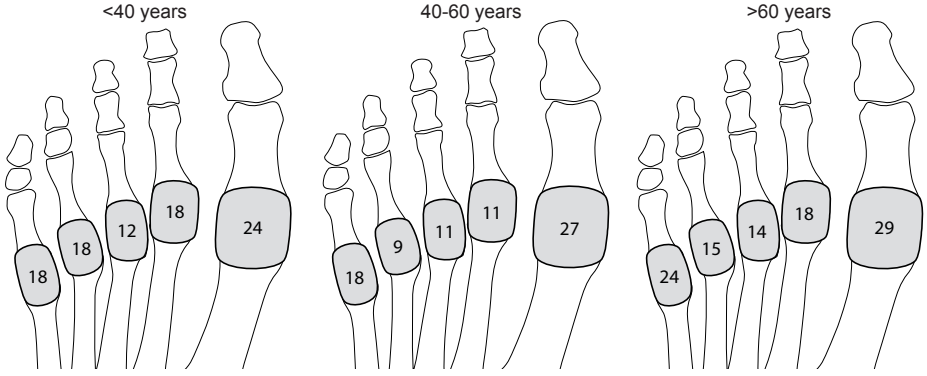
C) Tenosynovitis in the hand



D) Bone marrow edema in the foot



E) Synovitis in the foot



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Subanalysis: the localization of severe inflammation scores in RA
Thus far, the presence of MRI-detected inflammation was assessed, irrespective of the severity of inflammation (defined as scores ≥1). The distribution of more severe inflammation scores, that is, scores ≥2, were also assessed in RA (Supplementary Fig. 1A and E, available at Rheumatology Online). This revealed that older patients had more severe inflammation and that the locations with the highest prevalence for severe inflammation were similar to those presented in Fig. 3A and E. The median number of locations with a score of >2 in the age groups<40, 40-60 and >60 years were 0 (IQR: 0-1), 1 (0-2) and 1 (0-4), respectively (Kruskal-Wallis test: P = 0.002). This suggests that the increase in MRI inflammation scores with age was more influenced by more extended inflammation than by more severe inflammation.

Discussion

The present large cross-sectional study is the first that has thoroughly studied the association between age and MRI-detected inflammation in the hands and feet of early arthritis and early RA patients. Early arthritis and early RA patients who presented at older age had more MRI-detected inflammation than patients presenting at younger age. The higher MRI inflammation scores were mainly based on more extended inflammation, that is, more affected joints at an older age. In addition, although MRI inflammation was present in more joints at an older age, the locations with the highest prevalence of inflammation were similar in all age categories. Together these data demonstrate that age influences the extent of MRI-detected inflammation in early arthritis and in RA.

The results obtained in early arthritis and RA were also compared with those of symptom-free persons, as it was recently observed that the extent of MRI-detected inflammation observed in symptom-free persons was also associated with age. We questioned whether the effect of age was similar in arthritis and controls or whether the effect of age was enhanced in patients with inflammatory rheumatologic diseases. Interestingly, the effect size of the association between age and MRI-detected inflammation was similar in symptom-free controls and early arthritis or RA patients. The non-significant interaction term between age and group also suggests that the age effect is not disease dependent.

The results of the present study might have implications for the use of MRI for diagnostic purposes. For example, with the introduction of the 2010 ACR/EULAR classification criteria for RA, it was suggested that MRI could be used to assess the joint involvement.[10] The findings of this study suggest that older arthritis patients might fulfil the 2010 criteria more easily than younger patients. The MRI inflammation score increased with 3.2% per year, which means that persons who were 20 years older at disease presentation had 87.8% higher MRI scores.

Although this study did not include follow-up data, it might also have implications for the use of MRI for prognostic purposes. Previous studies have shown that MRI-detected inflammation is a predictor for radiographic destruction.[14–20] Our data shows that both disease status (patient/control) and age are independently associated with MRI-detected inflammation. It is still unclear whether the increase

in MRI inflammation with age explains the previously reported finding that older patients present with more severe joint damage.[2–8]

These data cannot provide answers regarding the biological mechanism underlying the observed associations. Different hypotheses can be generated to explain the observed effect of age. First, it could be speculated that the effect of age could be explained by degenerative processes or by OA, because age can also evoke mild inflammatory responses. However, the majority of inflammatory lesions at older age were not only located at sites that are prone for OA, such as in the CMC-I or MTP-1 joint, but at other sites as well. In contrast, inflammation in older patients was also frequently present in MCP-2, -3 and -5 and in the first row of carpal bones (scaphoid, lunate and triquetrum bones). Another possibility relates to immunosenescence; it has been shown that aging of the immune system creates a more proinflammatory environment.[21,22] Hypothetically, this could lead to an increase in (subclinical) MRI-detected inflammation. Further basic studies are required to unravel the mechanisms underlying the observation on age.

This study was performed using a 1.5-T dedicated extremity scanner. Although it remains as speculation, higher-field-strength scanners or other advances in MRI technology would likely result in similar results, as a possible increase in sensitivity to detect inflammatory lesions would apply to both groups.

Interestingly, although early arthritis and RA patients had more MRI inflammation than symptom-free controls, the locations most frequently affected were similar. For example, locations that frequently showed inflammation in symptom-free persons were MCP-2, MCP-3 and the wrist joints; these locations also most frequently showed inflammation in arthritis patients. The hypothesis that mechanical strains also play a role in the occurrence of MRI-detected inflammation might explain the similarity between the most frequently affected joints.

Strong points of our study were the number of consecutive arthritis patients that were evaluated with MRI. In addition, patients were scanned before DMARD treatment was initiated. Furthermore, all MRIs were scored blinded for age and other clinical information.

Our study also had limitations. BME was scored on a contrast-enhanced T1-weighted sequence with fat suppression instead of a T2-weighted sequence with fat suppression; the latter is recommended by the RA MRI scoring method. Both sequences are recommended by the European Society of Musculoskeletal Radiology.[23] In addition, in some of the early arthritis patients, the foot was scanned with a different MRI protocol (before the administration of contrast) than that used in the symptom- free controls. This might have affected the comparability of MRI findings of both groups. To address whether this might have influenced our findings, the regression analyses were repeated for each of the two groups of early arthritis patients separately (i.e. separated for each protocol). These analyses yielded similar results; the effect size of age was similar and the interaction term was nonsignificant (data not shown).

In conclusion, arthritis patients who are older at presentation have more MRI-detected inflammation. Because this effect was similar to that observed in

symptom-free persons, we presume that this is a general effect of age that is not disease dependent. This study underlines the importance of taking age into account in the interpretation of MRI findings.

References

1 Colebatch AN et al. *Ann Rheum Dis* Published Online First: 21 March 2013.
2 Mangnus L et al. *Arthritis Res Ther* 2015;17:222.
3 Innala L et al. *Arthritis Res Ther* 2014;16:R94.
4 Bukhari M et al. *Ann Rheum Dis* 2007;66:389–93.
5 Calvo-Alén J et al. *Clin Rheumatol* 2005;24:485–9.
6 Khanna D et al. *Arthritis Rheum* 2005;52:2284–92.
7 Kuiper S et al. *J Rheumatol* 2001;28:1809–16.
8 van der Heijde DM et al. *J Rheumatol* 1991;18:1285–9.
9 Mangnus L et al. *Arthritis Rheumatol* 2016;68:2593–602.
10 Aletaha D et al. *Ann Rheum Dis* 2010;69:1580–8.
11 de Rooy DPC et al. *Rheumatology* 2011;50:93–100.
12 Østergaard M et al. *J Rheumatol* 2003;30:1385–6.
13 Haavardsholm EA et al. *Ann Rheum Dis* 2007;66:1216–20.
14 Baker JF et al. *Ann Rheum Dis* Published Online First: 31 July 2013.
15 Bøyesen P et al. *Ann Rheum Dis* 2011;70:428–33.
16 Døhn UM et al. *Ann Rheum Dis* 2011;70:252–8.
17 Gandjbakhch F et al. *J Rheumatol* Published Online First: 15 December 2013.
18 Hetland ML et al. *Ann Rheum Dis* 2009;68:384–90.
19 Hetland ML et al. *Ann Rheum Dis* 2010;69:1789–95.
20 McQueen FM et al. *Arthritis Rheum* 2003;48:1814–27.
21 Chalan P et al. *Curr Aging Sci* 2015;8:131–46.
22 Franceschi C et al. *Ann N Y Acad Sci* 2000;908:244–54.
23 Sudoł-Szopińska I et al. *Semin Musculoskelet Radiol* 2015;19:396–411.