MRI in the earliest phases of rheumatoid arthritis

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Chapter 3:
Magnetic Resonance Imaging-detected features of inflammation and erosions in symptom-free persons from the general population

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Abstract

Introduction. The use of magnetic resonance imaging (MRI)-detected inflammation and joint damage in the diagnosis of rheumatoid arthritis is recommended by a European League Against Rheumatism imaging task force. This recommendation is based on the sensitivity of MRI and not on specificity. Knowledge of the prevalence of MRI-detected features in symptom-free persons, however, is pivotal when considering MRI for diagnostic purposes.

Methods. From November 2013 to December 2014, 196 symptom-free persons of different ages were recruited from the general population. Inclusion criteria were no history of inflammatory arthritis, no joint symptoms during the previous month, and no clinically detectable arthritis on physical examination. Contrast-enhanced MRIs of the dominant metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints were obtained using a 1.5T scanner and scored by 2 readers for synovitis, bone marrow edema, tenosynovitis, and erosions. For analyses at the joint level, MRI-detected inflammation was considered present if both readers scored the image as positive.

Results. Of 193 persons scanned (ages 19-89 years), only 28% had no single inflammatory feature and 22% had no erosions. Primarily low-grade features were observed. All MRI-features were positively correlated with age ($P < 0.001$). Preferential locations for synovitis were MCP2, MCP3, the wrists, and MTP1. Bone marrow edema was frequently present in MCP3, the scaphoid, and MTP1. Tenosynovitis was infrequent, except for in the extensor carpi ulnaris. Preferential locations for erosions were MCP2, MCP3, MCP5, the distal ulna, MTP1, and MTP5. Tables with age-, location-, and inflammation type-dependent frequencies were constructed. Simultaneous colocalized presence of synovitis, bone marrow edema, tenosynovitis, or erosions occurred.

Conclusion. MRI-detected inflammation and erosions are prevalent in symptom-free persons from the general population, especially at older ages and at preferential locations.

Introduction

Magnetic resonance imaging (MRI) findings are increasingly used as outcome measures in clinical trials in rheumatoid arthritis (RA). According to a European League Against Rheumatism (EULAR) imaging task force, MRI is also helpful in the diagnosis of RA.[1] The first recommendation of this task force states that MRI can be used to improve the certainty of a diagnosis when there is doubt. This recommendation is largely based on the fact that MRI is more sensitive than physical examination for detecting local inflammation.[1-3] As such, MRI may increase the ability to identify arthritis or RA very early.

Computed tomography may be more sensitive than MRI for the detection of erosions,[4] but if MRIs are obtained to evaluate local inflammation, erosive lesions can also be detected. An imaging task force of the American College of Rheumatology concluded that MRI assesses structural damage more sensitively than other imaging modalities.[5] The EULAR imaging task force also recommended that MRI be considered for detecting local damage at an earlier time point if conventional radiographs do not show damage.[1] Similar to the recommendation regarding using MRI for the detection of inflammation, this recommendation is based on MRI-studies of RA-patients, which thus assessed the sensitivity of the method.

The specificity of MRI-findings has not yet been determined, because the prevalence of MRI-detected inflammation and erosions in the general population has not been explored extensively. Recently, we reviewed the literature for studies of MRI in healthy subjects.[6-12] Taken together, the findings of those studies suggested that erosions, synovitis, and bone marrow edema occur regularly in the general population. However, the available studies had some limitations. They included few symptom-free persons, recruitment methods were often not reported or not entirely population based, and age was not taken into account. Furthermore, specific locations were not assessed because analyses were mostly done at the level of the person but not at the level of individual bones.

Currently available data, therefore, do not allow a description of the prevalence of MRI-detected inflammation and erosions in the general population. Before MRI-findings can be used for diagnostic purposes in clinical practice, information

on their specificity is required. In this light, we aimed to address the following questions: 1) What is the occurrence of different MRI-features (synovitis, bone marrow edema, tenosynovitis, and erosions) in symptom-free persons? 2) Is the frequency of these MRI-features dependent on anatomic location, sex, or age? 3) Do different MRI-features occur simultaneously at the same joint in symptom-free persons?

Subjects and methods

Participants

This cross-sectional study was performed between November 2013 and December 2014 in Leiden, The Netherlands. Symptom-free individuals were recruited via advertisements in local newspapers and web sites. Inclusion criteria were: age 18 years or older, no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the previous month, and no clinically detectable arthritis on physical examination. Persons who volunteered were screened for these criteria by telephone and a subsequent visit at the outpatient clinic. At inclusion, information was collected on age, sex, weight, height, dominant hand, smoking history, alcohol consumption, comorbidity, and medical history. Physical examinations of the hands and feet were performed to exclude the presence of arthritis and to evaluate the presence of asymptomatic Heberden's nodes or Bouchard's nodes or hallux valgus. We decided not to exclude persons with these asymptomatic signs of osteoarthritis (OA), since prior exclusion would result in a "too healthy" study population.

The presence of these signs was recorded, allowing subanalyses excluding these individuals. At the second visit, MRI was performed. After the 2 visits, participants received a voucher for e20 as compensation for their time and travel costs. Participants did not receive a report of their MRI-findings. The study was approved by the local medical ethics committee, and written informed consent was obtained from all subjects.

MRI-protocol and scoring

MRI of the metacarpophalangeal (MCP) joints, wrist joints, and metatarsophalangeal (MTP) joints on the dominant side was performed within 15 days after the screening visit. Sequences acquired were coronal precontrast T1-weighted fast spin-echo (FSE) and coronal and axial postcontrast T1-weighted FSE with frequency-selective fat suppression. Further details on the scan protocol are provided in the Supplementary Methods, available on the Arthritis & Rheumatology website.

MRI-scoring was done independently by 2 trained readers (LM and HWvS). In an attempt to exclude observer bias introduced by knowing that persons had no symptoms, the MRIs of symptom-free individuals were mixed with MRIs of RA-patients and patients with arthralgia without clinical synovitis (total n = 99).[13,14] The readers were blinded with regard to any personal or clinical data. Scoring of synovitis, bone marrow edema, and erosions was performed following the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) method (see Supplementary Methods). Tenosynovitis in the MCP and wrist was scored according to the method described by Haavardsholm et al.[15,16] The total MRI inflammation score was calculated by summing the scores for all inflammatory features, including the synovitis, bone marrow edema, and tenosynovitis scores in the MCP and wrist joints and the synovitis and bone marrow edema scores in the MTP joints.

The within-reader intraclass correlation coefficient (ICC), based on 40 MRI-scans, was 0.99 for reader 1 and 0.98 for reader 2, and the interreader ICC, based on 193 MRI-scans, was 0.96. When evaluating the inflammation or erosion scores at the subject level, the mean scores of both readers were studied. When performing analyses at the joint level evaluating MRI-features at specific locations, the data were categorized. In the case of disagreement between the 2 readers, the lower score was used. For instance, when 1 reader scored a feature as 1 and the other reader scored the same feature as 0, the final score for that feature at that location was 0. Differences between readers in scores at individual locations of >1 did not occur. Hence, a conservative method for categorization was used.

Statistical analysis

Frequencies were assessed. Comparisons between sexes were conducted using the Mann-Whitney U test. Correlations of MRI-findings with age were determined using Pearson's correlation coefficient. SPSS V20.0.0 was used.

Results

Characteristics of the participants

Of 199 volunteers screened between November 2013 and December 2014, 196 fulfilled the inclusion criteria. Three individuals were excluded because of hand symptoms. After inclusion, 3 others did not undergo MRI and were excluded because of personal problems, vasovagal response to intravenous puncture, and anxiety, respectively. Consequently, MRIs for 193 persons (ages 19-89 years) were obtained. Baseline characteristics of the subjects are presented in Table 1. On clinical examination, signs of OA (e.g., Heberden's nodes, Bouchard's nodes, and hallux valgus) were observed in 68 persons (33 participants ages 40-59 years and 35 participants older than 60 years). No clinically relevant incidental findings were observed.

Presence of MRI-detected inflammation and erosions

The median total MRI inflammation score was 2 (interquartile range (IQR] 0.5-4.5). For synovitis, bone marrow edema, tenosynovitis, and erosions, the median total scores were 0.5 (IQR 0.0-2.0), 1.0 (IQR 0.0-2.0), 0.0 (IQR 0.0-0.0), and 2.0 (IQR 1.0-4.0), respectively. Forty-two participants (22%) had no erosions, and 54 participants (28.0%) had a total MRI inflammation score of 0 (see Supplementary Table 1, available on the Arthritis & Rheumatology website). A total synovitis score of≥1 was recorded for 48.2% of the subjects, a total bone marrow edema score of≥1 for 57.5%, and a total tenosynovitis score of≥1 for 16.6%. Hence, tenosynovitis was less prevalent than the other features.

Location of MRI-detected inflammation and erosions

Next, we assessed the 3 different joint regions (MCPs, wrist, and MTPs). The highest total inflammation score was obtained in the wrist (median 1.0 [IQR 0.0-2.5]). The median total inflammation score at the MCP and MTP joints was 0.0 (IQR 0.0-1.0) and 0.0 (IQR 0.0-1.0). Synovitis, bone marrow edema, tenosynovitis, and erosion scores of≥1 in the wrist were present in 33.2%, 45.1%, 9.3%, and 68.4% of the participants, respectively; these percentages were higher than those for the MCP and MTP joints (Supplementary Table 1).

We next assessed the MRI-features at the individual joint level. At the level of the MCP joints, synovitis, bone marrow edema, and erosions were most frequently present in MCP3 (in 11.4%, 3.6%, and 14.5% of the subjects, respectively) and MCP2 (in 8.8%, 2.6%, and 17.1% of the subjects, respectively). Flexor tenosynovitis was most frequently present in MCP3 (in 4.7% of the subjects) (see Supplementary Table 2, available on the Arthritis & Rheumatology website).

In the 3 wrist joints, synovitis was frequently observed (in the distal radioulnar joint in 8.3%, in the radiocarpal joint in 17.1%, and in the intercarpal carpometacarpal [CMC] joint in 15.5% of the subjects). In the carpal bones, bone marrow edema was most frequently present in the lunate, scaphoid, and distal ulna (in 19.2%, 8.8%, and 5.2% of the subjects, respectively). Erosions were frequently found in the capitate (in 23.3% of the subjects), lunate (in 21.8% of the subjects), and distal ulna (in 11.9% of the subjects). Tenosynovitis was almost absent in the wrist, with the exception of the extensor carpi ulnaris tendon (extensor compartment VI), which showed tenosynovitis in 7.3% of the subjects (Supplementary Table 2).

At the level of the MTP joints, inflammation preferentially occurred in MTP1, with synovitis in 10.4% of the subjects and bone marrow edema in 17.1% of the subjects; erosions were present in MTP1 in 18.1% of the subjects. Erosions were also frequently present in MTP5 (in 7.8% of the subjects) (Supplementary Table 2).

The anatomic location of the MRI-detected erosion and the cortical break was studied in detail for several bones that were frequently affected (Figures 1A-D). The erosions were more frequently seen in the proximal side of the joint than in the distal part of the joint, and the erosions were not located centrally but at the bone margins.

Figure 1 **(Next page) Schematic overview of observed RAMRIS defined erosions. Schematically depicted are the locations of cortical breaks in MCP-2 and MCP-3 (A), MCP-5 (B), distal ulna (C), and MTP-1 (D) in coronal and axial plane, and an MRI example of erosions (arrows) at these locations. MR sequences include coronal T1 FSE and axial T1 FSE with fat suppression after contrast enhancement.**

Association between sex and MRI-features

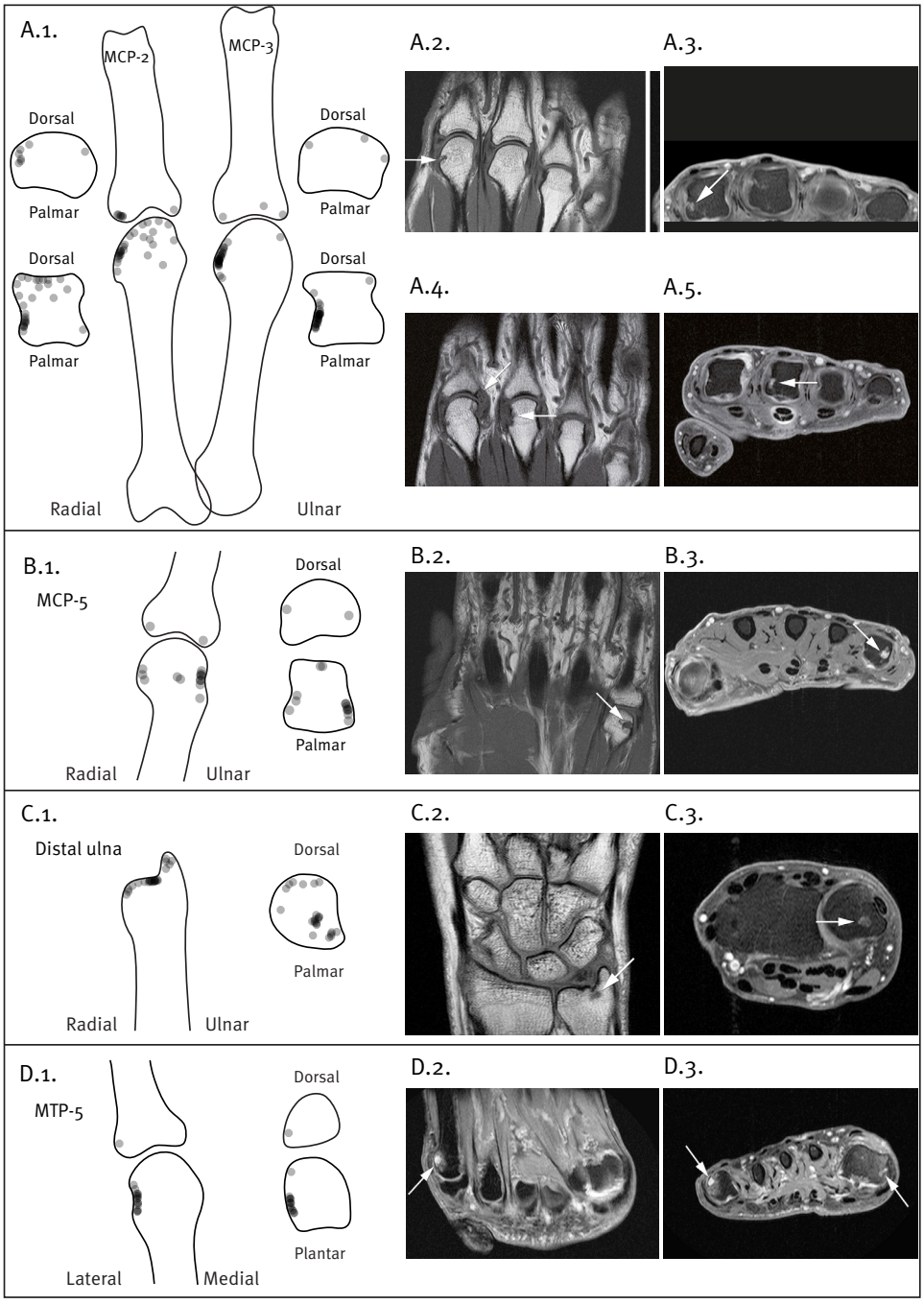
We next investigated whether men and women had different MRI scores. The median total inflammation score for men was 2.0 (IQR 1.0-4.5) and that for women was 2.0 (IQR 0.5-4.4), showing no difference between the sexes ($P = 0.36$). Similarly, the total synovitis, bone marrow edema, tenosynovitis, and erosion scores were compared and showed no differences ($P = 0.79$, $P = 0.14$, $P = 0.41$, and $P = 0.11$, respectively).

Association between age and MRI-features

We next investigated whether age was correlated with MRI-detected inflammation. We observed that older age was positively correlated with a higher total inflammation score ($r = 0.57$, $P < 0.001$) (Figure 2A). This positive correlation with older age was also found for synovitis, bone marrow edema, tenosynovitis, and erosions separately ($r = 0.55$, $r = 0.51$, $r = 0.28$, and $r = 0.69$, respectively) (all $P < 0.001$) (Figures 2B-E).

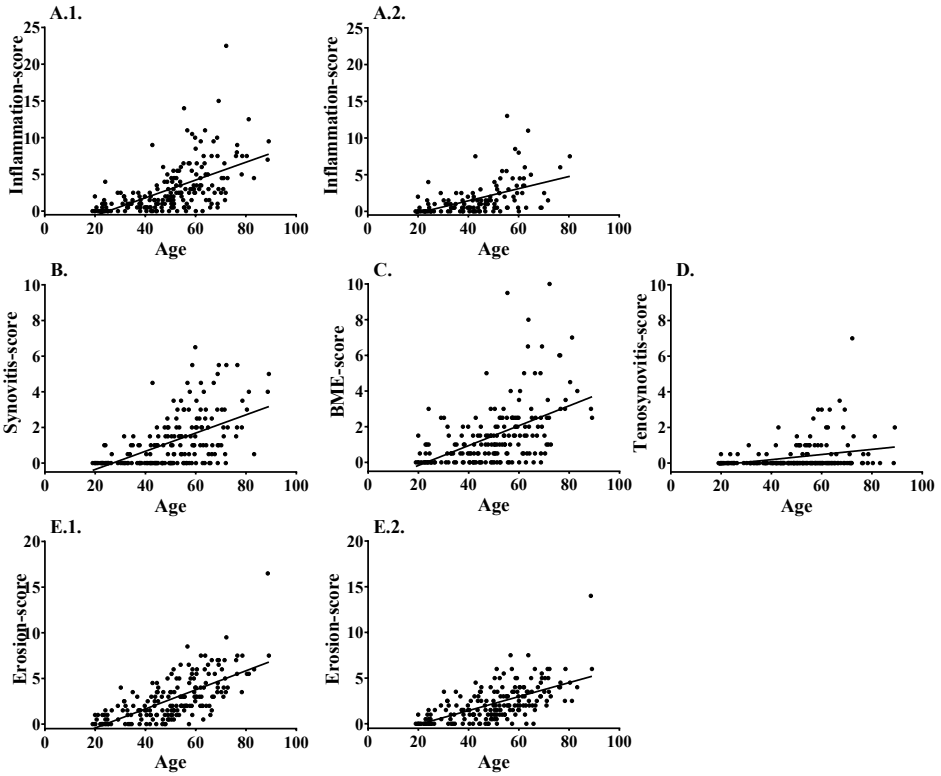
To explore the possibility that these correlations were caused by the presence of asymptomatic OA, the prevalence of which also increases with age, we performed subanalyses. First, subjects with any sign of (asymptomatic) OA at physical examination were excluded. The correlations between age and the total inflammation score and between age and the erosion score remained similar to those obtained

Figure 1: (Next page) The grey dots present the location of the cortical breaks; when more cortical breaks are present at the same location the dots have a darker shade of grey.


A.1.
MCP-2
MCP-3
Dorsal
Palmar
Dorsal
Palmar
Dorsal
Palmar
Dorsal
Palmar
Radial
Ulnar
A.2.
A.3.
A.4.
A.5.
B.1.
MCP-5
Dorsal
Palmar
Radial
Ulnar
B.2.
B.3.
C.1.
Distal ulna
Dorsal
Palmar
Radial
Ulnar
C.2.
C.3.
D.1.
MTP-5
Dorsal
Plantar
Lateral
Medial
D.2.
D.3.

before exclusion of these subjects (r = 0.53, P < 0.001 and r = 0.66, P < 0.001, respectively). When anatomic locations that are included in the RAMRIS method but also

Figure 2 **Correlations between age and total inflammation-score(A.1.), total synovitis-score(B.), total BME-score(C.), total tenosynovitis-score(D.) and total erosions-score(E.1.) in all 193 symptom-free persons, and correlations between age and total inflammation and total erosion-scores after exclusion of persons with Heberden's nodes, Bouchards nodes, or hallux valgus (n = 68) and CMC-1 and MTP-1 joints (A.2., E.2.)**



Correlation coefficient of age with (A.1.) inflammation-score was r = 0.57, (A.2.) inflammation-score r = 0.52, (B.) synovitis-score was r = 0.55, (C.) BME-score was r = 0.51, (D.) tenosynovitis-score was r = 0.28, (E.1.) erosion-score r = 0.69, and (E.2.) erosion-score r = 061, all p < 0.001.

are known to be predilection sites for OA (CMC1 and MTP1) were removed from the analysis, the correlation coefficient for the association of inflammation with age was r = 0.55 (P < 0.001), and the correlation coefficient for the association of erosions with age was r = 0.62 (P < 0.001). Finally, these individuals and anatomic locations were both excluded from the data set, after which the correlation of inflammation score with age was still observed (r = 0.52, P < 0.001) (Figure 2A). Similarly, age remained correlated with the erosion score (r = 0.61, P < 0.001) (Figure 2E).

Generation of tables with age-, location-, and feature-dependent prevalence of MRI-detected inflammation and erosions.

The data presented thus far indicate that the prevalence of MRI-findings in the symptom-free population is dependent on the age of the individual, the anatomic location, and the feature assessed. Therefore, we constructed tables that incorporate these 3 characteristics. These tables present the frequency of synovitis, bone marrow edema, tenosynovitis, and erosions per joint per age category (< 40, 40-59, and ≥ 60 years) and per grade of severity (Tables 2-4). As Tables 2-4 show, in general MRI-detected inflammation was rare in individuals younger than 40 years. Furthermore, features were very rarely assigned scores of 2 or 3.

At the MCP joints, synovitis was present in MCP2 in 8% and in MCP3 in 14% of the participants ages 40-59 years and in MCP2 in 19% and in MCP3 in 17% of the participants age 60 years or older (Table 2). Flexor tenosynovitis at MCP2-4 was present in 6-12% of the participants age 60 years or older.

At the wrist, grade 1 synovitis of the distal radioulnar, radiocarpal, and intercarpal CMC joints was frequent in persons age 40 years or older (Table 3). Bone marrow edema was prevalent in the scaphoid and lunate, and the prevalence increased with older age. In the bones forming the CMC1 joint (proximal metacarpal 1 and trapezium), inflammation occurred more frequently at older ages. (The frequencies of bone marrow edema at proximal metacarpal 1 in the 3 age categories were 0%, 3%, and 8%.) Tenosynovitis seldom occurred in the wrist, with the exception of the extensor carpi ulnaris tendon in persons age 40 years or older (9% and 12% in the groups ages 40-59 years and 60 years or older, respectively) (Table 3).

At the MTP joints, the highest prevalence of MRI-detected inflammation was seen at MTP1. For instance, 23% of the subjects age 60 years or older had bone marrow edema of grade 1 in MTP1. Bone marrow edema and synovitis each occurred in MTP5 in 4% of the symptom-free persons age 60 years or older (Table 4).

When MRI-detected erosions were evaluated, similar patterns were seen. The prevalence of erosions at joints that are known as predilection sites for OA (CMC1 and MTP1) increased with age, but the same was observed for locations that are not considered typical for OA, such as MCP2 and MCP3 (Tables 2-4). Examples of MRI-detected inflammation and erosions observed in the symptom-free participants are shown in Supplementary Figure 1, available on the Arthritis & Rheumatology website.

Co-occurrence of several MRI-detected inflammatory features at the same joint

It is known that simultaneous occurrence of synovitis, bone marrow edema, and/or tenosynovitis is frequent in arthritis and RA (2). If different inflammatory features do not occur simultaneously at the same joint in symptom-free persons, this might be a characteristic differentiating patients from age-matched controls.

At the MCP joints, bone marrow edema, synovitis, and tenosynovitis were studied. Although predominantly only one inflammatory feature was present, synovitis and bone marrow edema or synovitis and tenosynovitis were also regularly simultaneously present. Of 29 persons with any sign of inflammation in MCP3, 10 had colocalization of ≥ 2 features. Similarly, of 22 persons with inflammation in MCP2, 3 had ≥ 2 inflammatory features at this joint (see Supplementary Table 3A, available on the Arthritis & Rheumatology website). At the wrist, synovitis in the radiocarpal joint was evaluated in relation to bone marrow edema in the surrounding bones (scaphoid, lunate, triquetrum, pisiform, distal ulna, and distal radius). Likewise, synovitis of the intercarpal CMC joint was studied in relation to bone marrow edema of the proximal metacarpals 2-5 and all carpals. Both analyses showed that in almost one-third of the participants with any type of inflammation in these wrist joints, synovitis and bone marrow edema were both present (Supplementary Table 3B).

At the level of the MTP joints, bone marrow edema and synovitis frequently occurred together in MTP1 (Supplementary Table 3C). Taken together, these data show that MRI-detected synovitis, bone marrow edema, and tenosynovitis can be present simultaneously in the same joint in symptom-free persons.

Co-occurrence of MRI-detected inflammation and erosions

Similarly, we investigated to what extent MRI-detected erosions were seen at locations that also showed inflammation. These analyses revealed that the parts of the joints with erosions also showed inflammation. For example, of the 33 MCP2 joints with an erosion, 9 also showed inflammation, and of these 9 joints, 3 joints even had ≥ 2 inflammatory features. Of the 23 symptom-free persons with erosions at the distal ulna, 6 also had bone marrow edema (see Supplementary Table 4, available on the Arthritis & Rheumatology website).

Number of joints or bones affected

Finally, the prevalence of MRI-features in ≥ 2 joints was studied. Twenty-two % of the subjects had synovitis in ≥ 2 joints, 23% had bone marrow edema in ≥ 2 bones, 4% had tenosynovitis in ≥ 2 tendons, and 50% had erosions in ≥ 2 bones. This shows that inflammation or erosions can occur at several locations within the same symptom-free person.

Discussion

MRI is a promising tool because of its high sensitivity for the detection of local inflammation of Joints.[1,2] In addition, MRI depicts erosions. When using MRI for diagnostic purposes, the specificity of the findings should be considered. This study revealed that MRI-detected inflammation and erosions are prevalent in symptom-free persons, especially at specific joints or bones and at older ages. We also observed the simultaneous occurrence of different inflammatory features in the same joint in symptom-free persons. Apparently, this might not always indicate

abnormality since the persons studied had no arthritis, no joint symptoms, and no previous inflammatory rheumatic disease.

This is the first large-scale study of MRI in symptom-free persons. Even after stratifying for age, the 3 different strata each contained more than the total number of healthy controls in previous MRI-studies.[6-12] Furthermore, the use of contrast-enhanced MRI obtained using a 1.5T scanner allowed sensitive assessment of MRI-features. Another strength is that our recruitment method is different from previous studies that mostly evaluated hospital staff, which harbors a risk of a "too healthy" population.[6] We recruited volunteers via advertisements in local newspapers and web sites; hence, people could in no way feel forced to participate. To prevent selection bias due to inclusion of persons who would personally benefit from participating, participants did not receive MRI-results and were only partly compensated for travel costs. A completely random selection would entail actively approaching (randomly selected) individuals; we did not have ethics permission for such recruitment. We have not followed up the persons who were studied.

In our view, knowledge of clinical status (being healthy) might result in underscoring. To avoid this, the scans of the symptom-free persons were blinded and mixed with scans of patients. Hence, the readers were unaware of clinical status.

According to the scoring method used, imaging artifacts and normal structures should not be scored. The MRIs were scored accordingly.[17,18] We acknowledge that at several carpalia (e.g., the capitate and lunate) it can be difficult to differentiate erosions from physiologic indentations due to enlarged insertion areas of interosseous ligaments or vascular channels. The availability of serial MRIs might make this differentiation easier, but in the present study persons were scanned once. Differentiation of erosions from anatomic variants was performed by experienced readers (each reader had read >500 scans), and readers were instructed not to score an erosion in case of doubt. Furthermore, we used 2 readers and applied a very conservative method for analysis when categorizing the data. A joint could only be scored as 1 if both readers had scored it as 1. When readers disagreed, erosions were not considered to be present. If a different method had been used (e.g., a third adjudicator), it is likely that more erosions and inflammatory features would have been found.

The RAMRIS method was developed to sensitively follow the level of inflammation in RA-patients in clinical trials and was not designed for diagnostic purposes. If MRI is to be used for diagnostics, data on symptom-free persons are relevant to consider. Evaluation methods other than RAMRIS may be more accurate or more feasible, but this was beyond the scope of the present study.

A challenging question is what processes underlie the occurrence of MRI-detected inflammation and erosions in symptom-free persons. First, the MRI-findings observed could be degenerative in nature. Persons with symptomatic OA were not studied. To prevent recruiting a "too healthy" study population, symptom-free persons with Heberden's nodes, Bouchard's nodes, or hallux valgus were not excluded beforehand. Excluding these persons gave similar results. MRI-features were also present at locations that are not specific to OA (such as MCP2 and the distal ulna). Erosions were located marginally at the joint surface, which is unlike OA. In sum, the observation of more MRI-detected inflammation and erosions at older ages is not solely caused by the inclusion of persons with asymptomatic OA (as identified by physical examination), but it is possible that degenerative processes have contributed. Some observed preferential locations (MCP2, MCP3, and the distal ulna) are also known as preferential locations for arthritis and destruction in RA.[19] This might suggest that findings at these locations are partly mediated by mechanical strains. Furthermore, immunosenescence may also play a role, resulting in asymptomatic subclinical inflammation at older ages. Further studies are needed to identify the underlying mechanisms. Of note for bone marrow edema, it is possible that bone marrow edema in symptom-free persons relates to biologic processes that are different from those in RA-patients.

This observational study does not allow interpretation regarding the biologic nature of the findings. This limitation is inherent to imaging/MRI. However, this does not diminish the value of having a good reference when using MRI for diagnostic purposes.

The findings may be relevant if MRI is used to identify subclinical inflammation in patients with arthralgia without clinical arthritis who are presumed to be at risk for RA. In this setting it is relevant to prevent false-positive findings. If MRI is used for diagnosis and the RAMRIS method is used for MRI evaluation, the data presented

in Tables 2-4 could be used as a reference. For instance, a prevalence of<5% in the general population could be used as a cutoff to define a joint with abnormal MRI-detected inflammation.

In conclusion, this study showed that MRI-detected inflammation and erosions are prevalent in symptom-free persons, especially at older ages. The prevalence differed for the different MRI-features and also depended on the joint, bone, or tendon studied. Individual lesions were all assigned low grades. Interestingly, the joints that had the highest prevalence of MRI-features in symptom-free persons are similar to the joints that are frequently affected in RA.

Supplementary material

Supplementary material is published on the website of arthritis and rheumatology.

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Table 1 Characteristics of the 193 symptom-free participants

Total n = 193	
Age in years, mean (sd)	49.8 (15.8)
‹40 years, n (%)	51 (26.4)
40-60 years, n (%)	90 (46.6)
≥60 years, n (%)	52 (26.9)
Female, n (%)	136 (70.5)
Weight (kg), median (IQR)	71 (64-82)
Smoking	
Yes, present, n (%)	17 (8.8)
Yes, in past, n (%)	70 (36.3)
No, n (%)	106 (54.9)
Alcohol use †, n (%)	135 (69.9)
If yes, units per week, median (IQR)	7 (4-14)
Recent (less than 1 year) trauma ‡, n (%)	0 (0)
Comorbidity	
Hypertension, n (%)	13 (6.7)
Ischemic heart/cerebral disease, n (%)	4 (2.1)
Thyroid disease (current or past), n (%)	8 (4.1)
Diabetes mellitus, n (%)	1 (0.5)
Patient reported migraine, n (%)	6 (3.1)
Mood disorders (current or past), n (%)	10 (5.2)
Malignancies (current or past), n (%)	4 (2.1)
Other diagnoses, n (%)	53 (27.5)
Any sign of osteoarthritis of small joints at physical examination §, n (%)	68 (35.2)
Heberden nodes DIP, n (%)	55 (28.5)
Bouchard nodes PIP, n (%)	7 (3.6)
CMC-1 osteoarthritis, n (%)	2 (1.0)
Hallux valgus, n (%)	25 (13.0)

IQR = interquartile range; CMC-1 = carpometacarpal joint 1.

† Information on alcohol consumption was missing for 1 person.

‡ Trauma occurring ,1 year prior to magnetic resonance imaging.

§ The percentage of participants with signs of asymptomatic osteoarthritis in this study was similar to the prevalence observed in a large health survey in the US (20).

Table 2 Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the MCP joints of symptom-free participants

	< 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Synovitis			
MCP-2	0 / 0	8 / 0	19 / 0
MCP-3	0 / 0	14 / 0	17 / 0
MCP-4	0 / 0	2 / 0	4 / 0
MCP-5	0 / 0	1 / 0	6 / 0
BME*			
MCP-2	2 / 0	2 / 0	4 / 0
MCP-3	2 / 0	3 / 0	6 / 0
MCP-4	0 / 0	0 / 0	0 / 0
MCP-5	0 / 0	2 / 0	0 / 0
Tenosynovitis			
Extensor MCP-2	0 / 0	0 / 0	0 / 0
Extensor MCP-3	0 / 0	1 / 0	0 / 0
Extensor MCP-4	0 / 0	0 / 0	0 / 0
Extensor MCP-5	0 / 0	0 / 0	0 / 0
Flexor MCP-2	0 / 0	1 / 0	6 / 0
Flexor MCP-3	0 / 0	3 / 0	12 / 0
Flexor MCP-4	0 / 0	3 / 0	6 / 0
Flexor MCP-5	0 / 0	1 / 0	2 / 0
Erosions*			
MCP2	6 / 0	13 / 0	33 / 2
MCP3	8 / 0	12 / 0	17 / 6
MCP4	0 / 0	2 / 0	8 / 0
MCP5	2 / 0	6 / 0	21 / 0

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features rarely occurred; only 1% of participants ages 40-59 had a grade 3 erosion in metacarpophalangeal joint 3 (MCP3).

* Bone marrow edema and erosions were scored in the proximal and distal MCP bones separately. The scores for the 2 bones are summed into 1 score; therefore, the possible range of scores is 0-6 and 0-20, respectively. For MCP2, 1 bone had an erosion score of 2 (scores of 1 in both the proximal and distal bone); for MCP3, 4 bones had an erosion score of ≥ 2 (3 participants had a score of 2 or 3 in the proximal bone and 1 had a score of 1 in both the proximal and distal bone).

Table 3-a Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the wrist joints of symptom-free participants

	< 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Synovitis			
Intercarpal-CMC joint	4 / 0	16 / 0	27 / 0
Radio-carpal joints	0 / 0	17 / 0	35 / 0
Distal radio-ulnar joint	0 / 0	8 / 0	17 / 0
BME			
Metacarpal-1 basis	0 / 0	3 / 0	8 / 2
Metacarpal-2 basis	4 / 0	1 / 0	2 / 0
Metacarpal-3 basis	0 / 0	0 / 0	2 / 0
Metacarpal-4 basis	0 / 0	0 / 0	2 / 0
Metacarpal-5 basis	0 / 0	0 / 0	0 / 0
Trapezium	0 / 0	0 / 0	4 / 4
Trapezoid	2 / 0	1 / 0	6 / 0
Capitate	6 / 2	3 / 0	4 / 0
Hamate	0 / 0	3 / 0	8 / 0
Scaphoid	2 / 0	7 / 0	19 / 0
Lunate	6 / 0	19 / 1	27 / 4
Triquetrum	2 / 0	6 / 0	2 / 0
Pisiform	0 / 0	0 / 0	0 / 0
Distal radius	0 / 0	0 / 0	0 / 0
Distal ulna	0 / 0	7 / 0	8 / 0

Frequencies of Tenosynovitis and Erosions see table 3-b on the next page

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features rarely occurred; only 4% of participants ages ≥ 60 had grade 3 bone marrow edema in the metacarpal 1 base and in the trapezium.

Table 3-b Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the wrist joints of symptom-free participants

	‹ 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Frequencies of Synovitis and BME see table 3-a on the previous page			
Tenosynovitis			
I extensor	0 / 0	0 / 0	0 / 2
II extensor	0 / 0	0 / 0	0 / 0
III extensor	0 / 0	0 / 0	0 / 0
IV extensor	0 / 0	0 / 0	2 / 0
V extensor	0 / 0	0 / 0	0 / 0
VI extensor	0 / 0	9 /0	12 / 0
1 flexor	0 / 0	0 / 0	0 / 0
2 flexor	0 / 0	0 / 0	0 / 0
3 flexor	0 / 0	0 / 0	0 / 0
4 flexor	2 / 0	0 / 0	2 / 0
Erosions			
Metacarpal-1 basis	0 / 0	8 / 0	23 / 2
Metacarpal-2 basis	0 / 0	2 / 0	2 / 0
Metacarpal-3 basis	0 / 0	1 / 0	4 / 0
Metacarpal-4 basis	0 / 0	0 / 0	2 / 0
Metacarpal-5 basis	0 / 0	1 / 0	0 / 0
Trapezium	2 / 0	2 / 0	31 / 0
Trapezoid	4 / 0	11 / 0	17 / 0
Capitate	18 / 0	24 / 0	27 / 0
Hamate	0 / 0	4 / 0	13 / 0
Scaphoid	4 / 0	18 / 0	37 / 0
Lunate	8 / 0	19 / 0	40 / 0
Triquetrum	2 / 0	19 / 0	23 / 0
Pisiform	0 / 0	0 / 0	6 / 0
Distal radius	0 / 0	2 / 0	2 / 0
Distal ulna	6 / 0	9 / 0	23 / 0

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features did not occur.

Table 4 Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the MTP joints of symptom-free participants

	< 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Synovitis			
MTP-1	4 / 0	11 / 0	13 / 2
MTP-2	0 / 0	1 / 0	0 / 0
MTP-3	0 / 0	1 / 0	0 / 0
MTP-4	0 / 0	0 / 0	0 / 0
MTP-5	0 / 0	0 / 0	4 / 0
BME *			
MTP-1	10 / 0	12 / 1	23 / 8
MTP-2	2 / 0	0 / 1	0 / 0
MTP-3	0 / 0	1 / 0	0 / 0
MTP-4	0 / 0	1 / 0	0 / 0
MTP-5	0 / 0	1 / 0	4 / 0
Erosions *			
MTP1	2 / 0	14 / 0	37 / 4
MTP2	0 / 0	1 / 0	0 / 0
MTP3	0 / 0	0 / 0	2 / 0
MTP4	0 / 0	0 / 0	0 / 0
MTP5	2 / 0	10 / 0	10 / 0

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features rarely occurred; only 1% of the participants ages 40-59 years had bone marrow edema in metatarsophalangeal joint 3 (MTP3).

* Bone marrow edema and erosions were scored in the proximal and distal MTP bones separately. The scores for the 2 bones are summed into 1 score; therefore, the possible range of scores is 0-6 and 0-20, respectively. For MTP1, 5 bones had a bone marrow edema score of 2 (4 participants had a score of 1 in both the proximal and distal bone and 1 participant had a score of 2 in the proximal bone). For MTP2 and MTP3, 2 bones had a bone marrow edema score of ≥ 2 (both had a bone marrow edema score of 2 or 3 in the proximal bone). For MTP1, 2 bones had an erosion score of 2 (2 persons with an erosion score of 1 in both the proximal and the distal bone).