The use of MRI in early inflammatory arthritis

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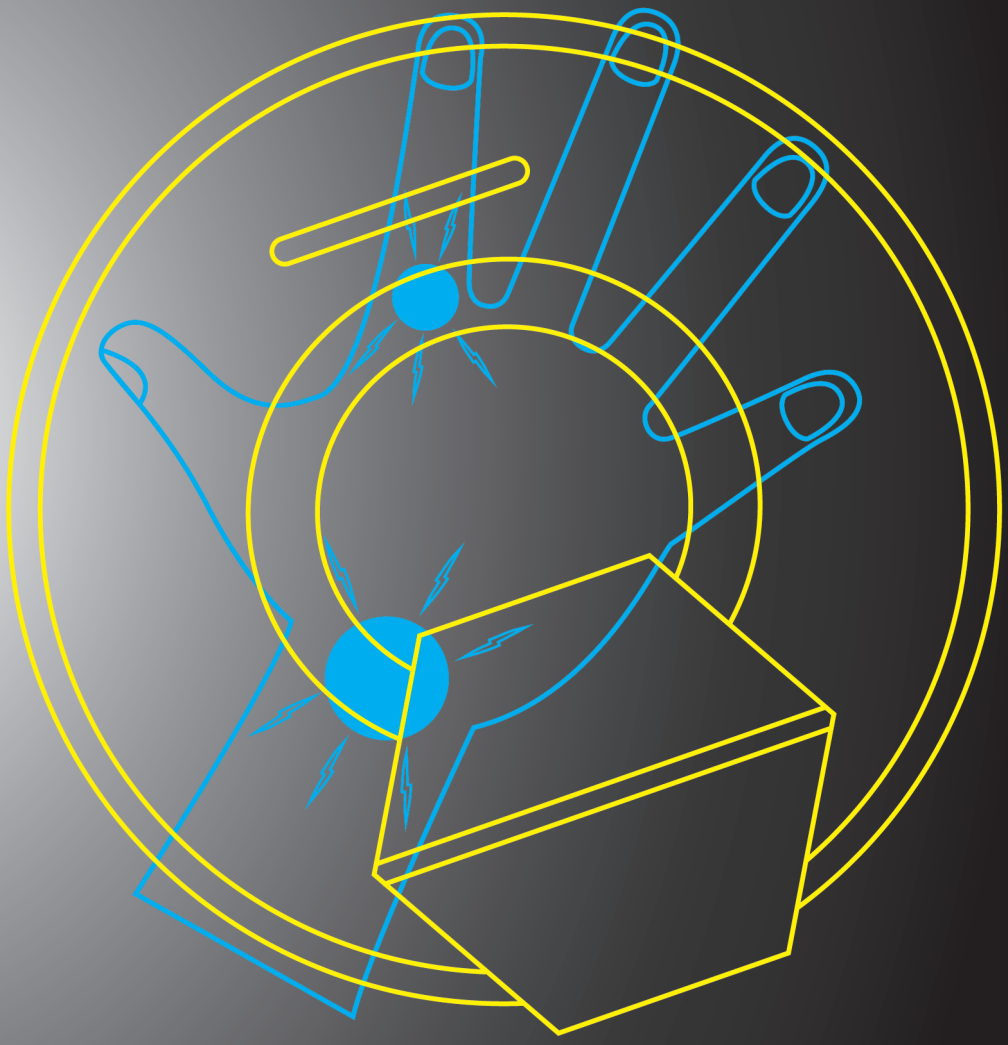

Wouter Nieuwenhuis

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Introduction 1

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Rheumatoid arthritis

The term rheumatoid arthritis (RA) was first mentioned in the second half of the 19th century by Alfred Garrod. Before Garrod, terms like (chronic) rheumatism, gout and hybrid terms like rheumatic gout were used to describe a disease with inflammation of multiple joints resulting in distortion of the joints. Moreover, (pre)historic findings suggest that RA existed long before that.[1] Nowadays, RA is described as a chronic, systemic, inflammatory, immune-mediated disease, which is characterized by arthritis, more specifically symmetric polyarthritis affecting the small joints of the hands. Yet, the initial presentation and the course of RA vary broadly within patients. Most likely RA is a collection of different disease entities with a similar clinical manifestation.[2]

A prevalence of 0.5-1% and an annual incidence of 5-50 new cases per 100.00 person years have been described in Caucasians. RA is 3 times more frequent in women than it is in men and the incidence rises with age. Uncontrolled, the chronic joint inflammation leads to erosive joint destruction resulting in disabling joint deformities. Besides painful and swollen joints, systemic symptoms as morning stiffness and fatigue are frequently reported. In addition extra-articular manifestations of RA expressed in pulmonary and cardiovascular disease are described.[2] Furthermore, it has been shown that the disease processes ultimately leading to “classical” RA are already active before joint inflammation becomes clinically detectable.[3]

In the last decades considerable advances in the management of RA have been made. It has become apparent that early treatment with disease-modifying anti-rheumatic drugs (DMARDs) improves the disease outcome of RA-patients: patients develop less erosive joint damage and the number of patients that are able to achieve clinical remission increases. Some patients are even able to stop all medication and maintain in remission.[4] Tight treat-to-target therapy is recommended, aiming for clinical remission.[5]

Early initiation of therapy also requires the identification of RA-patients early in the disease process. This has led to changes to the diagnosis and classification of RA. These changes and their implications will be discussed in more detail hereafter.

Diagnosis and classification

There is no gold standard for the diagnosis RA, i.e. there is no test result that is pathognomonic for RA. In the clinical setting, the diagnosis is made by the rheumatologist by combining clinical, laboratory and imaging findings. In the research setting, classification criteria are used to select relatively homogeneous patient groups for the comparison of study results. The first classification criteria were proposed in 1956 and revised in 1958, these divided patients in classical, definite, probable and possible RA.[6] Although these criteria proved useful, new insights in RA and other forms of arthritis led to the development of new criteria. The 1987 ACR classification criteria for RA were developed to increase the specificity compared to the revised 1958 ACR criteria.[7] The 1987 criteria were derived to discriminate patients with established RA from those with other definite

rheumatologic diagnoses and they are well accepted for this purpose.

A drawback of the 1987 criteria is that although patients with established RA are well recognized, the identification of patients in earlier stages of disease is something left to be desired. With the recognition of the benefits of early therapeutic intervention, there was a growing need for clinical trials focusing on early RA. Thus, classification criteria which allowed the selection of patients in an earlier disease stage were needed: this led to the development of the 2010 ACR/EULAR classification criteria.[8] The 1987 and 2010 criteria are compared in Table 1. The most important changes were that findings in established disease e.g. rheumatoid nodules and radiographic erosions were no longer included and that acute phase reactants and anti-citrullinated peptide antibodies (ACPA) were added.

The 2010 classification criteria have indeed shown to be more sensitive than the 1987 criteria at the cost of a slight decrease in specificity.[9] The goal of classification in an earlier stage of disease seems to be realized by the 2010 criteria. It is important to take in mind that using new classification criteria has consequences for the composition of the studied patient groups. For example, in the 2010 criteria

Table 1 Comparison of 1987 and 2010 classification criteria for RA

1987 ACR criteria	2010 ACR/EULAR criteria	Points
● Morning stiffness >1 hour	● Joint involvement	
● Arthritis of ≥3 joint areas	◦ 1 large joint	0
● Arthritis of hand joints	◦ 2-10 large joints	1
● Symmetric arthritis	◦ 1-3 small joints	2
● Rheumatoid nodules	◦ 4-10 small joints	3
● Serum RF	◦ >10 small joints	5
● Radiographic changes	● Serologic tests	
	◦ Negative RF and ACPA	0
	◦ Weakly positive RF/ACPA	2
	◦ Strongly positive RF/ACPA	3
	● Acute phase reactants	
	◦ Normal CRP and ESR	0
	◦ Elevated CRP/ESR	1
	● Symptom duration	
	◦ <6 weeks	0
	◦ ≥6 weeks	1
At least 4 out of 7 criteria must be positive for classification of RA	At least 6 out of 10 points are needed for classification of RA	

RF, Rheumatoid Factor. ACPA, anti-citrullinated peptide antibodies. CRP, c-reactive protein. ESR, erythrocyte sedimentation rate. Target population of 2010 criteria: patients with at least 1 joint with clinical synovitis in which the synovitis is not better explained by another disease.

the presence of antibodies associated with RA (RF and ACPA) have a bigger role in the classification of RA than in the 1987 criteria. This increases the difference between RA with the presence of auto-antibodies (seropositive) and patients without these antibodies (seronegative). Whereas seropositive patients can be classified with arthritis of one small joint, seronegative patients need over 10 involved joints to be classified as RA.

There is also a group of patients presenting with inflammatory arthritis that cannot be classified as RA or another form of arthritis at initial presentation; these patients have undifferentiated or unclassified arthritis (UA). Although arthritis disappears spontaneously in the majority of these patients, some still go on to develop RA during follow-up. This makes UA patients interesting to study as ideally, the patients that go on to develop RA are identified as soon as possible.

Using either the 1987 or the 2010 classification criteria also results in a different population of patients with UA (hereafter 1987UA and 2010UA respectively). One of the important differences is the presence of ACPA in these patients. Studies in 1987UA had shown that ACPA is a strong predictor for RA development.[10] Because ACPA is included and heavily weighted in the 2010 criteria, 2010UA consists of predominantly seronegative patients. Predictors of RA development in 1987UA are less discriminating in 2010UA. Earlier studies have reported that up to 25% of the 2010UA patients will still develop RA during follow-up.[11] Part of the work presented in this thesis focused on the use of magnetic resonance imaging (MRI) to identify these patients.

Imaging in RA

Imaging of the joints is used for several purposes in RA: diagnosis, prognostication, disease monitoring, and as outcome measure in trials.[12] Although radiographs of the hands and feet are still the most frequently used imaging modality in the field of RA, MRI and ultrasound (US) are increasingly performed. Radiographs show structural damage of bones, including erosions and joint space narrowing. MRI and US however, allow visualization of inflammatory soft tissue changes shown as synovitis and tenosynovitis, in addition to more sensitive detection of small erosions.

With the recognition of the importance of early initiation of DMARD-treatment, and thus early identification of RA patients and the presence of little to no radiographic damage in early disease stages, MRI and US are imaging modalities of increasing interest. Furthermore, erosive joint destruction in RA has been massively reduced because of the improvements in the management of RA. In clinical trials nowadays, there is very little progression of radiographic joint damage in different treatment arms, hampering its use as outcome measure. Therefore, imaging modalities which are able to depict inflammatory lesions instead of the long-term consequences of inflammatory lesions are interesting for the comparison of treatment arms of clinical trials.

A unique feature of MRI is the capability to detect bone marrow changes described as bone marrow edema (BME) or osteitis. In established RA it has

been shown that bone marrow fat is replaced by an inflammatory cellular infiltrate in BME-lesions.[13–15] MR inflammatory changes as synovitis, tenosynovitis, but especially BME, has been shown to be a strong predictor for the development of erosions.[16–20]

Although the use of MRI and US is already recommended for these purposes by the imaging guidelines of EULAR, the level of evidence for these recommendations is low.[12] Further studies are needed to increase our knowledge on the use of MRI in inflammatory arthritis.

The outline of this thesis

This thesis is primarily aimed to further expand on the value of MRI in early (rheumatoid) arthritis. All studies in this thesis were performed in the population of the Leiden Early Arthritis Clinic (EAC). This observational cohort was started in 1993 with the increasing awareness of the importance of early initiation of DMARDS. The EAC contains consecutively included patients presenting at the rheumatology outpatient clinic of the Leiden University Medical Center with arthritis confirmed by physical examination and symptom duration less than 2 years. This is the only rheumatology outpatient clinic in an area of >400.000 inhabitants. Questionnaires, extensive clinical information and serum samples were obtained in these patients. The cohort does not have a treatment protocol and patients receive regular rheumatologic care. Patients are followed up till discharge of the outpatient clinic. Since 2010 MRI of the hand and foot joints was also performed in all consenting patients. MRI inflammation and erosive damage was assessed using the RA MRI Scoring system (RAMRIS).[21,22]

After the introduction of the RAMRIS scoring system, which consisted of a semi-quantitative scoring system for erosions, BME and synovitis in the wrist and MCP joints, an additional semi-quantitative score for tenosynovitis was introduced a couple of years later.[21,22] In Chapter 2 we have focused on MRI-detected tenosynovitis at the level of the MCP and wrist joints using this score. Although tenosynovitis is a common finding in RA, thus far the presence of MRI-detected tenosynovitis was only studied in relatively small numbers of patients and selected patient groups. We studied the prevalence of tenosynovitis in the patients of the EAC, assessed whether patients with RA presented with tenosynovitis more often than other arthritis patients, and assessed whether the presence of tenosynovitis is associated with a more severe course of RA. We did not only look at the presence of any tenosynovitis, but also analyzed the separate tendon groups.

The association with erosive progression of both MRI-detected synovitis and BME has been shown by several studies. However, previous studies focused on the total BME, synovitis and erosion scores. It had not been shown how specific BME and synovitis lesions change over time and how this relates to development of erosions. In Chapter 3 we tried to answer these questions. We studied the presence of MRI detected BME and synovitis per bone at three time points and assessed the relationship of the course of these lesions with erosive development in the same bone. Because synovitis and bone marrow edema are often simultaneously present, we also assessed whether the course of BME and

synovitis were independently associated with erosive progression.

In Chapter 4 and Chapter 5 we studied the diagnostic value of MRI for the early identification of RA-patients. Earlier recognition of RA-patients allows for earlier initiation of DMARD therapy and better disease outcome. The 2010 already focused on earlier identification, still about 25% of the patients presenting with undifferentiated arthritis develop RA. We assessed whether MRI is able to identify these patients at first presentation in the outpatient clinic and its additional value to other findings (e.g. those used in the 2010 criteria).
In Chapter 4 we replicated a study[23] which suggested that the diagnostic performance of the 2010 criteria for identifying those early arthritis patients that develop RA within a year would improve by also letting the criteria be fulfilled if the specific MRI findings were present in the wrist or MCP joints. It was suggested that especially the presence of BME would improve the diagnostic performance because of the increased sensitivity, despite a decrease in specificity.
In Chapter 5 we studied the diagnostic value of MRI of hand and feet to identify early RA in daily practice. Previous studies had some important limitations hampering clinical application. Most studies were performed before the introduction of the 2010-criteria in relatively small populations with selection criteria that resulted in a study population not resembling daily practice. Therefore Chapter 5 was performed in the large study population of the EAC using all consecutively included patients (n=589) . Previous studies showed that it is hard to distinguish different forms of arthritis with MRI.[24,25] Moreover, our group has shown that in symptom free controls also signs of inflammation are depicted on MRI, especially at higher age.[26] By including the MRI-data of the symptom-free controls we tried to reduce false-positive MRI findings. Several analyses were performed to assess the additional value of MRI to other clinical findings (e.g. clinically inflamed joints and elevated acute phase reactants).

In Chapter 6 we used the data in the EAC to replicate the results of a study[27] which used MRI-detected synovitis and BME in order to develop new composite scores to assess disease activity. The replicated hypothesis was that composite scores derived from MRI findings are a better reflection of the inflammatory disease burden than the current composite scores (DAS-28, SDAI and CDAI) which were derived from erosive progression on radiographs and clinical decision making.

In Chapter 7 we assessed the effect of age on MRI-inflammation in arthritis patients, since it was shown in symptom-free controls that MRI-inflammation increases with age.[26] The presence of an effect of age on MRI-inflammation could have consequences on the interpretation of MRI findings. Moreover, we assessed whether there is a general effect of age on MRI findings or whether the effect age is different (bigger or smaller) in arthritis patients than in symptom-free controls. We also assessed whether the presentation of inflammation was different for RA-patients presenting at different ages.

The last decades there has been an increasing focus on early identification of RA patients. Besides long term disease outcome, it is interesting to study whether earlier identification also leads to RA patients presenting with less severe disease. In Chapter 8 we evaluated whether RA-patients are now indeed earlier recognized over the 23 years of existence of the EAC and whether the presentation of

RA-patients at the rheumatologist changed over this time period.

In Chapter 9 the studies in this thesis are summarized followed by a general discussion.

References

1 Storey GO et al. *Ann Rheum Dis* 1994;53:557–60.
2 Scott DL et al. *The Lancet* 2010;376:1094–108.
3 van Steenbergen HW et al. *Arthritis Rheum* 2013;65:2219–32.
4 van Nies JAB et al. *Ann Rheum Dis* Published Online First: 9 April 2013.
5 Smolen JS et al. *Ann Rheum Dis* 2016;75:3–15.
6 Ropes MW et al. *Arthritis Rheum* 1959;2:16–20.
7 Arnett FC et al. *Arthritis Rheum* 1988;31:315–24.
8 Aletaha D et al. *Arthritis Rheum* 2010;62:2569–81.
9 Radner H et al. *Ann Rheum Dis* 2014;73:114–23.
10 van der Helm-van Mil AHM et al. *Arthritis Rheum* 2007;56:433–40.
11 Krabben A et al. *Rheumatology* 2013;52:1265–70.
12 Colebatch AN et al. *Ann Rheum Dis* Published Online First: 21 March 2013.
13 McQueen FM et al. *Ann Rheum Dis* 2007;66:1581–7.
14 Dalbeth N et al. *Ann Rheum Dis* 2009;68:279–82.
15 Jimenez-Boj E et al. *Arthritis Rheum* 2007;56:1118–24.
16 McQueen FM et al. *Arthritis Rheum* 2003;48:1814–27.
17 Haavardsholm EA et al. *Ann Rheum Dis* 2008;67:794–800.
18 Palosaari K et al. *Rheumatology* 2006;45:1542–8.
19 Hetland ML et al. *Ann Rheum Dis* 2009;68:384–90.
20 Mundwiler ML et al. *Arthritis Res Ther* 2009;11:R94.
21 Østergaard M et al. *J Rheumatol* 2003;30:1385–6.
22 Haavardsholm EA et al. *Ann Rheum Dis* 2007;66:1216–20.
23 Tamai M et al. *Ann Rheum Dis* Published Online First: 2 September 2014.
24 Stomp W et al. *J Rheumatol* 2014;41:1630–7.
25 Boutry N et al. *Radiology* 2005;236:593–600.
26 Mangnus L et al. *Arthritis Rheumatol* 2016;:n/a-n/a.
27 Baker JF et al. *Arthritis Rheumatol* 2014;66:794–802.

Evaluation of Magnetic Resonance Imaging–Detected Tenosynovitis in the Hand and Wrist in Early Arthritis

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Abstract

Objective
Magnetic resonance imaging (MRI) is a sensitive method to detect inflammation in rheumatoid arthritis (RA), visualizing synovitis, bone marrow edema, and tenosynovitis. The prevalence of MRI-detected tenosynovitis and its diagnostic value in early arthritis are unclear. This study was undertaken to identify the frequency of MRI-detectable tenosynovitis at the metacarpophalangeal (MCP) and wrist joints in early arthritis and the association of these with RA and the severity of RA.

Methods
A total of 178 patients with early arthritis underwent unilateral 1.5T extremity MRI at baseline. The MCP and wrist joints were scored using the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system and Haavardsholm's tenosynovitis score. Sixty-nine patients fulfilled the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA during the first year and were compared with the non-RA patients. Among the RA patients, comparisons were made with regard to anti–citrullinated protein antibody (ACPA) positivity and radiographic progression during year 1.

Results
Of all patients, 65% had MRI-detected tenosynovitis. RA patients had tenosynovitis more often than non-RA patients (75% versus 59%; P = 0.023). The flexor tendons at MCP5 and the extensor tendons at MCP2 and MCP4 and in extensor compartment I of the wrist were more frequently affected in RA patients than in other patients (odds ratios 2.8 [95% confidence interval (95% CI) 1.2–7.0], 9.1 [95% CI 1.9–42.8], 14.2 [95% CI 1.7–115.9], and 4.0 [95% CI 1.4–11.1], respectively). These associations were independent of local MRI synovitis. Specificities were all >82%. Within the group of RA patients, tenosynovitis scores were not associated with ACPA positivity or radiographic progression.

Conclusion
MRI-detected tenosynovitis is commonly seen in early arthritis. The flexor tendons at MCP5, the extensor tendons at MCP2 and MCP4, and the first extensor compartment of the wrist are more often affected in RA, independent of local synovitis.

Introduction

Magnetic resonance imaging (MRI) of hand, wrist, and foot joints is increasingly used in early arthritis and rheumatoid arthritis (RA), though mainly for research purposes. The advantage of MRI is its ability to sensitively depict both local inflammation and structural damage.[1,2] For MRI of the hands and wrists, a validated scoring system (Rheumatoid Arthritis Magnetic Resonance Imaging Scoring [RAMRIS]) has been developed.[3] Bone marrow edema, or osteitis, which cannot be detected by physical examination or ultrasound, is a potent predictor of future erosions in RA.[4,5]

In addition to the RAMRIS method, which allows scoring of erosions, bone marrow edema, and synovitis in the metacarpophalangeal (MCP) and wrist joints, a separate tenosynovitis scoring method has been developed.[6] Although this method allows the evaluation of the presence and extent of tenosynovitis in a standardized way, at present knowledge of the discriminative ability of MRI-detected tenosynovitis for RA in patients with early arthritis is still limited. This hampers the appreciation of tenosynovitis both for research purposes and potentially for the diagnostic process in daily clinical practice.

Tenosynovitis is defined as inflammation of the synovial lining of the tendon sheath, with or without synovial thickening; synovial fluid may be present. Inflammation around tendons without tendon sheaths is also observed, and its origin is less clear. Underlying joint synovitis potentially plays a role. The extensor tendons of the fingers and the flexor carpi ulnaris at the wrist lack a tendon sheath.[7] The anatomy of all tendons around the wrist and MCP joints 2–5 is shown in detail in Figure 1. Tenosynovitis can be detected by physical examination, ultrasound, and MRI. Previous studies have shown that ultrasound and MRI have a higher sensitivity than physical examination.[1,8]

Studies of MRI-detected tenosynovitis thus far have included relatively small numbers of patients, evaluated a selected patient group, or studied groups of extensor and flexor tendons instead of separate anatomically defined compartments.[9–12] For instance, it was observed that RA patients more often had involvement of the group of extensor tendons than psoriatic arthritis patients,[10] that tenosynovitis of the flexor tendons (analyzed as a group) was associated with RA development in undifferentiated arthritis,[9] and that tenosynovitis of the flexor tendons of the second finger and the extensor carpi ulnaris was associated with progression to RA.[11] However, none of those studies performed detailed analyses in a large inception cohort of patients with early arthritis.

The purpose of this study was to assess the prevalence of MRI-detected tenosynovitis at the level of the wrist and MCP joints using separate anatomic regions, to associate this with underlying synovitis, and to determine the discriminative ability of tenosynovitis for early RA in an unselected population of patients with early arthritis. Finally, we evaluated whether the presence of tenosynovitis is a feature associated with a severe course of RA.

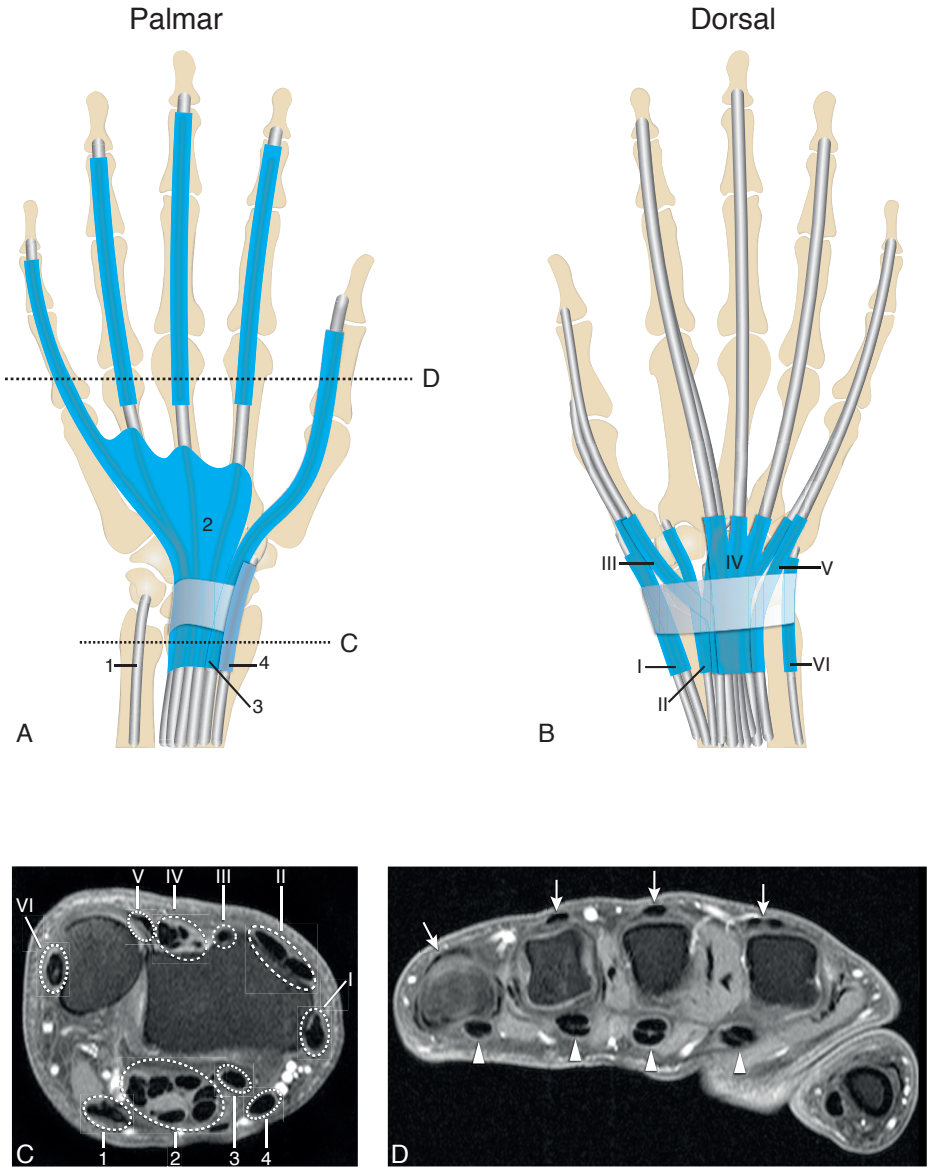

Figure 1 Tendons and tendon sheaths (shown in blue) of the hand and wrist
A, Schematic illustration of the palmar side of the hand and wrist. The broken lines show the areas depicted in C and D. B, Schematic illustration of the dorsal side of the hand and wrist. C, Axial T1, postgadolinium, fat-saturated magnetic resonance image (MRI) at the level of the wrist without signs of inflammation. D, Axial T1, postgadolinium, fat-saturated MRI at the level of the metacarpophalangeal (MCP) joints without signs of inflammation. At the dorsum of the wrist 6 extensor compartments are defined under the extensor retinaculum and covered with a synovial sheath (numbered I–VI) containing the extensor pollicis brevis and abductor pollicis longus (I), extensor carpi radialis brevis and extensor carpi radialis longus (II), extensor pollicis longus (III), extensor digitorum communis and extensor indicus

proprius (IV), extensor digiti quinti proprius (V), and extensor carpi ulnaris (VI). However, moving distally, the tendons are connected to the bone by a complex ligamentous system; the extensor tendons at the level of the MCP joint have no synovium (arrows in D). On the palmar side, the 9 tendons in the carpal tunnel are covered by the synovium of the radial (3) and ulnar (2) bursa. The radial bursa contains the flexor pollicis longus tendon and extends to the thumb, and the ulnar bursa contains the 8 flexor tendons and extends distally to the fifth finger in the majority of cases. A connection between the ulnar and radial bursa is present in a majority of cases. A gap exists at the palm of the hand between the tenosynovium in the carpal tunnel and the second, third, and fourth fingers, which have a separate tenosynovial coverage that starts at the level of the metacarpal heads (arrowheads in D). Outside the carpal tunnel the flexor carpi ulnaris tendon (1) does not have a synovial sheath, but the flexor carpi radialis tendon (4) does (see refs. 7 and 20)[7,20].

Patients and methods

Patients

From August 2010 to April 2012, 350 patients were included in the Leiden Early Arthritis Clinic (EAC). MRI was performed at baseline in 179 patients, based on voluntary participation. One patient was excluded because no gadolinium (Gd) chelate contrast agent was administered. The EAC is a prospective population-based inception cohort including patients with confirmed arthritis and symptom duration of <2 years. At baseline, the patients and rheumatologists completed questionnaires, joint counts were performed, serum samples were obtained, and hand and foot radiographs were obtained. The cohort has been described in detail previously.[13] The diagnoses established after 1 year of followup were used in this study. RA was classified according to the American College of Rheumatology/ European League Against Rheumatism 2010 classification criteria ,[14] and 69 of the 178 patients fulfilled the criteria. Written informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

MRI scanning and scoring

MCP joints 2–5 and the wrist of the most painful side, or the dominant side in cases of equally severe symptoms on both sides, were scanned. MRI was performed using an MSK Extreme 1.5T extremity MRI system (GE) and a 100-mm coil.

The following sequences were acquired before contrast injection: T1-weighted fast spin-echo (FSE) sequence in the coronal plane (repetition time [TR]/echo time [TE] 650/17 msec, acquisition matrix 388 x 88, and echo train length [ETL] 2) and T2-weighted FSE sequence with frequency-selective fat saturation in the coronal plane (TR/TE 3,000/61.8 msec, acquisition matrix 300 x 224, and ETL 7). After intravenous injection of Gd chelate contrast agent (gadoteric acid; Guerbet) (standard dose of 0.1 mmole/kg), the following sequences were obtained: T1-weighted FSE sequence with frequency-selective fat saturation in the coronal plane (TR/TE 650/17 msec, acquisition matrix 364 x 224, and ETL 2) and T1-weighted FSE sequence with frequency-selective fat saturation in the axial plane (TR/TE 570/7 msec, acquisition matrix 320 x 192, and ETL 2). The field of view was 100 mm. Coronal sequences had 18 slices with a slice thickness of 2 mm and a slice gap of 0.2 mm. All axial sequences had a slice thickness of 3 mm and a slice gap of 0.3 mm, with 20 slices for the hand.

Synovitis was scored at MCP joints 2–5 separately and, according to the RAMRIS method, in 3 regions of the wrist: the distal radioulnar joint, the radiocarpal joint,

and the intercarpal and carpometacarpal joints.[15] Tenosynovitis was scored as described by Haavardsholm et al,[6] on a scale of 0–3, where 0 = normal, 1 = <2 mm peritendinous effusion or synovial proliferation with enhancement, 2 = >2 and <5 mm peritendinous effusion or synovial proliferation with enhancement, and 3 = >5 mm peritendinous effusion or synovial proliferation with enhancement. Examples of MR images without inflammation are shown in Figure 1. Examples of scores 1 and 2 are available from the author upon request. Enhancement of tissue surrounding tendons without a tenosynovial sheath (the extensor tendons at the MCP joints and the tendon of the flexor carpi ulnaris) was scored following the same method. In the analyses we used the term tenosynovitis for both. A total of 18 tenosynovitis locations were scored in each patient: 10 at the wrist, including 6 extensor compartments and 4 regions on the volar side (the flexor digitorum profundus and flexor digitorum superficialis, the flexor pollicis longus, the flexor carpi ulnaris, and the flexor carpi radialis), and 8 locations at MCP joints 2–5 (paired flexor tendons and extensor tendons of the fingers) (Figure 1).

The MRIs were independently scored by 2 readers who were blinded with regard to the clinical data. The within reader intraclass correlation coefficients (ICCs) for the total RAMRIS score were 0.98 and 0.83; the between-reader ICC was 0.82. When scores were dichotomized as indicating the presence or absence of synovitis or tenosynovitis, a joint or tendon was scored positive for the presence of synovitis or tenosynovitis when both readers scored at least 1 for the feature. Groups of tendons (e.g., all MCPs or wrist) were considered positive when at least 1 of the locations evaluated in the group was scored as having synovitis or tenosynovitis present. When sensitivity analyses were performed, tenosynovitis was considered present when both readers assigned a score of at least 2 to the location.

Conventional radiography and scoring
Radiographs of the hands and feet of RA patients were scored according to the Sharp/van der Heijde (SHS) method[16] by a trained reader (within-reader ICC 0.91). Baseline radiographs were available for all 69 patients with RA, and radiographs obtained after 1 year were available for 56 (81%) of the patients. The progression in total SHS score (erosion and narrowing score) in the hands and feet over 1 year was used in the analyses.

Statistical analysis
Tenosynovitis and synovitis scores that could not be determined on MRI due to insufficient image quality, mostly due to inhomogeneous fat suppression or movement artifacts, were imputed with the median value for that feature across all locations within the same patient. For synovitis, 12 (0.5%) of 2,492 joints could not be scored, and for tenosynovitis, 49 (0.8%) of 6,408 locations could not be scored. To compare proportions, Pearson's chi-square test or Fisher's exact test, when appropriate, was used. Univariable and multivariable logistic regression analyses were used to analyze the associations between tenosynovitis, synovitis, and RA. In multivariable logistic regression all covariates were entered simultaneously. Spearman's rank correlation and the Mann-Whitney U test were used for analysis of the non– normally distributed total tenosynovitis score. IBM SPSS for Windows, version 20.0 was used. P values less than 0.05 were considered significant.

Results

Frequency of tenosynovitis in early arthritis

Baseline characteristics of the patients are presented in Table 1. In total, 3,204 separate anatomic locations were assessed for tenosynovitis in 178 patients. Tenosynovitis in at least 1 location was present in 65% of all of the patients with early arthritis. Figure 2 shows the frequency of tenosynovitis per location. The tendon of the extensor carpi ulnaris was most frequently affected (34% of all patients with early arthritis).

Table 1 Baseline characteristics of the patients with early arthritis*

	All (n=178)	RA (n=69)†	non-RA (n=109)‡
Age, mean (SD) years	54.2 (15.2)	54.5 (15.5)	53.9 (15.1)
Sex, no. (%) female	98 (55.1)	43 (62.3)	55 (50.5)
Symptom duration at first visit, weeks	17.8 (8.2-35.0)	19.7 (8.5-25.6)	17.1 (7.9-41.5)
Swollen joint count (66 joints)	3.0 (2.0-5.0)	5.0 (2.0-10.0)	2.5 (1.0-4.3)
ESR level above reference value, no. (%)	71 (39.9)	35 (50.7)	36 (33.0)
CRP level above reference value, no. (%)	56 (31.5)	31 (44.9)	25 (22.9)
ACPA above reference value, no. (%)	45 (25.3)	42 (60.9)	3 (2.9)
Baseline SHS	2 (0-5)	2 (0-4)	2 (0-6)

* Except where indicated otherwise, values are the median (interquartile range). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ACPA = anti–citrullinated protein antibody; SHS = Sharp/van der Heijde score.
† Fulfilled the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for rheumatoid arthritis (RA) during the first year.
‡ Of the patients without RA, 54 had undifferentiated arthritis, 13 had osteoarthritis, 12 had psoriatic arthritis, 4 had spondyloarthritis with peripheral arthritis, 4 had gout, and 22 had other diagnoses.

Association between tenosynovitis and RA

Subsequently, we studied the 69 patients with RA. In 75% of the RA patients, at least 1 location was scored positive for tenosynovitis, which was higher than the prevalence of tenosynovitis in patients with other arthritides (59%) (P = 0.023). Similar comparisons were performed for tenosynovitis at the MCP joints (54% in RA patients versus 36% in non-RA patients; P = 0.019) and the wrist (55% in RA patients versus 47% in non-RA patients; P = 0.282). Figure 2 also shows the frequency of tenosynovitis per anatomic location within the wrist and MCP joints for patients with RA and those with other diagnoses. RA patients had significantly more inflammation at the flexor tendons at MCP5, with an odds ratio (OR) of 2.8 (95% confidence interval [95% CI] 1.2–7.0), and at the extensor tendons at MCP2 (OR 9.1 [95% CI 1.9–42.8]) and MCP4 (OR 14.2 [95% CI 1.7–115.9]) and in wrist compartment I (OR 4.0 [95% CI 1.4–11.1]), wrist compartment II (OR 2.6 [95% CI 1.0–6.4]), and wrist compartment IV (OR 2.2 [95% CI 1.1–4.5]) (Table 2).

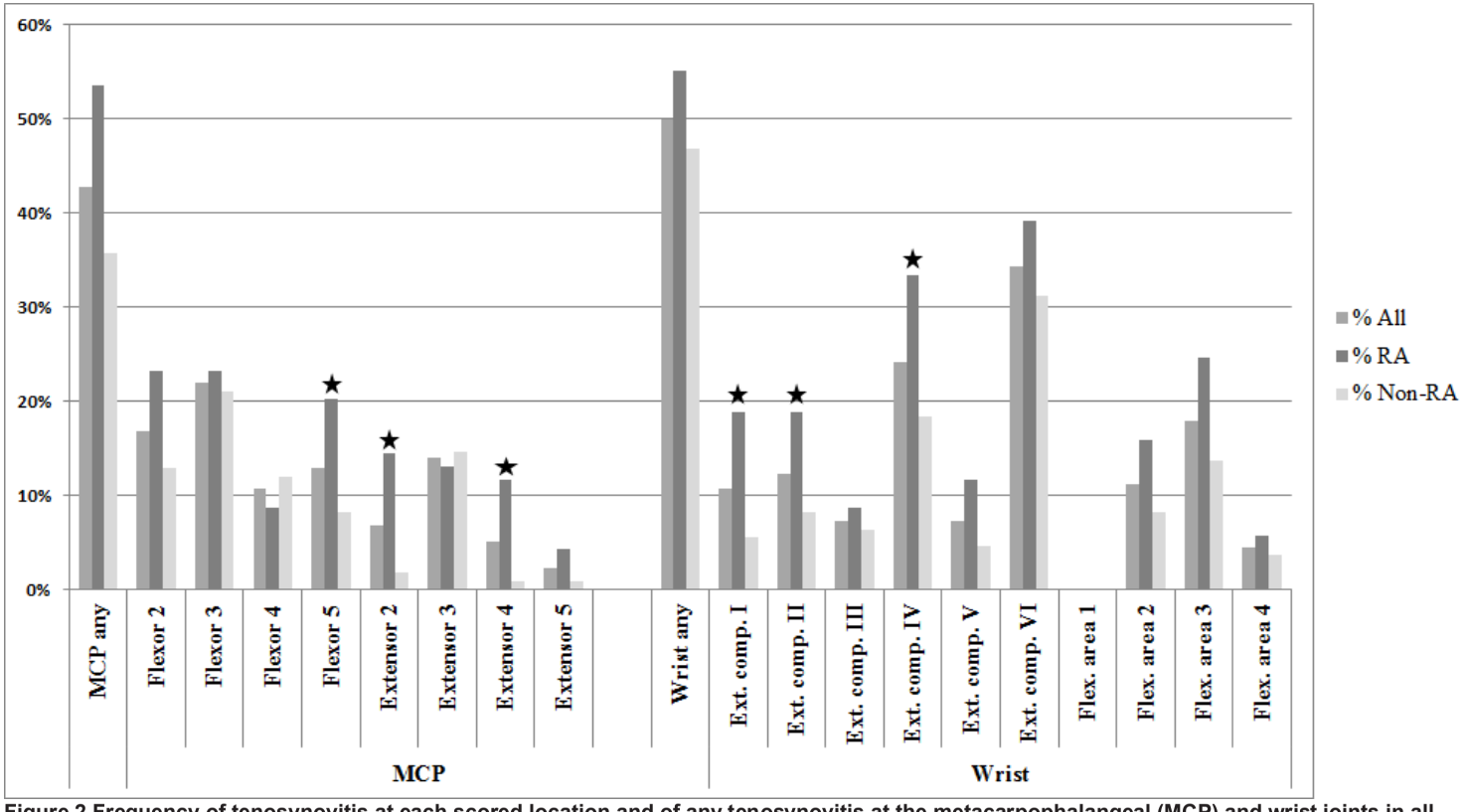

Figure 2 Frequency of tenosynovitis at each scored location and of any tenosynovitis at the metacarpophalangeal (MCP) and wrist joints in all patients with early arthritis, in patients with rheumatoid arthritis (RA), and in patients with other arthritides (non-RA).

Star: P < 0.05 versus non-RA. Ext. comp. I–VI = compartments of extensor tendons in the wrist containing the extensor pollicis brevis and abductor pollicis longus (I), extensor carpi radialis brevis and extensor carpi radialis longus (II), extensor pollicis longus (III), extensor digitorum communis and extensor indicus proprius (IV), extensor digiti quinti proprius (V), and extensor carpi ulnaris (VI); Flex. areas 1–4 = regions of flexor tendons in the wrist, including flexor carpi ulnaris (1), flexor digitorum profundus and flexor digitorum superficialis (2), flexor pollicis longus (3), and flexor carpi radialis (4).

Table 2 Diagnostic value of tenosynovitis for RA at locations that were more significantly affected in RA than in other arthritides*

Location	RA %	non-RA %	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	OR (95% CI)	p
Flexor mcp 5	20.3	8.3	20% (14%-26%)	92% (88%-96%)	61% (54%-68%)	65% (57%-72%)	2.46 (1.13-5.37)	0.87 (0.76-0.99)	2.83 (1.15-6.95)	0.020
Extensor mcp 2	14.5	1.8	14% (9%-20%)	98% (96%-100%)	83% (78%-89%)	64% (57%-71%)	7.9 (1.78-34.98)	0.87 (0.79-0.96)	9.07 (1.92-42.77)	0.002
Extensor mcp 4	11.6	0.9	12% (7%-16%)	99% (98%-100%)	89% (84%-94%)	64% (57%-71%)	12.64 (1.62-98.85)	0.89 (0.82-0.97)	14.16 (1.73-115.95)	0.002
Wrist extensor compartment I	18.8	5.5	19% (13%-25%)	94% (91%-98%)	68% (62%-75%)	65% (58%-72%)	3.42 (1.37-8.58)	0.86 (0.76-0.97)	3.99 (1.44-11.06)	0.005
Wrist extensor compartment II	18.8	8.3	19% (13%-25%)	92% (88%-96%)	59% (52%-66%)	64% (57%-71%)	2.28 (1.03-5.05)	0.88 (0.78-1)	2.58 (1.04-6.41)	0.037
Wrist extensor compartment. IV	33.3	18.3	33% (26%-40%)	82% (76%-87%)	53% (46%-61%)	66% (59%-73%)	1.82 (1.08-3.05)	0.82 (0.68-0.99)	2.23 (1.11-4.47)	0.023

* RA = rheumatoid arthritis; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; LR =likelihood ratio; OR = odds ratio.

† The total numbers of patients affected per location were 23 for flexor metacarpophalangeal (MCP) joint 5, 12 for extensor MCP2, 9 for extensor MCP4, 19 for wrist extensor compartment I, 22 for wrist extensor compartment II, and 4 for wrist extensor compartment IV.

The sensitivity of these features for RA was low (generally <20%), indicating that although RA patients had tenosynovitis at these locations more frequently than patients with other arthritides, the majority of RA patients did not have tenosynovitis at these specific locations. The specificity, however, was high (generally >90%), indicating that tenosynovitis at these locations rarely occurred in patients with early arthritis without RA (Table 2). Furthermore, the positive likelihood ratios for inflammation at the extensors at MCP2 and MCP4 were relatively high (7.9 and 12.64, respectively) (Table 2).

Association between synovitis and tenosynovitis

Next, since synovitis was often present in joints next to tendons showing tenosynovitis (range 70–100%) (data are available from the author upon request), we examined if the associations observed were all driven by the association between synovitis and RA or whether the associations of tenosynovitis with RA were independent of the presence of local synovitis. Four locations of tenosynovitis were associated with RA independent of the presence of local synovitis: the flexor tendons at MCP5 (OR 4.2 [95% CI 1.4–12.9]), the extensor tendons at MCP2 (OR 9.4 [95% CI 1.9–45.8]) and MCP4 (OR20.1 [95% CI 2.2–186.0]), and extensor compartment I of the wrist (OR 3.7 [95% CI 1.3–10.4]) (Table 3). The extensor tendons at the MCP joints lack a tenosynovium, which makes them different from the other tendons studied. Interestingly, in the patients with early arthritis

Table 3 Association of tenosynovitis with RA adjusted for local synovitis*

Location		OR	95%CI	p
MCP 5				
	Flexor	4.22	(1.38-12.85)	0.01
	Synovitis	0.52	(0.19-1.42)	0.20
MCP 2				
	Extensor	9.38	(1.92-45.81)	0.01
	Synovitis	0.93	(0.48-1.81)	0.84
MCP 4				
	Extensor	20.08	(2.17-185.95)	0.01
	Synovitis	0.60	(0.22-1.62)	0.32
Wrist†				
	Extensor comp. I	3.69	(1.3-10.42)	0.01
	Synovitis	1.29	(0.67-2.46)	0.45
	Extensor comp. II	2.32	(0.89-6.03)	0.08
	Synovitis	1.27	(0.66-2.47)	0.48
	Extensor comp. IV	2.08	(0.97-4.45)	0.06
	Synovitis	1.17	(0.58-2.33)	0.66

* Data were analyzed by multivariable logistic regression for an association with fulfilling the American College of Rheumatology/ European League Against Rheumatism 2010 classification criteria for rheumatoid arthritis (RA) during the first year. Analyses were performed per location. OR = odds ratio; 95% CI = 95% confidence interval; MCP5 = metacarpophalangeal joint 5.

† Local synovitis of the wrist is defined as synovitis in at least 1 of the following joints: the distal radioulnar joint, the radiocarpal joint, or the intercarpal and carpometacarpal joints.

without RA, extensor tendon involvement at the MCP joints always coexisted with local synovitis, while isolated extensor tendon involvement at MCP2, MCP3, and MCP4 was seen in 11–25% of the RA patients (Table 4). Inflammation was seen in the absence of local synovitis in the flexor tendons at the MCP joints, which have a tenosynovium, in up to 31% and 33% of RA patients and non-RA patients, respectively (Table 4). Three areas in the wrist were scored for synovitis and each tendon (group) was scored as a whole, hampering adequate assessment of the relationship between synovitis and tenosynovitis. Nonetheless, tenosynovitis without any synovitis in the wrist was uncommon (range 0–12%) (data are available from the author upon request).

Table 4 Frequency of local MRI-detected synovitis at locations with MRI-detected tenosynovitis at the MCP joints*

Location	All	RA	non-RA
Flexors			
Flexors MCP 2	73.3	68.8	78.6
Flexors MCP 3	82.1	81.3	82.6
Flexors MCP 4	84.2	100.0	76.9
Flexors MCP 5	69.6	71.4	66.7
Extensors			
Extensors MCP 2	83.3	80.0	100.0
Extensors MCP 3	96.0	88.9	100.0
Extensors MCP 4	77.8	75.0	100.0
Extensors MCP 5	100.0	100.0	100.0

* Values are the percent. MRI = magnetic resonance imaging; MCP =metacarpophalangeal; RA = rheumatoid arthritis.

Association between tenosynovitis and features of RA severity

Last, we studied whether MRI-detected tenosynovitis within the group of RA patients is a feature of more severe disease, reflected by anti– citrullinated protein antibody (ACPA) positivity and radiographic progression in the first year. Tenosynovitis scores at baseline were studied. The total tenosynovitis score did not differ significantly between ACPA-positive and ACPA-negative RA patients (median 3 and 3, respectively; P = 0.52). The mean progression in total SHS, the combination of the erosion and narrowing scores in both the hands and feet, over 1 year was 1. There was no correlation between the total tenosynovitis score and progression of the total SHS during the first year (Spearman's p = 0.081; P = 0.55). Because of the low level of radiographic progression, it was not possible to compare tenosynovitis with structural damage at specific locations. For instance, only 2 patients had radiographic progression at the ulna of the scanned wrist, yielding insufficient power to evaluate whether tenosynovitis of the extensor carpi ulnaris was associated with local structural damage.

Sensitivity analysis

In the analyses described above, tenosynovitis was considered to be present in cases in which both readers assigned a score of at least 1. We also performed analyses in which tenosynovitis at a specific location was considered to be present

in cases in which both readers assigned a score of 2 or higher.

Given this more stringent cutoff, the prevalence of tenosynovitis at any location was 8.4% in the total group of patients with early arthritis, 6% in patients with arthritides other than RA, and 13% in patients with RA (P = 0.078). The locations with the highest frequency of tenosynovitis scored >2 were the tendon of the extensor carpi ulnaris at the level of the wrist joints and the flexor tendons of the second finger at the level of the MCP joints. Using this more stringent cutoff, the frequency of tenosynovitis at individual locations was too low to perform further analyses.

Discussion

This study aimed to explore MRI-detected tenosynovitis at the wrist and MCP joints in early arthritis. We observed that MRI-detected tenosynovitis was present in 65% of all patients with early arthritis and that the flexor tendons at MCP5 and the extensor tendons at MCP2 and MCP4 and in the first extensor compartment of the wrist were more frequently affected in RA than in other arthritides; these locations were independent of the presence of local synovitis.

A strength of this study is that it was performed in a large inception cohort of patients with early arthritis, implying that the test characteristics observed may be generalizable to the diagnostic process in patients with early arthritis in daily practice. Other advantages are that tendons were not only assessed at the level of the wrist, but also at the level of the MCP joints, that analyses were done for all tendons, and that the number of patients in this study was larger than that in previous MRI studies.[9,11,12,17]

Interestingly, in our study, inflammation of the extensor tendons at the level of the MCP joints was only seen in combination with local synovitis in patients with early arthritis with diagnoses other than RA. The presence of synovitis in an MCP joint might affect the overlying, closely related extensor tendons due to continuous inflammation. The fact that there is no tendon sheath demarcating and protecting the finger extensor tendon might explain the high correlation between synovitis and extensor tendon involvement. In an ultrasound and MRI study, inflammation at the extensor tendons was named periextensor inflammation.[17] The only other tendon without a tendon sheath, the flexor carpi ulnaris tendon, was never scored positive in any of the patients with early arthritis in this study. Its relatively separate location with its insertion at the pisiform might be an explanation for this. In contrast to the finding in arthritides other than RA, in patients with RA, inflammation of the extensor tendons at the MCP joints also occurred in isolation, without underlying synovitis of these joints. This suggests a direct effect of RA, which is not related to the synovium or tenosynovium.

Notably, this study evaluated MRI-detected tenosynovitis and not clinically detectable tenosynovitis; the latter variable was not recorded. Since the large majority of the MRI-detected tenosynovitis lesions had a score of 1, we anticipate that the large majority of these tenosynovitis lesions were not clinically detectable.

This study has several limitations. Although it is the largest study to date of

MRI-detected tenosynovitis, it was not large enough to make comparisons for diagnoses other than RA, such as psoriatic arthritis or spondyloarthritis. A second limitation is that there was little radiographic damage progression. This could be due to the short followup period, but it is likely that treatment effects occurred as well. Larger longitudinal studies are required to validate our findings and explore the prognostic value of MRI-detected tenosynovitis in more detail. A high prevalence of tenosynovitis of the extensor carpi ulnaris tendon and the flexor tendons of digits 2 and 3 was found in our patients. The inclusion of a control group could have given more insight into the prevalence of tenosynovitis secondary to overuse.

Finally, it should be considered that the MRI scanning and the scoring method used are sensitive and that most lesions had the lowest positive MRI score of 1. To prevent false-positive scores, tenosynovitis was only considered to be present in cases in which both readers assigned a score of at least 1. Discordant scores were regarded as negative. When scores of >2 were defined as positive, the prevalence of tenosynovitis was considerably lower.

MRI is increasingly used instead of radiographs as an outcome measure in randomized clinical trials. The advantage of MRI is its sensitivity to measure inflammation and structural damage, which might increase the power to find differences between treatment groups. Tenosynovitis is increasingly assessed in trials.[18] Although the predictive value of bone marrow edema and synovitis for future radiologic joint destruction is known, the prognostic value of tenosynovitis in this respect is unknown. In a cross-sectional analysis, we did not find higher tenosynovitis scores in ACPA-positive RA patients, a group that is characterized by more severe joint destruction. In addition, we found no correlation between the severity of tenosynovitis and radiographic progression during the first year of the disease. As mentioned above, larger studies with longer followup are needed to determine the prognostic value of tenosynovitis. However, since the presence of radiographic progression during the first year is strongly associated with long-term radiologic progression, the present data suggest that MRI-detected tenosynovitis is less relevant with regard to the long-term disease outcome than are bone marrow edema and synovitis.[19] The question remains whether evaluating MRI-detected tenosynovitis is of value in clinical practice. We observed that tenosynovitis at several locations is associated with RA independently of the presence of local MRI-detectable synovitis. Further studies are needed to evaluate the value of MRI-detected local inflammation in determining the prognosis of patients with early undifferentiated arthritis.

In conclusion, when considering the tendons and tenosynovial sheaths of the hand and wrist in early arthritis, we observed that any sign of inflammation was frequently present in early arthritis and in particular in RA. Locations with a high specificity for RA are the tendons of the flexors at MCP5, the extensors at MCP2 and MCP4, and the first extensor compartment of the wrist.

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References

1 Colebatch AN et al. *Ann Rheum Dis* Published Online First: 21 March 2013.
2 Group AC of RRACTTFI et al. *Arthritis Rheum* 2013;65:2513–2523.
3 Østergaard M et al. *J Rheumatol* 2003;30:1385–6.
4 Haavardsholm EA et al. *Ann Rheum Dis* 2008;67:794–800.
5 Hetland ML et al. *Ann Rheum Dis* 2009;68:384–90.
6 Haavardsholm EA et al. *Ann Rheum Dis* 2007;66:1216–20.
7 Doyle JR. Lippincott Williams & Wilkins 2003.
8 Krabben A et al. *Ann Rheum Dis* 2013;74:506–12.
9 Eshed I et al. *Rheumatology* 2009;48:887–91.
10 Narváez J et al. *Semin Arthritis Rheum* Published Online First: 15 May 2012.
11 Navalho M et al. *Radiology* 2012;264:823–33.
12 Boutry N et al. *J Rheumatol* 2003;30:671–9.
13 de Rooy DPC et al. *Rheumatology* 2011;50:93–100.
14 Aletaha D et al. *Arthritis Rheum* 2010;62:2569–81.
15 Østergaard M et al. *Ann Rheum Dis* 2005;64 Suppl 1:i3-7.
16 Heijde DVD et al. *The Lancet* 1989;333:1036–8.
17 Wakefield RJ et al. *Arthritis Care Res* 2007;57:1158–1164.
18 Axelsen MB et al. *Ann Rheum Dis* Published Online First: 10 January 2014.
19 Lindqvist E et al. *Ann Rheum Dis* 2003;62:611–6.
20 Scheldrup EW. *Surg Gynecol Obstet* 1951;93:16–22.

The Course of Bone Marrow Edema in Early Undifferentiated Arthritis and Rheumatoid Arthritis A Longitudinal Magnetic Resonance Imaging Study at Bone Level

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3

Abstract

Objective
In patients with rheumatoid arthritis (RA), bone marrow edema (BME) scores are associated with development of erosions. However, little is known about the course and outcome of BME at bone level. We undertook this study to determine the association of BME and synovitis with the development of erosions in the same bone longitudinally.

Methods
Using 1.5T magnetic resonance imaging at baseline and at 4- and 12-month follow-up, we studied 1,947 bones of the metacarpophalangeal, wrist, and metatarsophalangeal joints in 59 patients presenting with RA or undifferentiated arthritis. Scanning and scoring of BME, synovitis, and erosions were performed according to the Outcome Measures in Rheumatology Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system. We evaluated the relationship of the course of BME and synovitis with erosive progression at bone level during 1 year.

Results
Of the bones showing BME at baseline (n = 203), BME persisted in 56%, disappeared in 39%, and disappeared and then reappeared in 5%. Stratified analyses at baseline revealed that BME was associated with erosive progression both in the presence and in the absence of local synovitis, with odds ratios (ORs) of 7.5 (95% confidence interval [95% CI] 3.8-14.9) and 6.9 (95% CI 1.9-25.6), respectively. However, local synovitis was not associated with erosive progression in the presence or in the absence of BME (ORs of 2.0 [95% CI 0.6- 7.0] and 1.9 [95% CI 0.8-4.1], respectively). In multivariable generalized estimating equation analyses, persistent BME was strongly associated with erosive progression (OR 60.5 [95% CI 16.8-218.1]) in contrast to persistent synovitis (OR 1.3 [95% CI 0.4-4.4]).

Conclusion
BME frequently persists during the first year. Persistent BME was strongly associated with erosive progression in the same bone, independently of local synovitis. No independent association was observed for persistent synovitis. These findings are relevant for comprehending the development of erosions in RA.

Introduction

Inflammation of joints is the hallmark of rheumatoid arthritis (RA). Traditionally, joint inflammation is assessed by physical examination. However, modern imaging techniques, such as Doppler ultrasound and magnetic resonance imaging (MRI), are increasingly used to evaluate joints for the presence of local synovitis. Of these, MRI is the only modality that is able to depict bone marrow edema (BME) in addition to synovitis and tenosynovitis. Several histologic studies of BME lesions have shown that these lesions contain lymphocytic infiltrates; therefore, BME in RA is also called osteitis.[1–3] The interest in BME has been further increased by several studies which clearly showed that total BME scores are associated with erosive progression.[4–8]

Although the association between BME and erosive progression in RA is evident, the course of BME lesions is largely unknown. To our knowledge, it has never been investigated thoroughly how frequently BME lesions disappear, are "waxing and waning," or are persistently present over time in patients with newly diagnosed RA. In addition, the relationship between the course of BME over time and the development of erosions at bone level has not been explored.

Furthermore, BME and synovitis are often present simultaneously, and it is unclear to what extent the presence and course of BME, synovitis, or both markers of inflammation precede the development of local erosions. Reported studies on this topic performed multivariable analyses, mostly on the patient level, and showed that BME scores,[4,5,7–13] synovitis scores,[14–16] or both[6,17–19] were associated with radiographic progression. Stratification provides insights that are useful for disentangling the effects of related risk factors on an outcome; stratification also does not involve the assumptions underlying multivariable regression analysis. To our knowledge, stratified analyses at bone level that evaluate the risk attributed to BME lesions for developing erosions, both in the absence and presence of synovitis, have not been performed thus far.

We aimed to answer 3 questions. First, what is the course of individual BME lesions over time? Second, is the course of BME associated with erosive progression in the same bone? Finally, is the association between the presence or persistence of BME and erosive progression different when local synovitis is absent or present? To address these study questions, we performed serial MRIs of hand and foot joints and performed analyses at bone level.

Patients and Methods

Patients

We studied patients included in the Leiden Early Arthritis Clinic cohort, which is an inception cohort that includes consecutive patients with arthritis confirmed by physical examination and with symptom duration of <2 years. The cohort was started in 1993 and has been extensively described elsewhere.[20] From August 2010 onward, patients voluntarily underwent MRI at baseline. According to the study protocol, MRIs were repeated at 4 and 12 months in patients with RA or undifferentiated arthritis (UA; not fulfilling the criteria for RA or for other diagnoses)

at baseline. RA in this study was defined according to the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria.[21] It was considered appropriate to include UA patients as we hypothesized that the association between the presence or persistence of BME and erosive progression was not dependent on whether patients achieved a total score of ≥6 on the 2010 classification criteria for RA at baseline.[22,23] Fifty-nine patients who underwent serial scans during the first 12 months of their disease were studied. Of these 59 patients, 26 fulfilled the 2010 classification criteria for RA at baseline and 33 were classified as having UA. Disease-modifying antirheumatic drugs (DMARDs) were started in 46 patients (78%) during the first year; these included methotrexate (n = 36), sulfasalazine (n = 2), hydroxychloroquine (n = 5), prednisolone (n = 2), and tocilizumab in a trial setting (n = 1). The median interval between inclusion and the first MRI was 0.7 weeks. Written informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

MRI

MRI of the second through fifth metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints was performed on the most painful side or, in the case of symmetric symptoms, on the dominant side. Follow-up MRIs were performed on the same side that was scanned at baseline. MRI was performed using an MSK Extreme 1.5T extremity MR imaging system (GE Healthcare). In the hand, the following sequences were acquired before contrast agent injection: T1-weighted fast spin-echo (FSE) sequence and T2-weighted FSE sequence with frequency-selective fat saturation in the coronal plane. After intravenous contrast injection, T1-weighted FSE sequences with frequency-selective fat saturation in the coronal and axial plane were obtained. The forefoot was scanned using a T1-weighted FSE sequence in the axial plane and a T2-weighted FSE sequence with frequency-selective fat saturation in the axial plane. Due to time constraints, MRI of the foot was only done before contrast agent injection. A more detailed description of the scan protocol is available upon request from the corresponding author.

MRI scoring

MRIs were scored for BME, synovitis, and erosions according to the Outcome Measures in Rheumatology Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) system.[24] Briefly, BME is scored from 0 to 3 based on the volume of edema (0%, 1-33%, 34-66%, 67-100% of edematous bone), synovitis is scored from 0 to 3 (none, mild, moderate, severe), and erosions are scored from 0 to 10 based on the proportion of eroded bone (from 0% to 91-100%).[24] One reader (WPN) who was trained and experienced in scoring according to the RAMRIS system (.1,000 MRIs for several projects) scored all MRIs for each patient. The reader was blinded to any clinical data but not to the order in which the scans were made, since scoring scans in chronological order is the most sensitive method for detecting progression.[25,26] The intrareader intraclass correlation coefficient (ICC) for total RAMRIS baseline scores was 0.93, determined from 27 baseline readings scored twice, and the intrareader ICC for scoring progression was 0.98, determined from the total progression scores of 5 series of scans that were scored twice.

Analyses were performed at bone level. A total of 1,947 bones (33 bones [10

at MTP joints, 8 at MCP joints, and 15 at wrist joints] in 59 patients) could be scored for BME and erosions at 3 time points, resulting in a maximum of 5,841 observations. A total of 708 joints could be scored for synovitis (12 joints [MTP joints 1-5, MCP joints 2-5, distal radioulnar joint, radiocarpal joint, and intercarpal plus carpometacarpal joints] in 59 patients), resulting in a maximum of 2,124 observations. Seven patients did not undergo an MRI at 4 months because of a temporary breakdown of the MRI scanner (this concerned 231 bones and 84 joints). Twenty bones could not be scored due to being located outside the field of view, and 6 bones were missing due to an amputated hallux (3 joints) in 1 patient. Additionally, 64 bones and 31 joints could not be reliably evaluated for BME and synovitis, respectively, due to inhomogeneous fat suppression. A total of 257 observations on erosions (4.4%), 321 observations on BME (5.5%), and 118 observations on synovitis (5.6%) were missing. All these missing data were regarded as missing completely at random (assuming no association between missingness and patient characteristics or outcome) and were not imputed.

MRI data were dichotomized according to predefined cutoffs. Bones with a score of ≥1 were considered positive for BME. Joints with a score of ≥1 were considered positive for synovitis. Erosive progression was defined as an increase in erosion score of ≥1 between baseline and year 1. BME and erosive progression were studied at bone level. To study local synovitis, the joint(s) surrounding the bone was assessed. For the bones of the MTP and MCP joints, this concerned simply the local joint. For the carpal bones (including the metacarpal bases), local synovitis was considered present when the score for synovitis was ≥1 in the radiocarpal or intercarpal joint. For the distal ulna and radius, local synovitis was also considered present if the distal radioulnar joint had a score of ≥1. These choices were made because the wrist joints surround several bones, and synovitis is generally not confined to the part of the joint located next to certain bones. Subsequently, the dichotomized scores for BME and synovitis for each bone at each time point were summarized in patterns. For example, a bone with BME only at baseline was labeled as 1-0-0, while a bone with BME at baseline and 1 year but not at 4 months was labeled as 1-0-1. Next, we counted the number of MRIs per bone that showed BME or synovitis and called this the “load” of BME or local synovitis. Therefore, for a bone with the pattern 1-0-0 the load is 1, while for a bone with the pattern 1-0-1 the load is 2.

Sensitivity analyses
Although we anticipated that the association between local inflammation and erosive progression was comparable in patients who at first presentation were classified as having RA or UA, analyses were repeated in the subgroup of RA patients. Furthermore, dichotomization of MRI data was also done with a cutoff of ≥2.

Statistical analysis
Pearson’s chi-square test (or Fisher’s exact test when appropriate) was used for analyses of baseline MRI data. Spearman’s rank correlation was used for (partial) correlation analyses. Associations of BME and synovitis (both at baseline and course over time) with erosive progression were analyzed using logistic regression with generalized estimating equations (GEEs), which allowed adjusting

for correlations of bones and joints within patients. The exchangeable correlation structure was used. P values less than 0.05 were considered significant. Odds ratios (ORs) are presented with 95% confidence intervals (95% CIs). SPSS software version 20.0 (IBM) was used.

Results

Baseline characteristics

Baseline characteristics of the 59 patients are presented in Table 1. At disease presentation, BME was present in 239 bones (12%), and synovitis was observed in surrounding joints at 825 bones (43%).

Table 1 Baseline characteristics of the patients with early UA and RA*

Variable	All (N=59)	RA (N=26)	UA (N=33)
Age, mean (sd) years	57.2 (14)	58.5 (10)	56.1 (16)
Women, no (%)	31 (53)	14 (54)	17 (52)
Symptom duration, weeks†	16.7 (9-26)	20.9 (13-34)	12.5 (7-25)
Time to MRI, weeks‡	0.7 (0.1-1.7)	0.8 (0-2.1)	0.7 (0.1-1.4)
TJC (68 joints)	4 (2-8)	6 (4-9)	3 (2-4)
SJC (66 joints)	3 (2-6)	5 (2-7)	3 (1-4)
CRP (mg/L)	4 (3-13)	5 (3-18)	4 (3-11)
ACPA positive, no (%)	22 (37)	18 (69)	4 (12)
Fulfilled 2010 RA classification criteria, no. (%)	26 (44)	26 (100)	0 (0)
Total RAMRIS score	12 (7-22)	12 (8-25)	11 (6-21)
Total BME score	3 (1-6)	5 (2-8)	2 (1-5)
Total synovitis score	5 (1-8)	4 (1-7)	6 (2-9)
Total erosion score	4 (2-7)	5 (2-7)	3 (2-7)
Change in total RAMRIS score, baseline-12-month follow-up	-2 (-9-1)	0 (-9.3-5)	-3 (-8.5-1)
Change in BME score, baseline-12-month follow-up	0 (-2-1)	0 (-2.3-3)	0 (-1.5-1)
Change in synovitis score, baseline-12-month follow-up	0 (-3-1)	0 (-3-2.3)	-1 (-3-0)
Change in erosion score, baseline-12-month follow-up	0 (0-1)	1 (0-2.3)	0 (0-1)

* Except where indicated otherwise, values are the median (interquartile range).
UA=undifferentiated arthritis; RA=rheumatoid arthritis; TJC=tender joint count; SJC=swollen joint count; CRP=C-reactive protein; ACPA=anti–citrullinated protein antibody; RAMRIS=Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system; BME=bone marrow edema. † Time between onset of symptoms and inclusion in cohort. ‡ Time between inclusion in cohort and undergoing first magnetic resonance imaging (MRI).

Association of BME and synovitis at baseline with erosive progression
Erosive progression during the first year was present in 56 bones (3%) (locations of erosions are available upon request from the corresponding author); these 56 bones belonged to 29 patients, of whom 10 (34%) were positive for anti-citrullinated protein antibodies (ACPAs). First, we studied the association of baseline BME and synovitis with erosive progression (Table 2). Of 237 bones that scored positive for BME at baseline, 30 (13%) showed erosive progression. Bones with BME showed more frequent erosive progression than bones without BME (OR 9.7 [95% CI 5.6-16.8], P<0.001) (Table 2). Of all of the bones that were surrounded by synovitis, 41 (5%) showed erosive progression; bones with local synovitis had erosive progression more often than did bones without baseline synovitis (OR 3.8 [95% CI 2.1-7.0], P<0.001) (Table 2).

Baseline BME and local synovitis often occurred together; 197 bones with BME also had surrounding synovitis (82% of all bones with BME). Next, we performed stratified analyses to further explore the effects of BME and local synovitis. In the

Table 2 ORs for development of erosive progression at bone level during the first year, in the presence or absence of local synovitis or BME at baseline*

	Erosive progression			
	Yes	No	OR (95%CI)	p†
All data				
BME present	30	207	9.7 (5.6-16.8)	<0.001
BME absent	25	1667		
Synovitis present	41	783	3.8 (2.1-7.0)	<0.001
Synovitis absent	15	1098		
Stratification for synovitis				
Synovitis present				
BME present	27	169	7.5 (3.8-14.9)	<0.001
BME absent	13	612		
Synovitis absent				
BME present	3	38	6.9 (1.9-25.6)	0.016
BME absent	12	1054		
Stratification for BME				
BME present				
Synovitis present	27	169	2.0 (0.6-7.0)	0.26
Synovitis absent	3	38		
BME absent				
Synovitis present	13	612	1.9 (0.8-4.1)	0.12
Synovitis absent	12	1054		

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed. Of all 1,947 bones, 18 had missing bone marrow edema (BME) or erosion scores, 10 had missing synovitis or erosion scores, and 19 had missing BME, synovitis, or erosion scores. OR°odds ratio; 95% CI595% confidence interval. † Uncorrected for within-patient correlations.

absence of synovitis, presence of BME at baseline was associated with erosive progression (OR 6.9 [95% CI 1.9-25.6], P=0.016). Similarly, in the presence of synovitis, local BME was associated with erosive progression in the same bone (OR 7.5 [95% CI 3.8-14.9], P<0.001). Subsequently, the association between local synovitis and erosive progression was evaluated, showing that both in the presence and absence of BME, synovitis was not significantly associated with local erosive progression (OR 2.0 [95% CI 0.6-7.0], P=0.26 and OR 1.9 [95% CI 0.8-4.1], P=0.12, respectively) (Table 2).

Stratified analyses provided insights into the relationships between both risk factors and erosive progression. Because the stratified analyses did not take into consideration that multiple bones and joints could be involved in 1 patient, resulting in these observations not being completely independent, we subsequently performed a GEE analysis. When we analyzed the association of BME with erosive progression, a significant association was observed (OR 10.1 [95% CI 4.0-25.6], P<0.001). Univariable analysis of synovitis also showed a significant association (OR 5.2 [95% CI 2.0-13.2], P<0.001). When baseline BME and synovitis were analyzed together in 1 analysis, BME was strongly associated with erosive progression (OR 6.8 [95% CI 2.9-15.9], P<0.001), in contrast to a weaker association for synovitis (OR 2.5 [95% CI 1.2-5.3], P=0.02). To assess whether the presence of both synovitis and BME made an additive or multiplicative contribution to the development of erosive progression, an interaction term between BME and synovitis was also added in a separate model. This interaction term showed no significant effect (OR 0.5 [95% CI 0.1-2.4], P=0.54).

Course of BME and synovitis over time.
Next, we studied the course of BME assessed at baseline and at 4- and 12-month follow-up; this resulted in several patterns (Table 3). The large majority of bones (81%) had no BME at any point in time (pattern 0-0-0). The second most frequent pattern was 1-1-1, indicating that BME at baseline was also present at months 4 and 12. When BME was present at baseline, it remained present in 56% of bones (pattern 1-1-1), disappeared during follow-up in 39% of bones (patterns 1-1-0 and 1-0-0), and disappeared and reappeared in 5% of bones (pattern 1-0-1) (Table 3).

The course of MRI-detected synovitis was studied similarly. Synovitis was most often persistent when it was present at baseline (pattern 1-1-1, 75%). Disappearing patterns were present as well (pattern 1-0-0, 8%; pattern 1-1-0, 15%), and disappearing and reappearing patterns were infrequent (pattern 1-0-1, 3%) (Table 3).

Course of BME and synovitis and erosive progression.
Subsequently, we studied erosive progression in relation to the course of BME and synovitis. The 8 different patterns were summarized in 4 groups of loads reflecting the number of MRI scans for which a bone or joint was positive for BME or synovitis, respectively (for instance, the patterns 1-1-0, 1-0-1, and 0-1-1 were grouped as a load of 2, indicating that an MRI was positive 2 times for BME or synovitis). Erosive progression was infrequent when BME was absent in all 3 scans (0.2%) (Table 4). When BME was present at 2 or 3 time points, erosive progression was present in 19.2% and 15.2% of bones (Table 4). Similarly, erosive progression

Table 3 Patterns of BME in bones and local synovitis surrounding bones when magnetic resonance images were evaluated at baseline and after 4 and 12 months of follow-up*

Pattern†	No. of bones (% of total bones) ‡	Percent of total bones with baseline BME or baseline synovitis§	No. of bones with erosive progression (% per pattern)
BME			
0-0-0	1332 (80.9)	NA	3 (0.2)
0-0-1	58 (3.5)	NA	6 (10.3)
0-1-0	26 (1.6)	NA	3 (11.5)
0-1-1	28 (1.7)	NA	9 (32.1)
1-0-0	40 (2.4)	19.7	1 (2.5)
1-0-1	11 (0.7)	5.4	1 (9.1)
1-1-0	39 (2.4)	19.2	5 (12.8)
1-1-1	113 (6.9)	55.7	17 (15.2)
Synovitis			
0-0-0	839 (50.3)	NA	4 (0.5)
0-0-1	14 (0.8)	NA	0 (0)
0-1-0	14 (0.8)	NA	0 (0)
0-1-1	77 (4.6)	NA	10 (13)
1-0-0	57 (3.4)	7.9	1 (1.8)
1-0-1	19 (1.1)	2.6	2 (10.5)
1-1-0	105 (6.3)	14.5	2 (1.9)
1-1-1	543 (32.6)	75.0	27 (5)

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed. NA=not applicable.
† Pattern 1-0-0 indicates that this feature was present at baseline but not at 4 and 12 months (see Patients and Methods).
‡ The total number of bones sampled for bone marrow edema (BME) patterns was 1,647. The total number of bones sampled for synovitis patterns was 1,668.
§ The percent of total bones with baseline BME is shown only for BME patterns. The percent of total bones with baseline synovitis is shown only for synovitis patterns.

was most frequently present when synovitis was present at 2 or 3 time points (in 7% and 5% of bones, respectively) (Table 4).

Stratifying for all courses of BME and all courses of synovitis was not possible because it resulted in 64 (8x8) strata when evaluating patterns or 16 (4x4) different strata when evaluating loads, and these subgroups were too small. Some stratified analyses (for the load of synovitis within the bones with persistent BME) are available upon request from the corresponding author. To further increase our comprehension of the relationship of the courses of both BME and synovitis with erosive progression, we used partial correlation. The number of scans positive for BME (the load) was correlated with erosive progression (r_s=0.325, P<0.001). The load of synovitis was also correlated with erosive progression (r_s=0.133, P<0.001). In addition, the load of BME was associated with erosive progression

Table 4 Loads of BME in bones and local synovitis surrounding bones when magnetic resonance images were evaluated at baseline and after 4 and 12 months of follow-up*

Load†	Pattern‡	No. of bones (% of total bones) §	No. of bones with erosive progression (% per load or pattern)
BME			
0	0-0-0	1332 (80.9%)	3 (0.2%)
1	0-0-1, 0-1-0, 1-0-0	124 (7.5%)	10 (8.1%)
2	0-1-1, 1-0-1, 1-1-0	78 (4.7%)	15 (19.2%)
3	1-1-1	113 (6.9%)	17 (15.2%)
Synovitis			
0	0-0-0	839 (50.3%)	4 (0.5%)
1	0-0-1, 0-1-0, 1-0-0	85 (5.1%)	1 (1.2%)
2	0-1-1, 1-0-1, 1-1-0	201 (12.1%)	14 (7%)
3	1-1-1	543 (32.6%)	27 (5%)

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed.
† Number of scans positive for bone marrow edema (BME)/synovitis.
‡ Pattern 1-0-0 indicates that this feature was present at baseline but not at 4 and 12 months (see Patients and Methods).
§ The total number of bones sampled for BME loads and patterns was 1,647. The total number of bones sampled for synovitis loads and patterns was 1,668.

Table 5 ORs for the development of erosive progression in relation to load of BME and local synovitis during the first year of disease, corrected for within-patient correlations of features on magnetic resonance imaging*

		Univariable analysis		Multivariable analysis¶	
Load†	No. of bones (% of total bones) ‡	OR (95% CI)	P§	OR (95% CI)	P§
BME					
0	1332 (80.9%)	Reference		Reference	
1	124 (7.5%)	23.0 (8.6-62.0)	<0.001	19.3 (6.0-62.0)	<0.001
2	78 (4.7%)	66.4 (17.1-257.3)	<0.001	55.4 (13.0-235.5)	<0.001
3	113 (6.9%)	68.4 (20.9-223.9)	<0.001	60.5 (16.8-218.1)	<0.001
Synovitis					
0	839 (50.3%)	Reference		Reference	
1	85 (5.1%)	2.4 (0.2-24.4)	0.47	1.0 (0.1-9.8)	0.99
2	201 (12.1%)	10.7 (2.7-41.8)	<0.001	2.8 (0.8-9.5)	0.091
3	543 (32.6%)	11.0 (4.1-29.3)	<0.001	1.3 (0.4-4.4)	0.64

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed. OR=odds ratio; 95% CI=95% confidence interval.
† Number of scans positive for bone marrow edema (BME)/synovitis.
‡ The total number of bones sampled for BME loads was 1,647. The total number of bones sampled for synovitis loads was 1,668.
§ Corrected for within-patient correlations by generalized estimating equation analysis.

when adjusting for the load of synovitis using partial correlation (r_s 5 0.299, P<0.001). However, when the association between the load of synovitis and erosive progression was adjusted for the load of BME, significance was lost (r_s 5 20.004, P=0.89). This suggests that when controlling for the load of BME (i.e., with the variance explained by the load of BME), there is no significant correlation between the load of synovitis and erosive progression.

These partial correlation analyses did not adjust for within-patient correlations. GEE analyses were performed to account for this, showing statistical significance for the load of BME but not for the load of synovitis (Table 5). The OR for local erosive progression in case of persistent BME was 60.5 (95% CI 16.8- 218.1); in contrast, in case of persistent synovitis the OR was 1.3 (95% CI 0.4-4.4) (Table 5).

Findings of sensitivity analyses
Similar results were found when the latter GEE analyses were repeated in the subgroup of patients fulfilling the criteria for RA (further information is available upon request from the corresponding author). Similar results were obtained when we repeated the GEE analyses within the subgroup of patients treated with DMARDs (data not shown). Thus far, BME was considered present when a bone had a BME score of ≥1. We also explored using a score of ≥2 as a cutoff; we did the same for synovitis. However, the subgroups of patients with positive scores became small (further information is available upon request from the corresponding author), hampering further subanalyses.

Discussion

It was already known that the total burden of BME in patients with RA at the time of diagnosis (total BME score per patient) is associated with erosive progression.[4–6,8,11,12,19] The course of BME and synovitis at bone level and its association with erosive progression at the same location in patients with newly diagnosed RA has not been thoroughly studied thus far. We observed that when BME was present at disease presentation, it most often persisted during the first year and seldom disappeared followed by reappearing. Furthermore, we observed that persisting BME was strongly associated with erosive progression; this effect was independent of the effect of persistent synovitis. In contrast, persistent synovitis was not evidently associated with erosive progression independent of the presence of persistent BME.

The findings of this longitudinal study at bone level extend our comprehension of BME in RA. Since BME and synovitis frequently occurred together, stratified analyses were helpful for gaining insight into the relationship of BME and synovitis with erosive progression without the influence of assumptions such as the linearity assumption, which generally underlies multivariable regression analyses. Stratification showed that in the presence of baseline BME, baseline synovitis was not associated with erosive progression. Because stratification does not take into account the correlation between bones within a patient, GEE analyses were also performed. Overall, the results of stratified analyses, partial correlation analyses, and GEE analyses were fairly similar.

The present findings do *not* indicate that synovitis is not important for the development of erosions. The previously proposed inside-out or outside-in hypotheses for the development of erosions are not substantiated by our data.[27] Our measurements started at disease presentation and ended after 1 year of follow-up. It is possible that disease processes causing erosions (for instance, synovitis) are already active or transient in preclinical disease phases.[28,29] Since these phases were not studied, other studies are needed to further explore the role of local synovitis and BME in very early phases of disease in relation to erosion development.

The results of this study may have some implications for future clinical trials in which erosive progression is the outcome. Trials with treatments that aim to prevent erosive progression may benefit from the selection of patients with BME.

This study has several limitations. First, MRIs were scored in chronological order because this method has been proven to be sensitive.[25,26] A drawback of this choice is that this may have influenced the results to some extent; with this method, some detected erosions might have remained undetected if the scans had been scored in a blinded manner with regard to time sequence. Importantly, at the time of scoring, there was no a priori hypothesis as to whether BME or synovitis was associated differently with erosive progression. Second, we assessed the course of BME over time with 3 MRI scans during 1 year. However, BME and synovitis could disappear and/or appear in the time intervals between the scans. Had this been the case, BME or synovitis in RA would be less “persistent” or “absent” than suggested by the current data. We cannot exclude the possibility that serial scans with shorter intervals between the scans would show different results, but it was not feasible to perform scans more regularly.

Third, the number of patients included in this study was relatively small. Therefore, our study was insufficiently powered to perform subanalyses in ACPA-positive and ACPA-negative disease separately. We also had insufficient power to perform subanalyses with a higher cutoff of ≥2 for BME and synovitis, as these larger lesions were infrequent. We assume that similar results would have been obtained if only larger lesions were analyzed, but our data did not permit us to conclude this. A fourth limitation is that our MRI protocol did not contain sequences of the foot after the administration of contrast, which may have led to an underestimation of synovitis in the foot. In addition, higher resolution MRI sequences (e.g., 3-dimensional gradient-echo sequences) could have provided higher sensitivity for erosive progression.

Because “the wrist” contains 15 bones and 3 joints, choices were made to define local synovitis. We have repeated the analyses when it was defined as synovitis located in the synovium adjacent to the carpal bone only. This yielded comparable results (data not shown).

Treatment was not included in our analyses because we studied the association between MRI-detected inflammation and erosive progression. We hypothesized that treatment affects the level of inflammation but not the relationship between inflammation and destruction.[30] In other words, we assumed that treatments applied (conventional DMARDs) had no direct effect on erosive progression.

The relationship between location of inflammation and erosive progression was not evaluated. Although there are preferential locations for erosive progression (e.g., MTP joint 5 and MCP joint 2), this preference applies to both inflammation and erosive progression.[31] Therefore, we assumed that the association between inflammation and erosive progression was independent of location.

In conclusion, when BME was present at disease presentation, it frequently persisted at subsequent measurements during the first year. Persistent BME was strongly associated with erosive progression, both in the presence and absence of local synovitis. For persistent synovitis, no association with erosive progression independent of BME was observed. These findings increase our knowledge of the relevance of BME for erosive progression.

References

1 Jimenez-Boj E et al. *Arthritis Rheum* 2007;56:1118–24.
2 Dalbeth N et al. *Ann Rheum Dis* 2009;68:279–82.
3 McQueen FM et al. *Ann Rheum Dis* 2007;66:1581–7.
4 McQueen FM et al. *Arthritis Rheum* 2003;48:1814–27.
5 Haavardsholm EA et al. *Ann Rheum Dis* 2008;67:794–800.
6 Palosaari K et al. *Rheumatology* 2006;45:1542–8.
7 Hetland ML et al. *Ann Rheum Dis* 2009;68:384–90.
8 Mundwiler ML et al. *Arthritis Res Ther* 2009;11:R94.
9 Bøyesen P et al. *Ann Rheum Dis* 2011;70:176–9.
10 Døhn UM et al. *Ann Rheum Dis* 2011;70:252–8.
11 Gandjbakhch F et al. *Ann Rheum Dis* 2011;70:2159–62.
12 Lisbona MP et al. *J Rheumatol* Published Online First: 1 July 2014.
13 Hetland ML et al. *Ann Rheum Dis* 2010;69:1789–95.
14 Gandjbakhch F et al. *J Rheumatol* Published Online First: 15 December 2013.
15 Conaghan PG et al. *Ann Rheum Dis* 2014;73:810–6.
16 Conaghan PG et al. *Arthritis Rheum* 2003;48:64–71.
17 Bøyesen P et al. *Ann Rheum Dis* 2011;70:428–33.
18 Baker JF et al. *Ann Rheum Dis* Published Online First: 31 July 2013.
19 McQueen FM et al. *Ann Rheum Dis* 1999;58:156–63.
20 de Rooy DPC et al. *Rheumatology* 2011;50:93–100.
21 Aletaha D et al. *Arthritis Rheum* 2010;62:2569–81.
22 Krabben A et al. *Ann Rheum Dis* 2012;71:238–41.
23 Krabben A et al. *Rheumatology* 2013;52:1265–70.
24 Østergaard M et al. *J Rheumatol* 2003;30:1385–6.
25 Heijde D van der et al. *Rheumatology* 1999;38:1213–20.
26 Tuyl LHD van et al. *Ann Rheum Dis* 2014;73:391–5.
27 Schett G et al. *Ann Rheum Dis* 2010;69:787–9.
28 van Steenbergen H w. et al. *Arthritis Rheum* Published Online First: 2013.
29 Nielen MMJ et al. *Arthritis Rheum* 2004;50:2423–7.
30 Cutolo M et al. *Ann Rheum Dis* 2001;60:729–35.
31 Tan AL et al. *Arthritis Rheum* 2003;48:1214–1222.

Does adding the presence of MRI detected bone marrow oedema improve the accuracy of the 2010 EULAR/ACR criteria for rheumatoid arthritis?

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4

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With great interest we read the letter of Tamai et al who studied whether adding information obtained by MRI of wrist and metacarpophalangeal (MCP) joints to the existing 2010 European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis (RA) was helpful in improving the accuracy of these criteria. The study population was patients with undifferentiated arthritis according to the 1987 classification criteria. Two outcomes were studied: fulfilling the 1987 classification criteria for RA after 1-year of disease and the start of disease-modifying antirheumatic drugs (DMARDs) within the first year.[1] The results on MRI detected bone marrow oedema (BME) added to the 2010 criteria with the start of DMARDs as outcome were most interesting. The sensitivity and specificity of the 2010 criteria without addition of BME were 61.9% and 82.6% respectively and the accuracy 70.5%. After adding information on BME, an increase in sensitivity and accuracy was observed (76.3% and 75.9%, respectively); this was accompanied by a decline in specificity (75.4%). Area under receiver operator characteristic curves (AUCs) were not reported.[1]

It is known that the 2010 criteria for RA are fulfilled earlier in time than the 1987 classification criteria and that the 2010 criteria have a higher sensitivity and lower specificity than the 1987 criteria.[2–4] In order to seek for replication of the above mentioned findings, and thus to evaluate whether the addition of MRI findings (BME and erosions) to the 2010 criteria results in an increase in diagnostic accuracy, we performed the analyses as done by Tamai et al.

Similar to Tamai and colleagues, we studied patients with undifferentiated arthritis according to the 1987 criteria (n=205). Patients were included in the Leiden Early Arthritis Clinic between August 2010 and August 2013; all patients had 1-year follow-up.[5] The mean age was 55 (SD 15) years, 61% were women, the median number of swollen joints (66 swollen joint count) was 3 (IQR 1–5), the median symptom duration was 10.7 (IQR 5.1–24.5) weeks and 22% were anti-citrullinated protein antibody (ACPA) positive. Unilateral MRIs of the MCP and wrist joints were made at inclusion using a 1.5T extremity MRI (General Electric Healthcare). Scanning and scoring were done according to Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS); all scans were evaluated by an experienced reader (WN, within reader intraclass correlation coefficient total RAMRIS 0.93).

We used the same two outcomes. In our data, 47 (23%) of the 1987 undifferentiated arthritis (UA) patients fulfilled the 1987 criteria after 1 year and DMARDs were prescribed in 96 patients (47%). The test characteristics when analysing both outcomes are presented in table 1. When fulfilling the 1987 criteria after 1 year was used as outcome, the sensitivity of the 2010 criteria was 53% and the specificity 84%. When adding information on BME (a total score of ≥1), the sensitivity increased to 83% and the specificity decreased to 36%. Similar results, an increased sensitivity and decreased specificity, were observed when the start of DMARDs was used as outcome (table 1). The accuracy and AUC remained unchanged when DMARDs start was assessed as outcome (from 65% to 63%, p=0.67 and from

0.64 to 0.64, p=0.93, respectively) and decreased when fulfilling the 1987 criteria was studied as outcome (from 77% to 47%, p<0.001 and from 0.68 to 0.60,

p=0.024, respectively). When information on MRI detected erosions was added, a similar tendency in the data was observed (table 1). Furthermore, we wondered whether findings would change in case only higher BME or erosion scores were studied. Hence analyses were repeated using scores ≥2 as a cut-off for positive MRI findings; this also resulted in similar findings (table 1). It remains elusive to what extent our MRI data and the MRI data of Tamai et al are comparable. Tamai et al did not provide a definition of presence of BME and erosions; we used two different cut-offs based on RAMRIS. Differences in reading or differences in MRI technique may yield discrepancies and hamper extrapolation of findings.

In conclusion, in line with the findings of Tamai et al, we did observe an increase in sensitivity when adding information on MRI detected BME or MRI detected erosions to the 2010 criteria. However, this was at the cost of a considerable decrease in specificity. The accuracy and discriminative ability (expressed using AUCs) decreased or remained unchanged. Based on these results, we conclude that the addition of MRI detected features to the 2010 classification criteria for RA does not evidently improve the accuracy of these criteria when applied in patients with undifferentiated arthritis according to the 1987 criteria.

Table 1 Test characteristics of the 2010 EULAR/ACR criteria alone and after addition of information on MRI detected BME or MRI detected erosions for two outcomes (fulfilling the 1987classifcaiton criteria after 1 year or the prescription of DMARDs during the first year) in patients with undifferentiated arthritis according to the 1987 classification criteria for RA

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
A score of at least 1 was used as cut off				
DMARD-start				
2010-RA	40 (33-46)	88 (84-93)	75 (69-80)	62 (56-69)
+BME	83 (78-88)	45 (38-52)	57 (50-64)	75 (69-81)
+ERO	88 (83-92)	30 (24-37)	53 (46-59)	73 (67-79)
1987-criteria positivity				
2010-RA	53 (46-60)	84 (78-89)	49 (42-56)	86 (81-91)
+BME	83 (78-88)	36 (30-43)	28 (22-34)	88 (83-92)
+ERO	87 (83-92)	25 (19-31)	26 (20-32)	87 (82-91)
A score of at least 2 was used as cut off				
DMARD-start				
2010-RA	40 (33-46)	88 (84-93)	75 (69-80)	62 (56-69)
+BME	73 (67-79)	58 (51-65)	60 (54-67)	71 (65-77)
+ERO	73 (67-79)	49 (42-55)	56 (49-62)	67 (61-74)
1987-criteria positivity				
2010-RA	53 (46-60)	84 (78-89)	49 (42-56)	86 (81-91)
+BME	74 (68-80)	49 (42-56)	30 (24-36)	87 (82-91)
+ERO	77 (71-82)	43 (36-50)	29 (22-35)	86 (81-91)

Test characteristics are shown with a 95% CI. AUC, area under receiver operating characteristics curve; BME, bone marrow oedema; DMARD, disease-modifying antirheumatic drug; ERO, MRI detected erosion;LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; RA, rheumatoid arthritis

LR+	LR-	Accuracy (%)	AUC
3.32 (1.88-5.85)	0.69 (0.58-0.82)	65 (59-72)	0.64 (0.56-0.72)
1.51 (1.25-1.83)	0.37 (0.23-0.61)	63 (56-70)	0.64 (0.57-0.72)
1.25 (1.09-1.45)	0.41 (0.23-0.75)	57 (50-64)	0.59 (0.51-0.67)
3.23 (2.08-5.03)	0.56 (0.41-0.77)	77 (71-82)	0.68 (0.59-0.78)
1.3 (1.09-1.55)	0.47 (0.24-0.92)	47 (40-54)	0.60 (0.51-0.68)
1.16 (1.01-1.33)	0.52 (0.23-1.15)	39 (32-46)	0.56 (0.47-0.65)
3.32 (1.88-5.85)	0.69 (0.58-0.82)	65 (59-72)	0.64 (0.56-0.72)
1.73 (1.34-2.22)	0.47 (0.33-0.68)	65 (58-71)	0.65 (0.58-0.73)
1.42 (1.14-1.77)	0.56 (0.38-0.82)	60 (53-67)	0.61 (0.53-0.68)
3.23 (2.08-5.03)	0.56 (0.41-0.77)	77 (71-82)	0.68 (0.59-0.78)
1.45 (1.16-1.82)	0.52 (0.31-0.88)	55 (48-61)	0.62 (0.53-0.7)
1.34 (1.09-1.66)	0.54 (0.31-0.94)	51 (44-58)	0.60 (0.51-0.69)

REFERENCES

1 Tamai M et al. *Ann Rheum Dis* 2014;73:2219–20.
2 van der Linden MPM et al. *Arthritis Rheum* 2011;63:37–42.
3 Cader MZ et al. *Ann Rheum Dis* 2011;70:949–55.
4 Radner H et al. *Ann Rheum Dis* 2014;73:114–23.
5 de Rooy DPC et al. *Rheumatology* 2011;50:93–100.

Evaluation of the diagnostic accuracy of hand and foot MRI for early Rheumatoid Arthritis

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Abstract

Objectives
To assess the diagnostic value of MRI for early RA. In some RA patients, a classifiable diagnosis cannot be made at first presentation; these patients present with unclassified arthritis (UA). The use of MRI for early diagnosis of RA is recommended, yet the evidence for its reliability is limited.

Methods
MRI of hand and foot was performed in 589 early arthritis patients included in the Leiden Early Arthritis Clinic (229 presented with RA, 159 with other arthritides and 201 with UA). Symptom-free controls provided a reference for defining an abnormal MRI. In preliminary investigations, MRI of patients who presented with RA was compared with MRI of symptom-free controls and of patients with other arthritides. Thereafter, the value of MRI in early RA diagnosis was determined in UA patients using the 1-year follow-up on fulfilling the 1987 RA criteria and start of disease-modifying drugs as outcomes.

Results
Preliminary investigations were promising. Of the UA patients, 14% developed RA and 37% started disease-modifying treatment. MRI-detected tenosynovitis was associated with RA development independent of other types of MRI-detected inflammation [odds ratio (OR) = 7.5, 95% CI: 2.4, 23] and also independent of age and other inflammatory measures (swollen joints, CRP) (OR = 4.2, 95% CI: 1.4, 12.9). Within UA patients, the negative predictive value of abnormal tenosynovitis was 95% (95% CI: 89%, 98%) and the positive predictive value 25% (95% CI: 17%, 35%). The performance was best in the subgroup of UA patients presenting with oligoarthritis (18% developed RA): the positive predictive value was 36% (95% CI: 23%, 52%), the negative predictive value was 98% (95% CI: 88%, 100%), the sensitivity was 93% (95% CI: 70%, 99%) and the specificity was 63% (95% CI: 51%, 74%).

Conclusion
MRI contributes to the identification of UA patients who will develop RA, mostly in UA patients presenting with oligoarthritis.

Introduction

Patients with RA should receive disease-modifying treat-ment (DMARDs) as soon as possible because this increases the chance of a better disease outcome.[1,2] In some RA patients, the classic phenotype has not yet completely developed at the first presentation, hampering prompt diagnosis of RA. To improve early identification, the 2010 ACR/EULAR classification criteria for RA have been developed.[3] These novel criteria do indeed identify RA patients earlier in time than the 1987 ACR classification criteria.[4] However, timely diagnosis is still impossible in some patients: up to 25% of patients presenting with recent-onset arthritis who cannot be classified by the 2010 criteria and have unclassified arthritis (UA) develop RA later on (typically within 1 year).[5] RA patients who initially present with UA have a disease course equally severe to that of RA patients who already fulfil the criteria at first presentation.[6] Thus, although prompt diagnosis is required, for some RA patients, accurate methods for this are lacking. These patients are mainly ACPA-negative[5]. It has been suggested that novel imaging modalities may be valuable in the early diagnosis of RA.[7]

MRI sensitively depicts inflammation; it visualizes synovitis, tenosynovitis and bone marrow oedema (BME). BME (also called osteitis in RA) is not depicted by other imaging modalities.[8–10] Hand and foot MRI is increasingly used as a measure of outcome in clinical trials.[11] Because MRI detects subclinical inflammation (not evident at physical examination) in patients presenting with early arthritis, and MRI-detected inflammation is associated with erosive progression,[12] it is thought that MRI may have a role in the diagnostic process of RA. The use of MRI for the early diagnosis of RA is recommended by a taskforce of the EULAR, but it was acknowledged that the evidence supporting this recommendation is low.[7] Previous studies on this subject included relatively low numbers of patients (n < 50),[13–21] used low-field-strength MRI scanners,[14,18,22,23] or studied selected groups of patients,[13–25] which hampered extrapolation of results to rheumatologic practice. Finally, the definition of an abnormal MRI varied between different studies;[13–25] no study considered using the findings for a symptom-free control population for defining a cut-off point to distinguish a normal MRI from an abnormal MRI.

We set out to determine the accuracy of hand and foot MRI in identifying those UA patients who are in an early stage of RA. As preparatory work, we made MRI scans of hands and feet of 193 symptom-free persons from the general population and observed that MRI-detected inflammation was quite prevalent, especially at higher age and at preferred locations.[26] We hypothesized that including these findings in the definition of a positive MRI would reduce false-positive findings. Using a high-field-strength MRI scanner on an unselected early arthritis population visiting a rheumatologic outpatient clinic, this study aimed to (i) explore the discriminative value of MRI by comparing the MRI of patients with classifiable RA at presentation with MRI of symptom-free controls and patients with other arthritides and (ii) determine the value of MRI for the identification of those UA patients who are in an early phase of RA. UA patients were followed for RA development over 1 year. Because the differential diagnosis is slightly different for UA patients presenting with mono-, oligo- or polyarthritis, the diagnostic value of MRI was also explored in these subgroups of UA patients.

Methods

Setting and patients

The Leiden Early Arthritis Clinic is a longitudinal inception cohort including patients with clinically confirmed arthritis and symptom duration of <2 years who presented to the Leiden rheumatologic outpatient clinic. This is the only referral centre in a health care region of ~400 000 inhabitants. The cohort was initiated in 1993.[27] MRI was added to the study protocol in 2010. At first visit, questionnaires were completed by patients and rheumatologists, joint counts were performed, serum samples obtained and an MRI made. From August 2010 to October 2014, 598 consecutively included patients underwent MRI. Gadolinium chelate contrast was not administered in nine patients; those nine patients were excluded from this study. Two weeks after first presentation, when routine laboratory and radiographic results were known (but not MRI results), patients received their diagnosis; classification of RA was done according to the 2010 criteria.[3]

The symptom-free volunteers who served as a reference were recruited via advertisements in local newspapers and websites, and had no history of inflammatory rheumatic diseases, no joint symptoms during the last month and no evidence of arthritis at physical examination. A more detailed description of them is provided in reference.[26] This study was approved by the Leiden University Medical Center medical ethics committee, and all participants signed informed consent forms.

Outcomes

The study consisted of two parts. First, preliminary investigations were performed to explore the potential discriminative value of MRI. Patients who presented with RA were compared with symptom-free controls and with patients with other arthritides. Then the value of MRI was assessed in the target population of patients presenting with UA (flowchart in Supplementary (available at Rheumatology Online) Fig. S1). These patients were followed for 1 year. The primary outcome was RA development according to the 1987 criteria.[28] Although the 2010 criteria are fulfilled earlier in time, they have a lower specificity than the 1987 criteria, making them less suitable as long-term outcome measure.[4,29] Furthermore, ACPA-negative patients can only fulfill the 2010 criteria if >10 joints become involved; hence, they (and this reflects to the ACPA-negative patients) fulfill the 1987 criteria more easily. The secondary outcome was the initiation of DMARDs during the year of follow-up (see supplementary (available at Rheumatology Online) data, section DMARD therapy, for more detail). Rheumatologists may initiate DMARDs in UA patients if they anticipate that the patient will progress to RA. Early treatment may prevent progression to fulfilment of classification criteria. Compared with the natural course, this may result in an underestimation of the number of UA patients who progress to RA (the primary outcome). The secondary outcome, therefore, reflects the expert opinion of the rheumatologist on the presence of RA and may circumvent this underestimation.

MRI and scoring

At baseline, unilateral contrast-enhanced MRIs were made of the second to fifth MCPs, wrist and first to fifth MTP joints of the most painful side, or the dominant

side in the case of equally severe symptoms on both sides. MRI was performed on an Musculoskeletal Extreme 1.5 T extremity magnetic resonance (MR) system; see supplementary (available at Rheumatology Online) data, section detailed MRI protocol, for a detailed description of the protocol. Erosions, BME, synovitis and tenosynovitis were scored as described in the supplementary (available at Rheumatology Online) data, section MRI scoring and dichotomizing,[30,31] by two trained readers (W.P.N. and E.C.N., both having scored >800 MRIs), blinded to any clinical data. Within-reader intraclass correlation coefficients for the total RA MRI scoring system (RAMRIS) inflammation scores, based on 40 MRIs scored twice, were, respectively, 0.98 and 0.93; the betweenreader intraclass correlation coefficient, based on all 598 scans, was 0.95. The total inflammation score per patient was calculated by summing all BME, synovitis and tenosynovitis scores. The mean for both readers was used for analyses on continuous scores.

The MRI findings in 193 symptom-free persons, who were scanned according to same protocol,[26] were used as a reference for dichotomizing the MRI scores: a bone/joint/tendon was considered abnormal for BME/ synovitis/tenosynovitis if, according to both readers, the score for that finding was above the 95th percentile of scores at the same location in symptom-free persons of the same age category (18-40, 40-60 or >60 years).[26]

The locations that showed inflammation in >5% of controls are presented in supplementary (available at Rheumatology Online) Table S1. Subsequently, at the patient level, an MRI was considered abnormal if one (or more) bone/joint/tendon was considered abnormal. (See the supplementary (available at Rheumatology Online) data, section MRI scoring and dichotomizing, for an example.) In sub-analyses, a bone/joint/tendon was considered abnormal if the score was higher than all scores (100th percentile) of the symptom-free persons of the same age category at the same location.[26]

Analyses

Logistic regression analysis was used to assess the predictive value of MRI in UA patients. The additional value of MRI-detected inflammation to the swollen joint count (SJC) and CRP was evaluated using multivariable logistic regression analyses. Here, an elevated CRP was defined as 510 mg/l and the SJC was categorized into clinically relevant categories, because of high-leverage outliers. Test characteristics and predictive values were determined. Analyses were repeated after stratification for the number of swollen joints. Decision curve analysis[32] was performed to explore the additive value of MRI, also weighting the harms of over- and underprediction of RA development, comparing the predicted probabilities of models with and without MRI (supplementary (available at Rheumatology Online) data, section decision curve analysis). Statistical analyses were performed in IBM SPSS ver. 20 and Stata ver. 14. $P < 0.05$ were considered significant.

Results

Study population

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

	All early arthritis patients n=589	Subgroup RA patients n=229	Subgroup UA patients n=201
Age, mean(SD)	54.8 (15.5)	55.9 (14.4)	54.1 (15.8)
Female, n(%)	363 (61.6%)	155 (67.7%)	123 (61.2%)
Symptom duration, in weeks, median (IQR)	12 (5-26)	15 (8-28)	9 (4-24)
Swollen joint count, median (IQR)	3 (2-7)	6 (2-11)	2 (1-4)
CRP (mg/L), median (IQR)	6 (3-17)	9 (3-22)	4 (3-10)
RF positive, n(%)	195 (33.1%)	151 (65.9%)	19 (9.5%)
ACPA positive, n(%)	137 (23.3%)	124 (54.1%)	8 (4%)
Diagnosis at presentation			
Rheumatoid arthritis	229		
Unclassified arthritis	201		
Psoriatic arthritis or spondyloarthritis	39		
Inflammatory osteoarthritis	35		
Reactive arthritis	25		
Crystal arthropathy	15		
RS3PE	10		
SLE+MCTD	6		
Other diagnoses	29		

SD, standard deviation; IQR, Inter quartile range; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated-peptide-antibody; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease

A total of 589 early arthritis patients were studied: 229 had RA at presentation, 201 UA and 159 other arthritides. Baseline characteristics are shown in Table 1. The continuous RAMRIS scores in RA patients and UA patients are shown in Table 2.

Preliminary investigations

Patients presenting with RA (n = 229) were first compared with symptom-free controls (n = 193) and with early arthritis patients with other arthritides (n = 360). The continuous MRI inflammation scores were higher in RA patients than in symptom-free controls (supplementary (available at Rheumatology Online) Table S2). High continuous MRI inflammation scores were not only observed in RA, but also in some other arthritides, for example, RS3PE, SLE and MCTD (supplementary (available at Rheumatology Online) Fig. S2). The discriminative value of an abnormal MRI is shown in Table 3. Compared with synovitis and BME, tenosynovitis had the best discriminative accuracy (Table 3). In sub-analyses, a

Table 2 Continous RA MRI scores of patients who presented with RA or unclassified arthritis

	RA	UA	UA subgroups		
			Mono-arthritis	Oligo-arthritis	Poly-arthritis
Total RAMRIS score, median (IQR)	16.50 (9.00-32.00)	11.00 (4.00-19.50)	7.50 (3.00-15.50)	12.00 (5.00-20.00)	14.00 (6.50-24.00)
Inflammation Score, median (IQR)	13.50 6.50-26.00)	7.50 (2.50-15.50)	5.00 (1.50-10.50)	8.00 (3.50-15.00)	12.00 (4.50-21.00)
BME score, median (IQR)	3.75 (1.25-8.50)	2.00 (0.50-5.00)	1.50 (0.50-4.00)	2.50 (0.50-6.00)	1.50 (0.50-4.50)
Synovitis score, median (IQR)	5.00 (2.50-9.00)	3.00 (1.00-6.00)	2.00 (0.50-5.50)	3.50 (1.00-6.50)	4.00 (1.50-9.00)
Tenosynovitis score, median (IQR)	4.00 (1.50-7.50)	1.50 (0.00-5.00)	1.00 (0.00-3.00)	1.50 (0.00-4.50)	2.00 (0.50-8.00)
Erosion score, median (IQR)	3.00 (1.50-6.00)	2.50 (1.00-5.00)	2.00 (1.00-4.50)	3.00 (1.00-5.50)	2.50 (1.50-5.50)

Subgroups of UA patients are based on the number of inflamed joints at presentation: BME: bone marrow oedema; monoarthritis: 1 clinically swollen joint; oligoarthritis: 2-4 clinically swollen joints; polyarthritis:>4 clinically swollen joints; RAMRIS: RA MRI score; UA: unclassified arthritis.

Table 3 Preliminary investigations: test characteristics for an abnormal MRI to identify patients clinically presenting with RA

MRI abnormal for	Sensitivity, % (95%CI)	Specificity, % (95%CI)	AUC
RA versus symptom-free controls			
Any Inflammation	88% (83%-91%)	71% (64%-77%)	0.79
Bone marrow edema	61% (55%-67%)	78% (72%-83%)	0.70
Synovitis	66% (59%-71%)	93% (88%-96%)	0.79
Tenosynovitis	75% (69%-80%)	95% (91%-97%)	0.85
RA versus early arthritis patients with other arthritides			
Any Inflammation	88% (83%-91%)	33% (28%-38%)	0.60
Bone marrow edema	61% (55%-67%)	57% (52%-62%)	0.59
Synovitis	66% (59%-71%)	58% (52%-63%)	0.62
Tenosynovitis	75% (69%-80%)	56% (50%-61%)	0.65

Test characteristics of an abnormal MRI for discriminating patients who clinically present with RA from symptom-free controls and patients presenting with other arthritides. MRI abnormal for any inflammation indicates the presence of abnormal bone marrow oedema, synovitis or tenosynovitis. AUC: area under the receiver operating characteristic curve.

stricter definition for an abnormal MRI was used; these showed similar results (supplementary (available at Rheumatology Online) Table S3).

Accuracy of MRI in identifying those UA patients who developed RA within 1 year

The clinical characteristics of the UA patients are shown in supplementary (available at Rheumatology Online) Table S4. During the 1-year follow-up, 29 of 201 UA patients (14%) progressed to RA and 75 (37%) were prescribed DMARD therapy. Patients who progressed to RA were older and presented

with a higher SJC and higher CRP levels than patients who did not progress (supplementary (available at Rheumatology Online) Table S4). The total MRI inflammation, synovitis and tenosynovitis scores at baseline were higher in the UA patients who developed RA than in those who did not develop RA (all P < 0.001, supplementary (available at Rheumatology Online) Fig. S3); the BME scores were similar (P = 0.72). An abnormal MRI for any type of inflammation had an odds ratio (OR) for RA development of 7.2 (95% CI: 1.6, 31.2). The ORs of the individual inflammation types were 6.7 (95% CI: 2.4, 18.3) for tenosynovitis, 2.3 (95% CI: 1.0, 5.2) for synovitis and 0.9 (95% CI: 0.4, 2.1) for BME (Table 4). UA patients frequently had an abnormal MRI for several types of inflammation: 24% had tenosynovitis, synovitis and BME, 21% had two types of inflammation, 24% had only tenosynovitis, synovitis or BME and 62 patients (31%) had a normal MRI (supplementary (available at Rheumatology Online) Fig. S4). Multivariable logistic regression showed that tenosynovitis was associated with RA development, independent of synovitis and BME (OR = 7.5, 95% CI: 2.4, 23.1; Table 4). Also after adjusting for age, SJC and CRP, an abnormal MRI for tenosynovitis was associated with RA development (OR = 4.2, 95% CI: 1.4, 12.9; Table 4). Similar results were observed with the start of DMARD therapy as outcome (Table 4; supplementary (available at Rheumatology Online) Fig. S3) and when using a stricter definition for an abnormal MRI (supplementary (available at Rheumatology Online) Table S5). In addition to MRI inflammation, MRI-detected erosions were evaluated. These were not associated with RA development in univariable or multivariable analyses (supplementary (available at Rheumatology Online) Table S6).

Within UA patients, an abnormal MRI for tenosynovitis had better test characteristics for RA development than BME and synovitis [area under the receiver operating characteristic curve (AUC) of 0.70, vs 0.49 and 0.60]. The positive predictive value of tenosynovitis for RA development was 25% and the negative predictive value 95% (supplementary (available at Rheumatology Online) Table S7). Since the association of an abnormal MRI for tenosynovitis with RA development was stronger than that of an abnormal MRI for synovitis or BME, further analyses were confined to tenosynovitis. Similar results for tenosynovitis were seen using DMARD initiation as the outcome (supplementary (available at Rheumatology Online) Table S7).

Accuracy of MRI in subgroups of UA patients presenting with mono-, oligo and polyarthritis

The differential diagnoses for UA patients presenting with monoarthritis (1 swollen joint), oligoarthritis (2-4 joints) and polyarthritis (>4 joints) can differ. Because the value of MRI might also differ in these patients, the value of MRI was explored in these three subgroups. RA development was rare in UA patients presenting with monoarthritis (3%); of the UA patients presenting with oligo and polyarthritis, 18% and 29%, respectively, developed RA (Table 5). The continuous RAMRIS scores of the three subgroups are shown in Table 2. In UA patients with mono- and polyarthritis, an abnormal MRI for tenosynovitis was not associated with RA development (Table 5). In UA patients with oligoarthritis, in contrast, an abnormal MRI for tenosynovitis was associated with RA development (P < 0.001), the sensitivity was 93%, specificity 63%, positive predictive value 36% and negative predictive value 98%. Similar results were found when using initiation of DMARD

Table 4 Results of logistic regression analyses for RA development and DMARD initiation in unclassified arthritis patients

	Univariable analyses		Multivariable analysis: types of MRI-inflammation		Multivariable analysis: abnormal tenosynovitis adjusted for age, SJC, and CRP	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Outcome: RA						
Constant/Intercept			0.06 (-)	<0.001	0.01 (-)	<0.001
MRI abnormal for						
any inflammation	7.2 (1.6-31.2)	0.009				
BME	0.9 (0.4-2.1)	0.87	0.5 (0.2-1.2)	0.14		
synovitis	2.3 (1.0-5.2)	0.04	1.2 (0.5-3.2)	0.68		
tenosynovitis	6.7 (2.4-18.3)	<0.001	7.5 (2.4-23.1)	<0.001	4.2 (1.4-12.9)	0.01
Age, per year	1.03 (1.00-1.06)	0.02			1.01 (0.97-1.04)	0.68
Swollen joints,						
1 joint	ref				ref	
2-4 joints	8.3 (1.8-37.5)	0.006			7.5 (1.6-34.8)	0.01
2-4 joints	15.5 (3.3-73.6)	0.001			10.4 (2.1-51.5)	0.004
Elevated CRP	3.8 (1.7-8.5)	0.001			2.2 (0.9-5.4)	0.10
Outcome: DMARD initiation						
Constant/Intercept			0.30 (-)	<0.001	0.09 (-)	<0.001
MRI abnormal for						
any inflammation	2.3 (1.2-4.6)	0.01				
BME	1.1 (0.6-2)	0.70	0.7 (0.3-1.3)	0.27		
synovitis	2.1 (1.2-3.7)	0.01	1.2 (0.6-2.4)	0.67		
tenosynovitis	4.2 (2.3-7.8)	<0.001	4.4 (2.2-9.0)	<0.001	3.0 (1.5-6.0)	0.003
Age, per year	1.03 (1.01-1.05)	0.006			1.01 (0.98-1.03)	0.55
Swollen joints,						
1 joint	ref				ref	
2-4 joints	2.5 (1.2-5.1)	0.01			2.3 (1.1-4.9)	0.03
>4 joints	6.6 (2.9-15.3)	<0.001			5.2 (2.1-12.7)	<0.001
Elevated CRP	3.0 (1.6-5.7)	0.01			2 (1.0-4.2)	0.06

MRI abnormal for any inflammation indicates the presence of abnormal bone marrow oedema, synovitis or tenosynovitis; OR: odds ratio; SJC: swollen joint count.

therapy as the outcome (supplementary (available at Rheumatology Online) Table S8). When a stricter definition of an abnormal MRI was used, the results were similar (supplementary (available at Rheumatology Online) Table S9).

Table 5 Test characteristics of an abnormal MRI for tenosynovitis for RA development in unclassified arthritis patients

		RA	no-RA	p	Sens. , % (95%CI)
All UA-patients, n (%)		29 (14)	172 (86)		
	MRI-TS +	24	72	<0.001	83%
	MRI-TS -	5	100		(65%-92%)
	CRP +	15	38	0.001	52%
	CRP -	14	134		(34%-69%)
CRP +	MRI-TS +	15	22	0.002	100
	MRI-TS -	0	16		(80%-100%)
CRP -	MRI-TS +	9	50	0.05	64%
	MRI-TS -	5	84		(39%-84%)
Subgroup: Monoarthritis, n (%)		2 (3)	75 (97)		
	MRI-TS +	1	29	0.99	50%
	MRI-TS -	1	46		(9%-91%)
Subgroup: Oligoarthritis, n (%)		15 (18)	68 (82)		
	MRI-TS +	14	25	<0.001	93%
	MRI-TS -	1	43		(70%-99%)
	CRP +	8	14	0.020	53%
	CRP -	7	54		(30%-75%)
CRP +	MRI-TS +	8	8	0.051	100%
	MRI-TS -	0	6		(68%-100%)
CRP -	MRI-TS +	6	17	0.009	86%
	MRI-TS -	1	37		(49%-97%)
Subgroup: Polyarthritis, n (%)		12 (29)	29 (71)		
	MRI-TS +	9	18	0.49	75%
	MRI-TS -	3	11		(47%-91%)

Mono-, oligo- and polyarthritis, respectively: swollen joint count of 1, 2-4 and>4; RA, fulfilment of the 1987 RA criteria within the first year; P: P-values of Chi-square test (or Fisher's exact test when appropriate); Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; AUC: area under the receiver operating characteristic curve; MRI-TS: abnormal MRI-detected tenosynovitis; MRI-TS +: presence of abnormal MRI-detected tenosynovitis; MRI-TS-: absence of abnormal MRI-detected tenosynovitis; CRP+: elevated CRP; CRP-: normal CRP.

Spec. , % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	LR+, % (95%CI)	LR-, % (95%CI)	AUC
58%	25%	95%	1.98	0.30	0.70
(51%-65%)	(17%-35%)	(89%-98%)	(1.55-2.52)	(0.13-0.66)	
78%	28%	91%	2.34	0.62	0.65
(71%-83%)	(18%-42%)	(85%-94%)	(1.49-3.67)	(0.42-0.91)	
42%	41%	100	1.73	-	0.71
(28%-58%)	(26%-57%)	(81%-100%)	(1.32-2.27)	-	
63%	15%	94%	1.72	0.57	0.63
(54%-70%)	(8%-27%)	(88%-98%)	(1.10-2.70)	(0.28-1.16)	
61%	3%	98%	1.29	0.82	0.56
(50%-72%)	(1%-17%)	(89%-100%)	(0.31-5.32)	(0.20-3.30)	
63%	36%	98%	2.54	0.11	0.78
(51%-74%)	(23%-52%)	(88%-100%)	(1.81-3.57)	(0.02-0.71)	
79%	36%	89%	2.59	0.59	0.66
(68%-87%)	(20%-57%)	(78%-94%)	(1.33-5.04)	(0.34-1.02)	
43%	50%	100%	1.75	-	0.71
(21%-67%)	(28%-72%)	(61%-100%)	(1.11-2.75)	-	
69%	26%	97%	2.72	0.21	0.77
(55%-79%)	(13%-46%)	(87%-100%)	(1.66-4.47)	(0.03-1.29)	
38%	33%	79%	1.21	0.66	0.56
(23%-56%)	(19%-52%)	(52%-92%)	(0.78-1.86)	(0.22-1.95)	

Decision curve analyses

In all UA patients and in the subgroup of UA patients presenting with oligoarthritis, models with and without abnormal MRI tenosynovitis were compared (supplementary (available at Rheumatology Online) Table S10). This showed a higher net benefit for the model with MRI in both analyses (Fig. 1).

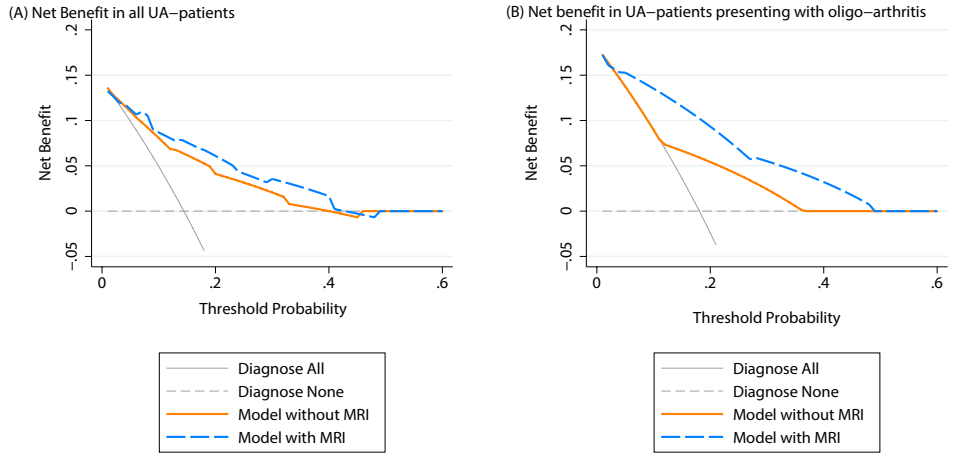

Figure 1 Decision curve analysis comparing models with and without MRI-detected tenosynovitis for identification of RA progression in unclassified arthritis patients

Decision curve analysis demonstrating the net benefit of different diagnostic models (supplementary (available at Rheumatology Online) Table S10) for identifying the patients who progress to RA among all unclassified arthritis (UA) patients (A) and among the subgroup of UA patients who presented with oligoarthritis (B). The net benefit (y-axis) is measured as the rate of correctly diagnosed patients developing RA within the first year without additional false-positive identified patients. The threshold probability (x-axis) represents the probability at which the benefit of early diagnosis is considered equivalent to the harm of overdiagnosis.

Discussion

It is recommended by the EULAR that treatment of RA should be initiated as soon as possible.[33] Early treatment requires early identification of RA. This is difficult if patients present with UA. It is inextricably linked to early recognition that the phenotype may not yet be completely matured; additional tests are therefore needed. When using the 2010 criteria, UA patients are mainly ACPA-negative, as was also shown here.[5,34] The regular predictors such as CRP and the number of swollen joints also have a limited predictive value. As it has been advocated that MRI-detected inflammation is valuable for the early identification of RA,[7] this study determined the diagnostic accuracy of hand and foot MRI in 2010 UA patients. Although an abnormal MRI did not yield high absolute risks for RA, the data showed that MRI contributed to the identification of UA patients that will progress to RA. Of all types of inflammation, tenosynovitis had the best accuracy and, of all UA patients, the test characteristics were highest in the subgroup of UA patients who presented with oligoarthritis. Furthermore, the absence of MRI-detected inflammation made progression to RA highly unlikely.

Generally, the development of a diagnostic tool starts with comparing established

patients with controls. This allows testing of the chosen cut-off value. The disadvantage is that this generally results in accuracies that are misleadingly high.[35,36] Subsequently, the test needs to be evaluated in clinically relevant settings. We set out to use this approach. We used information on MRIs of symptom-free persons from the general population to define an abnormal test and compared the MRI findings for patients who presented with RA with those of symptom-free controls and with patients with other arthritides. Indeed, we observed that the test characteristics were lower when comparing RA with other arthritides than with healthy controls; this is also in line with a smaller previous study that showed that early arthritis patients with other arthritides also show inflammation of the hands and feet on MRI.[37] After these explorative studies, the value of MRI was assessed in the clinically relevant setting of UA.

At baseline, RA was defined according to the 2010 criteria, and UA patients did not fulfil these criteria. Ninety-six percent of 2010 UA patients were ACPA-negative and only 4% was ACPA-positive. This is in line with the composition of the 2010 criteria, where ACPA-positive patients can fulfil the criteria with one (or more) swollen joint and ACPA-negative patients require >10 swollen joints.[3] This suggests that the 2010 criteria are less sensitive for the early detection of ACPA-negative RA. Indeed, a recent study proved that ACPA-negative RA patients had more extensive inflammation than ACPA-positive RA patients.[38] Consequently, ACPA-negative patients are nowadays more frequently classified as UA; this was also shown in our data.

Fulfilling the 1987 criteria was the primary outcome because these criteria had a higher specificity than the 2010 criteria[4,29] and because ACPA-negative UA patients can only become 2010-positive when they develop >10 involved joints; also, DMARDs may be initiated before the disease is as advanced. Intuitively it feels contradictory not to use the 2010 criteria as the outcome, but we balanced up the characteristics of the different criteria (the 2010 criteria being sensitive and fulfilled earlier than the 1987 criteria, the 1987 criteria being more specific over time). In our data only 5% of ACPA-negative patients fulfilled the 2010 criteria after 1-year, whereas 14% fulfilled the 1987 criteria and 36% were treated with DMARDs. Hence, our data confirm the observation that ACPA-negative patients fulfil the 1987 criteria more easily than the 2010 criteria. Still, in both ACPA-negative and ACPA-positive patients, treatment may have resulted in a decreased percentage of patients developing RA. Therefore DMARD initiation was also studied as outcome.

The present data emphasize that MRI is valuable in (APCA-negative) UA, especially in ACPA-negative UA patients presenting with oligoarthritis. Only 3% of ACPA-negative patients presenting with monoarthritis progressed to RA; with this low prior risk a predictive effect of MRI could not be detected. Also, in ACPA-negative patients presenting with polyarthritis, a predictive effect of MRI was not found; presumably in patients who presented with polyarthritis already, information on MRI-detected local joint inflammation was not of additional value.

The present finding that tenosynovitis was most discriminative is in line with previous studies.[14,20,22,23] Interestingly, tenosynovitis was also an early phenomenon in mice models of induced arthritis[39] and has recently also been shown to be predictive for the development of clinically apparent arthritis in patients who

present with clinically suspect arthralgia.[40] Tenosynovitis is also detectable with US. Although some studies suggested that US is less sensitive than MRI in detecting tenosynovitis, the question of whether MRI can be replaced with US in UA patients when identifying patients with impending RA remains to be answered.[20,41,42]

Importantly, the early arthritis patients studied were consecutively seen at the outpatient clinic and included in the cohort without further selection other than recent-onset arthritis;[27] this allows extrapolation of findings. Other strong elements are the comprehensive approach and the sample size. This study contains by far the largest number of consecutive included early arthritis patients with MRI data thus far. High-quality MRI data were obtained; we used a superconductive 1.5 T system with powerful gradients, allowing small acquisition matrices with relatively high SNR and frequency-selective fat suppression.

BME was assessed on contrast-enhanced T1-weighted fat-saturated sequences; RAMRIS suggests STIR/T2-sequences (see supplementary (available at Rheumatology Online) data, section detailed MRI protocol).[30] Previous studies, in diverse patient populations, have shown high similarities for BME between these sequences,[43–45] and both sequences are recommended by the European Society of Skeletal Radiology (ESSR).[46]

Previously, both in our study and the research of others, BME has been shown to be predictive for erosive progression in RA patients.[47–50] In the present study, BME and erosions were not predictive for RA development in UA patients. Possibly, this is related to the fact that most UA patients were ACPA-negative, or to the fact that predictors for erosive progression are different from those predicting RA development. Apparently, different markers perform differently when used in slightly different types of patients, in different disease phases, and with respect to different outcomes.

Our study has several limitations. First, the sample set: although we studied a large group of 201 UA patients, only 29 of these patients developed RA. This also resulted in a low number of cases in the subgroups of mono-, oligo- and polyarthritis. In general, low numbers of cases lead to a higher probability of a type II error. The RAMRIS method was used to score the MRIs. This method is the only validated method for evaluating hand and foot MRIs and is suitable for research, but it was not designed for diagnostic purposes. RAMRIS scoring is time-consuming, rheumatologists and radiologists are generally not experienced with the method, and the reproducibility may be moderate if readers are insufficiently trained. This may hamper direct clinical implementation. After showing the continuous MRI scores, the most important analyses were done by comparing abnormal with normal MRI results. Dichotomization generally leads to loss of information and possibly loss of discriminative value. However, using continuous scores would have hampered the use of findings done in symptom-free controls. More work is needed in order to make MRI feasible for diagnostic use. As in other fields of radiology, a small set of well-defined imaging parameters are needed to allow the use of MRI in the differential diagnostic process in a subjective clinical environment.

We did not address the cost-effectiveness of MRI. Although MRI is relatively

expensive, the possible benefits of an early RA diagnosis could be a multitude when resulting in reduced disability and reduced use of biologics. We also did not evaluate to what extent it is required to scan hand and foot joints, or if a limited region would be equally informative. These are subjects for further research.

In conclusion, this study revealed that MRI-detected inflammation contributes to the identification of UA patients who will develop RA. MRI-detected tenosynovitis was most helpful, and the accuracy was the highest in UA patients who presented with oligoarthritis. Furthermore, RA was unlikely to develop in UA patients with a normal MRI. This comprehensive study therefore indicates that MRI is of help in the diagnostic process of RA.

References

1 van der Linden MPM et al. *Arthritis Rheum* 2010;62:3537–46.
2 Combe B et al. *Ann Rheum Dis* 2007;66:34–45.
3 Aletaha D et al. *Arthritis Rheum* 2010;62:2569–81.
4 Radner H et al. *Ann Rheum Dis* 2014;73:114–23.
5 Krabben A et al. *Rheumatology* 2013;52:1265–70.
6 Aken J van et al. *Ann Rheum Dis* 2006;65:20–5.
7 Colebatch AN et al. *Ann Rheum Dis* Published Online First: 21 March 2013.
8 Jimenez-Boj E et al. *Arthritis Rheum* 2007;56:1118–24.
9 Dalbeth N et al. *Ann Rheum Dis* 2009;68:279–82.
10 McQueen FM et al. *Ann Rheum Dis* 2007;66:1581–7.
11 Peterfy C et al. *Ann Rheum Dis* 2013;72:794–6.
12 Krabben A et al. *Ann Rheum Dis* 2013;74:506–12.
13 Sugimoto H et al. *Radiology* 1996;198:185–92.
14 Klarlund M et al. *Ann Rheum Dis* 2000;59:521–8.
15 Sugimoto H et al. *Radiology* 2000;216:569–75.
16 Boutry N et al. *Radiology* 2005;236:593–600.
17 Solau-Gervais E et al. *J Rheumatol* 2006;33:1760–5.
18 Duer A et al. *Ann Rheum Dis* 2008;67:48–51.
19 Mori G et al. *Mod Rheumatol* 2008;18:247–51.
20 Navalho M et al. *J Rheumatol* 2013;40:1282–92.
21 Ji L et al. *Int J Rheum Dis* Published Online First: 2014.
22 Eshed I et al. *Rheumatology* 2009;48:887–91.
23 Duer-Jensen A et al. *Arthritis Rheum* 2011;63:2192–202.
24 Tamai M et al. *Ann Rheum Dis* 2006;65:133–4.
25 Tamai M et al. *Arthritis Care Res* 2009;61:772–8.
26 Mangnus L et al. *Arthritis Rheumatol* 2016;68:2593–602.
27 de Rooy DPC et al. *Rheumatology* 2011;50:93–100.
28 Arnett FC et al. *Arthritis Rheum* 1988;31:315–24.
29 van der Linden MPM et al. *Arthritis Rheum* 2011;63:37–42.
30 Østergaard M et al. *J Rheumatol* 2003;30:1385–6.
31 Haavardsholm EA et al. *Ann Rheum Dis* 2007;66:1216–20.
32 Vickers AJ et al. *Med Decis Making* 2006;26:565–74.
33 Smolen JS et al. *Ann Rheum Dis* 2013;:annrheumdis-2013-204573.
34 Krabben A et al. *Ann Rheum Dis* 2012;71:238–41.
35 Schünemann HJ et al. *Evid Based Med* 2008;13:162–3.
36 Rutjes AWS et al. *Can Med Assoc J* 2006;174:469–76.
37 Stomp W et al. *J Rheumatol* 2014;41:1630–7.
38 Nordberg LB et al. *Ann Rheum Dis* 2016;:annrheumdis-2015-208873.
39 Hayer S et al. *Arthritis Rheum* 2007;56:79–88.
40 van Steenbergen HW et al. *Ann Rheum Dis* 2015;:annrheumdis-2015-208138.
41 Wakefield RJ et al. *Arthritis Care Res* 2007;57:1158–1164.
42 Backhaus M et al. *Arthritis Rheum* 1999;42:1232–1245.
43 Stomp W et al. *Eur Radiol* 2014;24:2614–22.
44 Schmid MR et al. *Radiology* 2002;224:463–9.
45 Mayerhoefer ME et al. *J Magn Reson Imaging* 2005;22:788–93.
46 Sudoł-Szopińska I et al. *Semin Musculoskelet Radiol* 2015;19:396–411.
47 Nieuwenhuis WP et al. *Arthritis Rheumatol* Published Online First: 1 December 2015.

48 Hetland ML et al. *Ann Rheum Dis* 2010;69:1789–95.
49 Haavardsholm EA et al. *Ann Rheum Dis* 2008;67:794–800.
50 McQueen FM et al. *Ann Rheum Dis* 1999;58:156–63.

Is the modified Disease Activity Score superior to the Disease Activity Score in early arthritis and rheumatoid arthritis? Comment on the article by Baker et al

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To the Editor:

We read with great interest the recent article by Baker et al, in which the authors describe the development of a modified Disease Activity Score (M-DAS) based on correlations with concurrent synovitis scores as measured by magnetic resonance imaging (MRI) in patients with rheumatoid arthritis (RA).[1] The original DAS was developed in the early 1990s based on the clinical findings of rheumatologists; it consists of the Ritchie Articular Index, the number of swollen joints, the erythrocyte sedimentation rate (ESR), and the patient's global assessment of disease activity measured on a visual analog scale (PtGA). Since then, the DAS has been modified and validated several times, including for use with the C-reactive protein level (DAS-CRP) instead of the ESR and for use with smaller joint counts (28-joint count DAS [DAS28]). In the recently developed M-DAS, tender joint count (TJC) and PtGA, the variables that are most subject to subjectivity, are no longer included, and the evaluator's global assessment (EvGA) is included. The M-DAS was developed using data from the GO-BEFORE study and validated using data from the GOFORWARD study (both RA clinical trials). Compared to the DAS28, correlations between MRI-detected synovitis and the M-DAS28 were superior, and the M-DAS28 was shown to be a more precise predictor of radiographic progression.[1] Similarly, modified versions of the Simplified Disease Activity Index (M-SDAI) and Clinical Disease Activity Index (M-CDAI) were derived.[1] These modified measures need to be evaluated in independent studies to determine their validity. We therefore compared the original and modified measures in a population-based inception cohort of patients with early arthritis, using MRI-detected inflammation (synovitis and bone marrow edema) and radiographic progression as outcomes.

Baseline MRI data and DAS28 scores of 127 patients with early arthritis, included in the Leiden Early Arthritis Cohort between 2010 and 2012, were available; of these patients, 91 had data on EvGA. The cohort and the details of the MRI protocol are described elsewhere.[2] Using the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system, 2 readers scored MRIs for synovitis and bone marrow edema. The total synovitis and bone marrow edema scores of the metacarpophalangeal and wrist joint were calculated using the mean scores. Within-reader intraclass correlation coefficients (ICCs) for inflammation on MRI were 0.99 and 0.93 for the 2 readers, respectively; the between-reader ICC was 0.87 (2). Patients were followed up prospectively. Radiographs of the hands and feet of 87 patients were taken at baseline and after 1 year, and 1 reader chronologically scored the joints using the Sharp/van der Heijde scoring (SHS) method (withinreader ICC 0.86). Progression was defined as an increase in SHS of 1 (similar to the definition used by Baker et al). Sensitivity analyses defining progression as SHS of 3 were also performed. The following formulas were used: DAS28-CRP = 0.56 * sqrt(TJC28) +0.28 * sqrt(SJC28) +0.36*ln(CRP*10+1) + 0.14* PtGA+ 0.96 and m-DAS-CRP = 0.49*ln(CRP) + 0.15 * SJC28 + 0.22*EvGH, where SJC28 is the swollen joint count in 28 joints and ln(CRP) is the linear log-transformed CRP. When the CRP was 1 mg/dl, the linear log-transformed CRP was negative and was set to 0. The formulas used to calculate the CDAI and SDAI correspond to those used by Baker et al. Correlations between disease activity scores and MRI-detected inflammation were determined using the Pearson

correlation coefficient. Superiority of correlation coefficients (which were obtained in the same samples) was determined using the “corcor” command in Stata software. Areas under the curve (AUCs) were determined for the association with radiographic progression; differences in the AUC were compared using the “roccomp” Stata command.

Of the 127 patients with early arthritis, 58% were women and 28% were anti–citrullinated protein antibody (ACPA) positive. The mean age was 55.6 years, the median symptom duration at presentation was 13 weeks, the median SJC was 3, the median TJC was 4, the median ESR was 21.8 mm/hour, the median CRP level was 0.4 mg/dl, the median synovitis score on MRI was 3.5, and the median bone marrow edema score on MRI was 3.5. Radiographic progression (SHS 1) was present in 41% (SHS 3 in 17%). Fifty-one patients with early arthritis fulfilled the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA;[3] these patients had a median SJC of 3, a median TJC of 4, a median CRP level of 0.8 mg/dl, and a median ESR of 25 mm/hour; 69% were ACPA positive, 46% had a SHS of 1, and 17% had a SHS of 3. Correlations of the original scores and the modified scores with MRI-evident synovitis are shown in Table 1. The correlation coefficients for the modified disease activity scores were slightly higher than those for the DAS28-CRP and DAS28- ESR (0.32 and 0.31 for the M–DAS-CRP and the DAS28- CRP, respectively, and 0.36 and 0.34 for the M–DAS-ESR and the DAS28-ESR, respectively); these differences were not statistically significant. For the correlation between bone marrow edema and the M-DAS28 and the DAS28, correlation coefficients were slightly higher for the M-DAS28 (Table 1), but were not significantly different. When comparing the M–DAS28-CRP and DAS28-CRP with radiographic progression (SHS 1) as the outcome, the AUCs were slightly higher for the M-DAS28 (0.54 versus 0.49, respectively). The same was true for the M–DAS28-ESR versus the DAS28-ESR (0.56 versus 0.50, respectively) (Table 1). These differences did not yield statistical significance either. When defining radiographic progression as SHS 3, similar results were obtained (data not shown). Analysis of the 51 patients who fulfilled the 2010 classification criteria for RA resulted in comparable findings; the M-DAS28 scores were not significantly better than the DAS28 scores (Table 1). When analyzing the M-CDAI and M-SDAI, no significant improvements were obtained compared to the original CDAI and SDAI (Table 1).

In conclusion, we observed that the differences between the correlation coefficients for the M-DAS28 and the DAS28 were marginal and not statistically significant in demonstrating correlation with MRI measurements of inflammation. With regard to radiographic progression, we observed increases in the AUC of 0.05. This indicates that among random pairs of patients with and without radiographic progression, the M-DAS28 was higher than the DAS28 in 5% of pairs of patients with radiographic progression. These increases were not statistically significant, and whether they are clinically relevant is questionable, as the absolute AUCs were rather low. Our population of patients with early arthritis and early RA had less severe disease than the patients with longstanding RA studied by Baker et al, who had a mean SJC28 of 9.3 and TJC28 of 13.8.[1] Based on the present data, we cannot prove that the M-DAS28 is superior to the DAS28. More studies on this subject in other patient populations are needed.

Table 1 Associations of modified and original DAS, SDAI, and CDAI scores with MRI-detected synovitis and bone marrow edema, as well as radiographic progression (ΔSHS≥1) during 1 year of followup*

	MRI-detected synovitis		MRI-detected BME		radiographic progression	
	Correlation coefficient	p	Correlation coefficient	p	OR (95% CI)	AUC (95% CI)
Early Arthritis						
DAS-CRP						
M-DAS28-CRP	0.32	<0.01	0.34	<0.01	1.17 (0.65-2.10)	0.54 (0.38-0.69)
DAS28-CRP	0.31	<0.01	0.26	<0.01	0.98 (0.66-1.45)	0.49 (0.37-0.62)
DAS-ESR						
M-DAS28-ESR	0.36	<0.01	0.34	<0.01	1.17 (0.71-1.93)	0.56 (0.41-0.72)
DAS28-ESR	0.34	<0.01	0.29	<0.01	0.98 (0.72-1.34)	0.50 (0.38-0.62)
SDAI						
M-SDAI	0.34	<0.01	0.33	<0.01	1.03 (0.94-1.13)	0.53 (0.37-0.68)
SDAI	0.34	<0.01	0.33	<0.01	1.01 (0.95-1.06)	0.51 (0.34-0.69)
CDAI						
M-CDAI	0.25	0.02	0.31	<0.01	1.02 (0.92-1.12)	0.53 (0.38-0.68)
CDAI	0.28	0.01	0.30	<0.01	1.00 (0.94-1.06)	0.49 (0.32-0.66)
Subgroup of RA						
DAS-CRP						
M-DAS28-CRP	0.43	0.01	0.40	0.02	1.16 (0.58-2.33)	0.58 (0.35-0.81)
DAS28-CRP	0.41	<0.01	0.25	0.08	1.15 (0.67-1.95)	0.57 (0.39-0.74)
DAS-ESR						
M-DAS28-ESR	0.40	0.02	0.37	0.03	1.17 (0.62-2.21)	0.59 (0.36-0.82)
DAS28-ESR	0.46	<0.01	0.30	0.03	1.02 (0.64-1.63)	0.55 (0.36-0.73)
SDAI						
M-SDAI	0.42	0.01	0.37	0.03	1.03 (0.93-1.15)	0.61 (0.38-0.84)
SDAI	0.33	0.09	0.31	0.11	1.02 (0.95-1.10)	0.63 (0.37-0.88)
CDAI						
M-CDAI	0.29	0.09	0.36	0.04	0.99 (0.88-1.12)	0.53 (0.30-0.76)
CDAI	0.21	0.27	0.25	0.19	1.00 (0.92-1.09)	0.56 (0.30-0.82)

* There was no significant difference between the correlation coefficients for the modified scores and the original scores. Similarly, differences in the area under the curve (AUC) for the modified scores and original scores were not statistically significant. MRI = magnetic resonance imaging; SHS = Sharp/van der Heijde score; OR = odds ratio; 95% CI = 95% confidence interval; M–DAS28-CRP = modified Disease Activity Score in 28 joints using the C-reactive protein level; M–DAS28-ESR = modified DAS28 using the erythrocyte sedimentation rate; M-SDAI = modified Simplified Disease Activity Index; M-CDAI = modified Clinical Disease Activity Index; RA = rheumatoid arthritis.

References

1 Baker JF et al. *Arthritis Rheumatol* 2014;66:794–802.
2 Krabben A et al. *Ann Rheum Dis* 2013;74:506–12.
3 Aletaha D et al. *Arthritis Rheum* 2010;62:2569–81.

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.

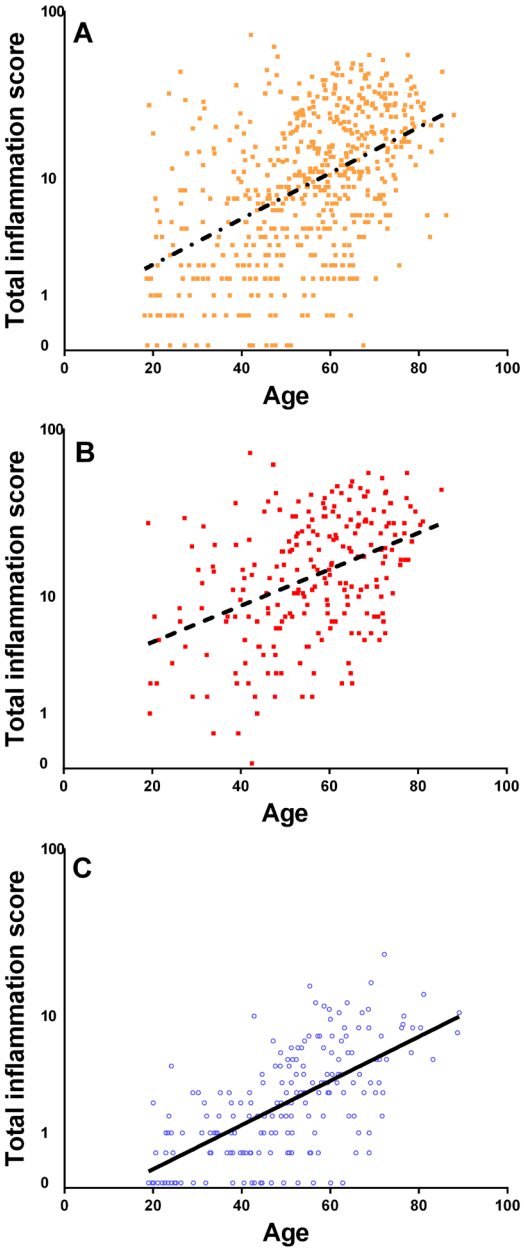


Figure 1 Total MRI inflammation score plotted against age at presentation

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

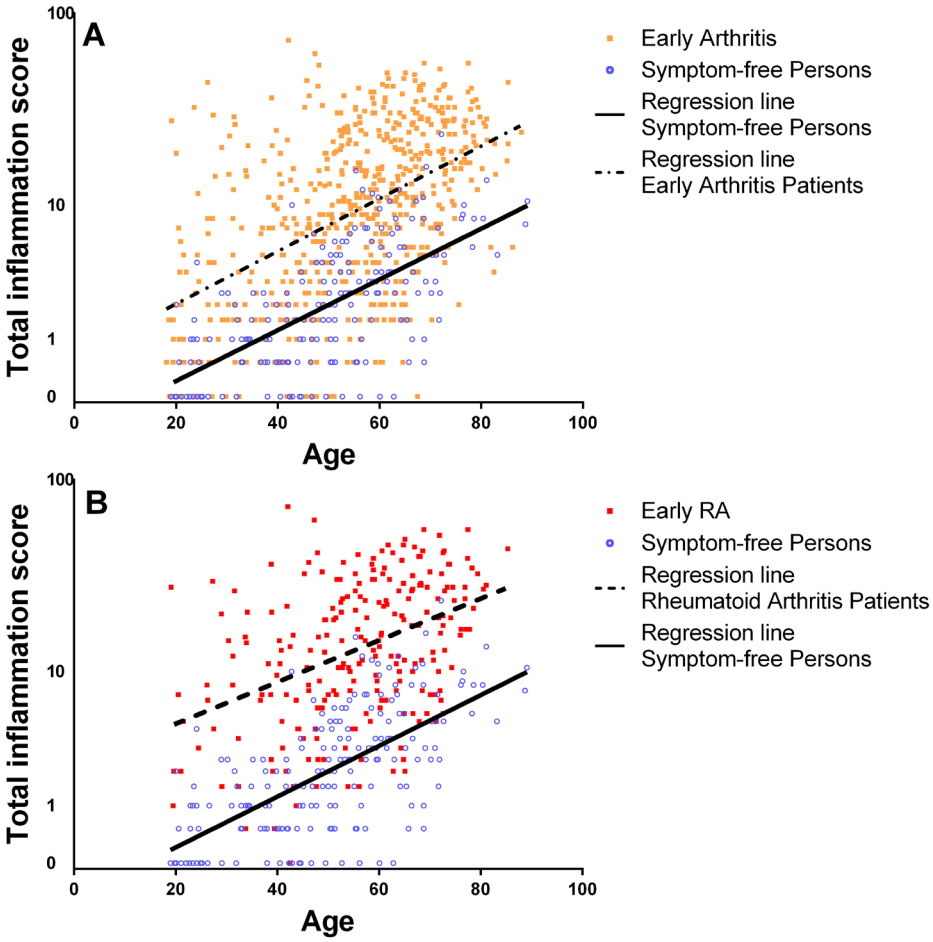


Figure 2 Comparing the relationship between age and total MRI inflammation with that for symptom-free controls

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).

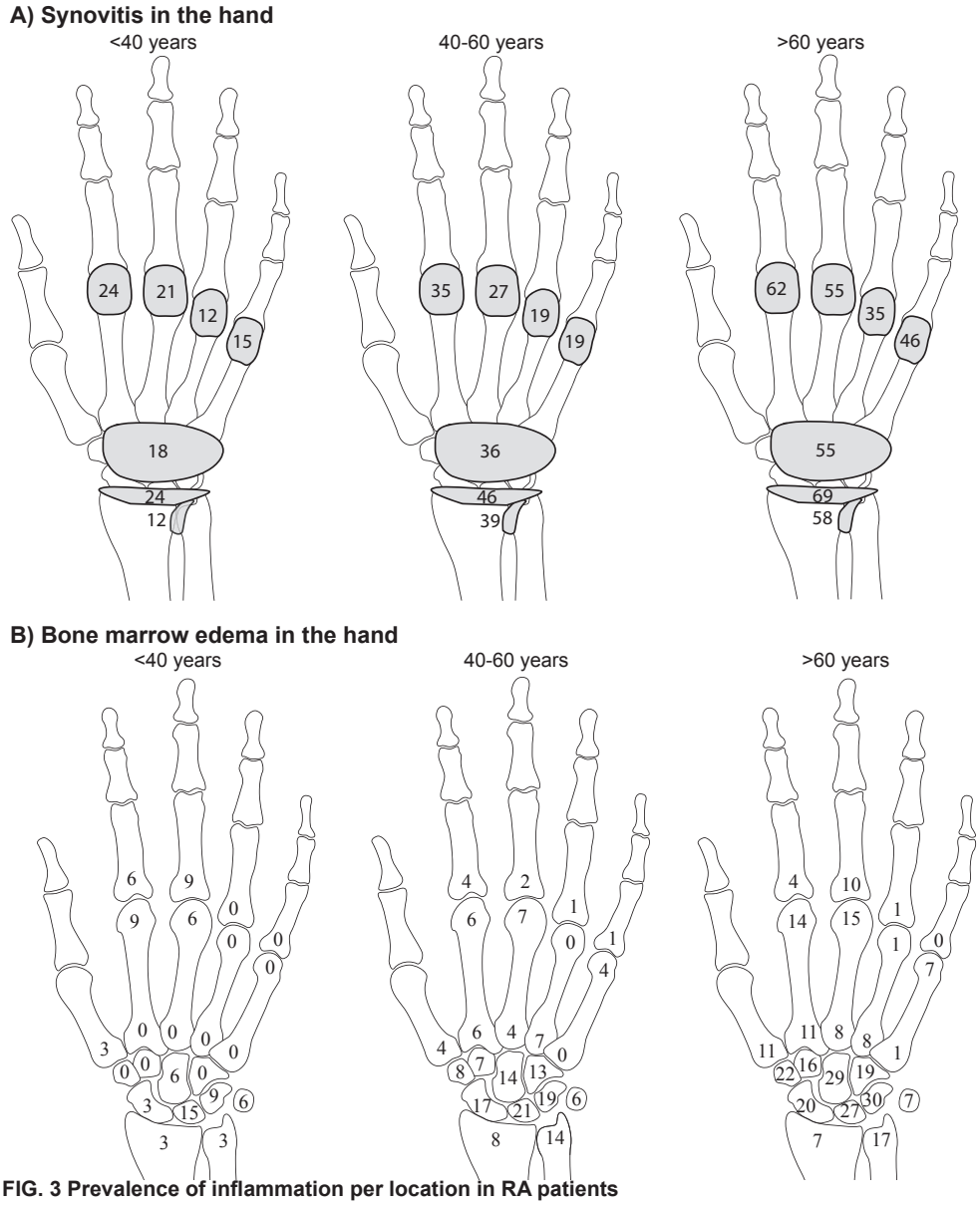
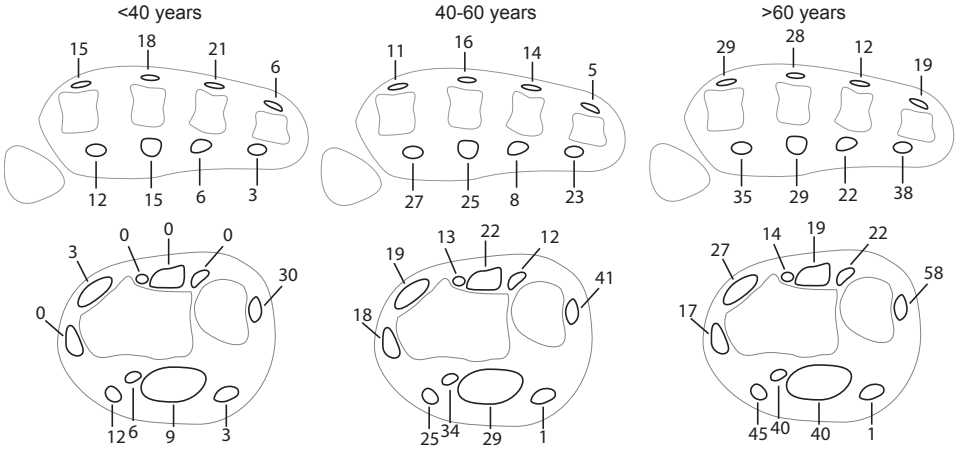


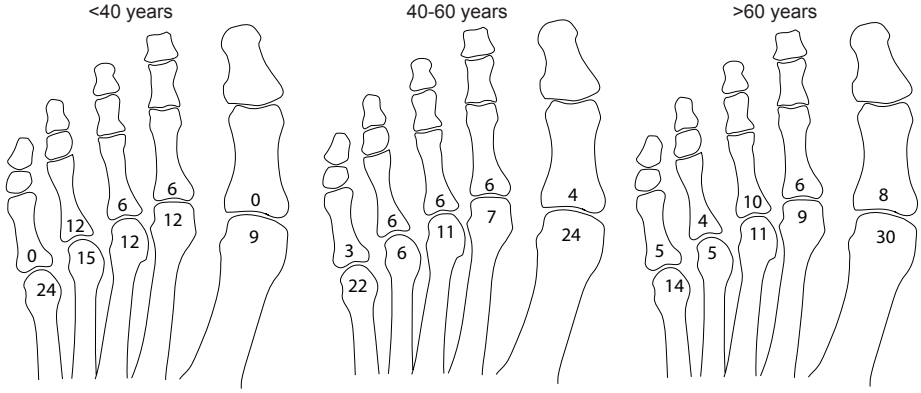
FIG. 3 Prevalence of inflammation per location in RA patients

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.

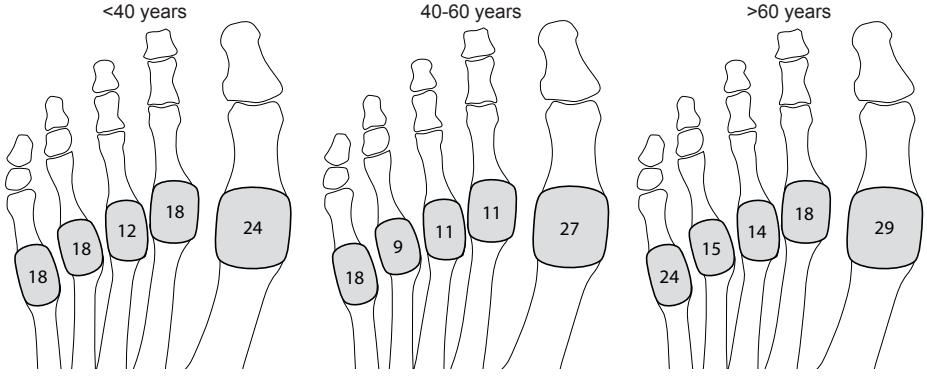
C) Tenosynovitis in the hand



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.

Changes in the clinical presentation of patients with rheumatoid arthritis from the early 1990s to the years 2010: earlier identification but more severe patient reported outcomes

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The relevance of early identification of rheumatoid arthritis (RA) is acknowledged for several decades. Over time the interpretation of early has changed: in the early 1990s a symptom duration <2 years was considered early. Nowadays earlier identification is recommended,[1] some suggest that identification within 12 weeks after symptom onset is optimal. In this study, we evaluated the presentation of RA over the past decennia. We assessed whether patients with RA were recognised earlier and if this affected the phenotype of RA at first presentation. We observed that patients with RA are indeed identified after a shorter symptom duration, that this was paralleled with less severe inflammation at presentation, but paradoxically also with increased severity of patient reported outcomes (PROMs).

All patients in the Leiden Early Arthritis Clinic (EAC) cohort that fulfilled the 2010 European League Against Rheumatism/ American College of Rheumatology RA criteria were studied (n=1406).[2,3] In short, the EAC was started in 1993 and inclusion criteria were arthritis at physical examination and symptom duration <2 years. At baseline, hence before treatment initiation, 68-tender and 66-swollen joint counts were performed, blood samples taken and the PROMs fatigue, pain, morning stiffness and disease activity obtained. Initially PROMs were recorded as visual analogue scales (VASs), from 2010 onwards numerical rating scales were used. Both scales correlate strongly.[4] Because changes in presentation were expected to occur gradually, patients with RA were compared over five periods. Variables were compared using Kruskal-Wallis H-test.

Symptom duration at presentation decreased over the years from median 138 days in 1993–1996 to 97 days in 2011–2015 ($p<0.001$, table 1). The frequency of autoantibodies did not differ significantly. Patients with RA presented with less swollen joints (median 11 decreased to six joints, $p<0.001$) and lower levels of acute phase reactants (median C-reactive protein (CRP)-level 24 decreased to 10 mg/L, $p<0.001$). The health assessment questionaire (HAQ) (measuring functional disability) remained stable (table 1). PROM values increased: patients reported more pain ($p<0.001$), more fatigue ($p=0.005$) and higher disease activity ($p<0.001$) (figure 1). Furthermore, the disease activity score (DAS)28-CRP (combining joint counts, CRP and patient global health) decreased ($p=0.001$).

These findings are paradoxical: while patients with RA over time presented with shorter symptom duration and less inflammatory findings, PROMs worsened. The finding that all evaluated PROMs increased makes it unlikely to be a coincidental finding. The VAS fatigue and pain are known to be strongly correlated[5] and it is known that patient perceptions are minimally explained by inflammatory findings.[6,7]

Presumably, the present findings are not specific for RA, but reflect a general increase in societal pressure posed upon the individual over the years (ie, society has become more demanding), whereby smaller health problems, which might be less visible, could be experienced as more disabling.[8] In parallel, patients may also have higher health expectations themselves. Both phenomena likely contribute to a shift of reference when reporting outcomes.

This is the first study describing temporal changes in presentation of new patients with RA, but discordance between inflammatory measures (SJC and erythrocyte sedimentation rate) and PROMs has been reported. First, differences

in inflammatory outcomes between countries were not paralleled by similar differences in VAS fatigue and global health.[9] Similarly, comparing patients with RA treated in 1985 with patients treated in 2000 revealed that the latter group had less inflammation, but similar VAS pain.[10]

The previous observations that PROMs were not responsive to changes in the severity of inflammation combined with the present finding raise the question if it is known what PROMs actually measure. Furthermore, this may have consequences for the monitoring of RA using PROMs or composite scores (eg, DAS or simple disease activity index (SDAI)) for defining remission.

In conclusion, over the last 23 years patients with RA in Leiden (the Netherlands) have presented with shorter symptom duration. Even though patients with RA presented with less inflammation, the disease burden as experienced by patients is higher.

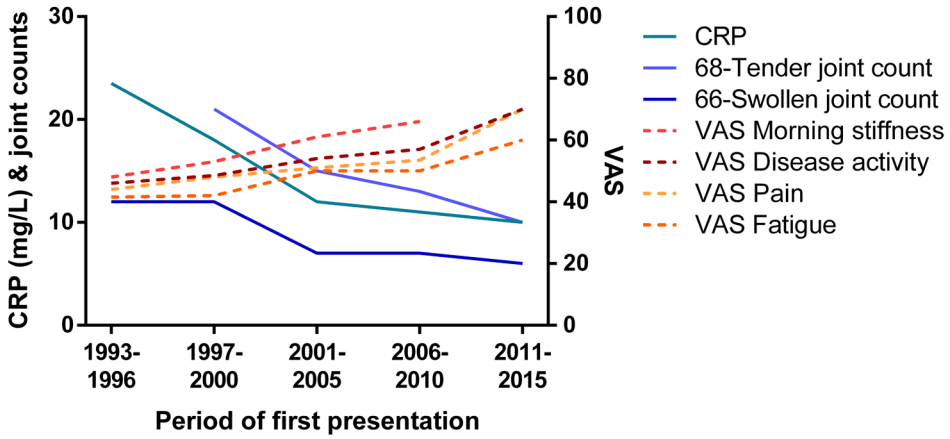

Figure 1 The severity of inflammation and of several patient reported outcomes measures for 2010-criteria positive RA-patients that presented in different time periods
Depicted are the medians per period. The inter-quartile ranges are shown in Table 1. VAS, visual analogue scale; CRP, c-reactive protein.

Table 1 Characteristics of patients with RA (according to the 2010-criteria) at first presentation to the rheumatologic outpatients clinic

	1993-1996		1997-2000		2001-2005		2006-2010		2011-2015		p-value
	N=177		N=216		N=304		N=367		N=342		
Women, n (%)	118	(66.7%)	142	(65.7%)	214	(70.4%)	240	(65.4%)	222	(64.9%)	0.61
Age in years, mean (SD)	56.0	(16.1)	56.0	(16.9)	56.1	(15.7)	56.6	(15.4)	57.2	(14.5)	0.91
Symptom duration in days, med (IQR)	138	(81-269)	135	(81-281)	147	(74-261)	131	(60-244)	97	(51-228)	<0.001
68-Tender joint count, med (IQR)		N/A	21	(15-35)	15	(9-25)	13	(8-20)	10	(5-16)	<0.001
66-Swollen joint count, med (IQR)	12	(6-16)	12	(6-20)	7	(3-13)	7	(3-11)	6	(3-11)	<0.001
ESR in mm/hour, med (IQR)	44	(6-16)	33	(6-19)	29	(3-12)	28	(3-11)	29	(3-11)	<0.001
CRP in mg/L, med (IQR)	24	(10-45)	18	(9-37)	12	(5-30)	11	(4-27)	10	(3-25)	<0.001
RF-positive, n (%)*	99	(55.9%)	124	(57.4%)	187	(61.5%)	213	(58.7%)	224	(65.7%)	0.142
ACPA-positive, n, (%)*	104	(60.5%)	120	(55.8%)	138	(50.9%)	173	(51.8%)	187	(55.2%)	0.29
VAS Pain (0-100), med (IQR)	44	(24-60)	48	(27-60)	51	(33-67)	54	(36-70)	70	(40-80)	<0.001
VAS Fatigue (0-100) , med (IQR)	42	(13-64)	42	(15-63)	50	(18-69)	50	(17-73)	60	(20-80)	0.005
VAS Morning Stiffness (0-100), med (IQR)	48	(24-76)	53	(26-73)	61	(35-81)	66	(40-79)	N/A		0.002
VAS Disease activity (0-100), med (IQR)	46	(21.5-70)	49	(26-68)	54	(33-73)	57	(35-74)	70	(50-80)	<0.001
HAQ, med (IQR)	1.0	(0.6-1.4)	1.0	(0.5-1.5)	1.0	(0.5-1.5)	1.0	(0.5-1.5)	1.0	(0.6-1.5)	0.78
DAS28-CRP, med (IQR)		N/A	5.3	(4.4-5.6)	4.7	(4.0-5.6)	4.7	(3.8-5.4)	4.4	(3.7-5.2)	0.001

VAS disease activity represents disease activity in last 24 hours. p Value; results of Kruskal-Wallis H-test (Pearson's $\chi 2$ for proportions); N/A, not available: from 1993 to 1999 a different tender joint count was used than the 68-TJC and the DAS28-CRP could not be calculated due to missing patient global health assessment. VAS morning stiffness was not assessed from 2010 to 2015. *Percentages from the number of patients with ACPA/RF data. ACPA, anticitrullinated peptide antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; TJC, tender joint count; VAS, visual analogue scale.

References

1 Combe B et al. *Ann Rheum Dis* 2007;66:34–45.
2 de Rooy DPC et al. *Rheumatology* 2011;50:93–100.
3 Aletaha D et al. *Ann Rheum Dis* 2010;69:1580–8.
4 Hjermstad MJ et al. *J Pain Symptom Manage* 2011;41:1073–93.
5 Nikolaus S et al. *Arthritis Care Res* 2013;65:1128–46.
6 Khan NA et al. *Arthritis Care Res* 2012;64:206–14.
7 Studenic P et al. *Arthritis Rheum* 2012;64:2814–23.
8 Huber M et al. *BMJ* 2011;343:d4163.
9 Putrik P et al. *Ann Rheum Dis* 2016;75:540–6.
10 Pincus T et al. *Arthritis Rheum* 2005;52:1009–19.

9

Summary, conclusions, discussion and future prospectives

Summary and Conclusions

The main subject of this thesis is the exploration of the value of magnetic resonance imaging (MRI) in rheumatoid arthritis (RA). Because MRI has the ability to show inflammatory changes (i.e. synovitis, tenosynovitis and BME) in addition to structural changes (i.e. erosions), it might be valuable for multiple purposes, both clinical and research oriented. The studies in this thesis represent several different potential applications of MRI in the field of early arthritis.

All studies were performed in patients of the Leiden Early Arthritis Clinic (EAC). This is an observational cohort in which all patients that present at the rheumatologic outpatient clinic of the Leiden University Medical Center with inflammatory arthritis and symptom duration of less than two years are included. The EAC was started in 1993. At the start of the EAC, but also in the years after the start, the importance of early treatment initiation in early arthritis patients was accentuated by campaigns and guidelines. In **Chapter 8** we assessed whether RA patients were indeed recognized with shorter symptom duration during the existence of the EAC and whether this was accompanied with less severe RA at first presentation. We found that patients were identified earlier and that this was paralleled with less severe inflammation (less affected joints and lower levels of acute phase reactants). However, the severity of patient reported outcomes (PROMs: fatigue, pain, morning stiffness and disease activity) gradually increased over the same period. These findings appear paradoxical: why does the severity of PROMs increase, while patients present with less inflammation? Apparently, these PROMs are multidimensional: involving not only inflammatory, but also psychosocial factors. This is also reflected by other studies. It has been shown for example that fatigue is only limitedly explained by inflammatory variables, but does strongly correlated with variables like pain.[1–3] Presumably, the increase in severity of PROMs reflects a general increase in societal pressure, where smaller health problems could be experienced as more disabling. Furthermore, higher health expectations could lead to a shift of reference when reporting PROMs. These findings bring to light possible difficulties when comparing (differences in) PROMs between different study populations; not only when comparing populations from different countries, but also when comparing populations from the same countries but from different time periods.

MRI of the metacarpophalangeal (MCP), wrist and metatarsophalangeal (MTP) joints is performed in all newly presenting patients of the EAC since 2010. In combination with the other data collected in the EAC, this enabled us to study many questions regarding the use of MRI in early arthritis patients.

The original RAMRIS method included scores for erosions, bone marrow edema (BME) and synovitis. Later an additional scoring system for tenosynovitis at the wrist and MCP joints was developed.[4,5] However, the prevalence, discriminative value and prognostic value of MRI detected tenosynovitis in early arthritis was still limitedly studied. In **Chapter 2** we assessed tenosynovitis at the wrist and MCP joints in 178 early arthritis patients at baseline using this method. The prevalence of MRI detected tenosynovitis was high (65% of early arthritis patients had tenosynovitis). The prevalence was higher in RA patients than in other early

arthritis patients (75% vs 59%). However, when looking at the separately scored tendon locations, most locations were not specific for RA but also involved in patients with other arthritides. Tendons that were more often affected in RA-patients were the flexor tendons at MCP 5, the extensor tendons at MCP 2 and 4, and the tendons in wrist extensor compartments I, II, and IV. Nevertheless, the discriminative value of tenosynovitis at these specific locations was limited: specificity was high (>90%), but sensitivity was low (<20%). This means that the majority of RA patients did not have tenosynovitis at one of these locations, but that tenosynovitis at these locations was uncommon in non-RA patients.
Synovitis of the joint next to the affected tendons was seen in 70-100%. The majority of locations of tenosynovitis associated with RA, were associated with RA independent of local synovitis, thus the association between tenosynovitis and RA seems not to be driven by underlying synovitis. The severity of tenosynovitis was not significantly associated with more severe RA (radiographic progression or ACPA-positivity). An interesting observation in RA was that although the extensor tendons lack a synovial sheath at the level of the MCP joints, we also found inflammation at these tendons. A previous study named this periextensor tendon inflammation.[6] It might be difficult to differentiate synovitis of the joint and periextensor inflammation and the question could be raised whether detected periextensor tendon inflammation does not actually reflect joint synovitis. Interestingly, we also found periextensor inflammation without synovitis of the specific MCP joint. Although the numbers were small, we only found this in patients with RA. It might suggest an effect of RA on other tissue than the tenosynovium, for example a direct effect on the tendons.
This study has shown that tenosynovitis is a common finding in early (rheumatoid) arthritis and that the presence of MRI detected tenosynovitis could have some diagnostic use. We were not able to show a relation with more radiographic joint damage. Still, tenosynovitis can cause pain, range of motion loss and (grip) weakness leading to disability. Therefore, the presence of MRI detected tenosynovitis can be of importance in early RA.

MRI also has potential prognostic use. It had been shown that patients with high BME and synovitis scores have more erosive progression during follow-up.[7–19] So far this was studied on patient level, i.e. the total BME, synovitis and erosion scores of a patient. In **Chapter 3** we assessed BME and synovitis lesions at bone level, i.e. we assessed per bone whether BME in that bone or synovitis around that bone (local synovitis) was present and whether there was erosive progression in that bone during follow-up. MRI was performed at three time points: at inclusion in the EAC, after 4 months and after 12 months of follow-up. This allowed us to not only study the association between baseline findings and erosive progression, but also to study the course of BME and synovitis lesions and whether the course of these lesions was associated with erosive progression.
The presence of BME and the presence of local synovitis at baseline were associated with erosive progression in that bone after follow-up in univariable analyses. Because BME and synovitis often occur concurrently, stratified analyses and multivariable generalized estimating equation (GEE) analyses were performed. In these analyses BME at baseline was still associated with erosive progression, however when adjusting for BME, the association of synovitis with erosive progression was weaker or lost.

The follow-up MRIs showed that the course of BME and local synovitis lesions were similar: lesions were most frequently present or absent at each time point. Lesions appeared or disappeared less frequently and only very rarely lesions disappeared and reappeared (or vice versa). This suggests that these inflammatory lesions are not very fluctuating or "waxing and waning". To assess the association between the course of BME and synovitis lesions and erosive progression, the number of MRI scans where BME or local synovitis was present was determined for each bone (e.g. if BME was present at all 3 MRI time points in a given bone, the load of BME for this bone was 3). GEE analyses showed that both higher loads of BME and synovitis were univariably associated with erosive progression. However, multivariable analyses with both the load of BME and the load of synovitis showed that only BME was independently associated with erosive progression. Presence of BME in 2 or 3 time points was strongly associated with erosive progression (OR >55). Although the absolute number of bones with BME at all three time points that had erosive progression was not very high (15%), this study showed that persistent BME is predictive of erosive progression in the same bone.
Assumptions regarding the pathogenesis of bone erosions based on this study should be made with care. However, the findings could be in line with the hypothesis that synovitis of a joint leads to inflammation in the bone, seen on MRI as BME, which can lead to erosive changes of the bone. This could explain why synovitis is associated with erosive progression, but loses this association when adjusted for the presence of BME. Erosive progression was seldom in the absence of BME. It might be interesting to further study the presence of BME as a prognostic factor. BME could play a role in the selection of treatment, leading to more personalized medicine.

Because MRI is a very sensitive imaging modality, MRI could also play a role in the assessment disease activity in RA-patients. There is no gold standard to measure disease activity. Previously, radiographic progression and clinical decision making were used as surrogate measures to develop clinical composite scores to assess disease activity. In **Chapter 6** we used data obtained in patients diagnosed with RA that were included in the EAC to evaluate new disease activity scores that were derived by correlation to MRI findings. The new disease activity scores of Baker et al were derived using 2 different clinical trial populations.[20] In the first clinical trial population (GO-BEFORE) MRI-detected synovitis and BME were used to derive modified disease activity scores (M-DAS), this was done by using the regression coefficients of the independent predictors of MRI-synovitis. These predictors were selected from all commonly utilized components in the standard disease activity scores (DAS28-ESR, DAS28-CRP, SDAI and CDAI). The second clinical trial population (GO-FORWARD) was used to validate the M-DAS and to assess whether the M-DAS improved the prediction of radiographic progression. The M-DAS correlated stronger with MRI-detected synovitis than the standard disease activity scores (DAS28-ESR, DAS28-CRP, SDAI and CDAI). In addition, the M-DAS were stronger associated with radiographic progression within the first year. However, replication in the RA patients of the EAC did not show superiority of the different M-DAS over the standard scores (DAS28-ESR, DAS28-CRP, SDAI and CDAI) on the association with MRI-detected synovitis, MRI-detected BME, or radiographic progression association. Furthermore, similar to the findings in the study of Baker et al both the standard and modified scores correlated only

moderately to weakly with MRI-findings and predicted radiographic progression poorly. These findings are illustrative for the difficulty to assess the disease activity and relate different disease measures to each other. Another replication of this study in the French early arthritis cohort ESPOIR also didn't find a difference between M-DAS and DAS.[21] Nevertheless, the use of different study populations could also play a role here. Further research is needed to find out how MRI can be used to improve the assessment of disease activity.

In 193 healthy, symptom-free controls it had been shown that MRI-detected inflammation increases with age.[22] In **Chapter 7** we studied the effect of age on MRI-detected inflammation in all 589 early arthritis patients and in a subgroup of 229 that fulfilled the 2010 ACR/EULAR classification criteria at presentation.[23] Next, we assessed whether the effect of age differed from that in healthy controls. Lastly, we compared the anatomic locations that were most commonly affected in RA-patients presenting at different age categories.
Both in all early arthritis patients and only those presenting with RA the total MRI-inflammation score was higher in patients presenting at higher age. The effect of age at presentation on the total inflammation score in all early arthritis patients and in RA patients was similar to the effect of age found in symptom-free controls (3% increase per year). Although the age-effect was similar, the total MRI-inflammation score in all early arthritis patients and RA-patients was higher (respectively 2.6 and 3.7 times higher). Comparing the localization of inflammation in RA patients presenting at different age categories (<40 years, 40-60 years, and >60 years) showed that at higher age more locations were affected. However, the locations that were most frequently inflamed were similar in younger and older age (e.g. synovitis at MCP 2 or BME at the first row of carpal bones).
The findings of this study suggest that there is a general effect of age on MRI-inflammation that is not disease specific, i.e. the effect in arthritis patients is similar to that in symptom-free controls. In RA-patients presenting at different ages, the most frequently affected locations are similar. Interestingly, these locations were also most frequently affected in symptom-free controls.[22] This study underlined the importance of taking age into account for the interpretation of MRI-findings.

The value of MRI in the early diagnosis of RA was assessed in **Chapter 4** and **Chapter 5**. Because early initiation of treatment increases the chance on a better disease outcome, the early identification of patients with RA is important.[24–26] The 2010 ACR/EULAR classification criteria for RA were developed to improve earlier identification of RA-patients.[23] Still, part of the RA-patients cannot be classified at first presentation. Up to 25% of patients presenting with UA (arthritis that cannot be classified by the 2010 RA criteria or by another disease) go on to develop RA.[27,28] MRI could be of value to identify these patients early.
In **Chapter 4** the addition of MRI-findings in the wrist and finger joints to the 2010-criteria, as described by Tamai et al, was evaluated.[29] Tamai et al studied whether MRI findings improved the diagnostic performance of the 2010 classification criteria in 166 early arthritis patients that did not fulfill the 1987 classification criteria for RA or criteria for other rheumatologic diseases (1987-UA).[30] Two outcome measures were used for the development of RA during follow up: fulfilling the 1987 criteria within one year and initiation of DMARDs

within one year. The test characteristics of only fulfilling the 2010-criteria were compared to the test characteristics of either fulfilling the 2010-criteria or the presence of specific MRI-findings. Their most interesting finding was the addition of the presence of BME to the 2010-criteria, this showed an increase in sensitivity, negative predictive value (NPV), and accuracy. However, the specificity and positive predictive value (PPV) decreased. In our study the addition of MRI-detected BME to the 2010-criteria also led to an increase in the sensitivity and NPV. However, this was at the cost of a considerable decrease in the specificity and PPV; overall this did not lead to an increase in accuracy. Our results suggested that using MRI for diagnostic purpose, with this method in patients not fulfilling the 1987 criteria is of limited diagnostic value. Moreover, with the used methods the results strongly depends on the prevalence of disease in the study population and how false positive and false negative tests are weighted.

In **Chapter 5** we chose a different approach; we aimed to assess the value of MRI to identify those arthritis patients that present with UA, but go on to develop RA. Furthermore, we hypothesized that false-positive MRI-findings would be reduced by using the MRI findings of the study in symptom-free controls as a reference to define an abnormal MRI. In symptom-free controls low grade MRI-detected inflammation was quite prevalent, especially at higher age and at preferential locations.[22] We used two outcome measures in this study: fulfillment of the 1987 criteria and initiation of DMARD-therapy within the first year of follow-up.
First, we explored the discriminative value of MRI by comparing patients that presented with classifiable RA to symptom-free controls and patients that presented with other arthritides. We observed that patients that presented with other arthritides than RA also had high MRI-inflammation scores. Compared to BME and synovitis, tenosynovitis discriminated best between patients presenting with classifiable RA and symptom-free controls and patients presenting with other arthritides.
We continued by assessing the value of an abnormal MRI in the clinical relevant group of patients: the 201 that presented with UA. Within one year of follow up, 29 (14%) UA patients fulfilled the 1987 RA criteria (RA development) and 75 (37%) were prescribed DMARD-therapy. An abnormal MRI for any inflammation was associated with RA development. Of the individual inflammation types synovitis and tenosynovitis were associated with RA-development, but BME was not. UA patients frequently had a positive MRI for several types of inflammation. Only an abnormal MRI for tenosynovitis was associated with RA development independent of the other types of inflammation. Also after adjusting for age, swollen joint count, and CRP an abnormal MRI for tenosynovitis was significantly associated with RA-development. Assessing the test characteristics of an abnormal MRI for tenosynovitis revealed a PPV of 25% and a NPV of 95%. Thus, whereas 95% of UA-patients with a normal MRI for tenosynovitis did not develop RA, only 25% of UA-patients with an abnormal MRI for tenosynovitis developed RA.
Lastly, we also assessed the test characteristics of an abnormal MRI for tenosynovitis in UA patients presenting with mono-, oligo- or polyarthritis. Because the differential diagnosis can differ in these patients the value of MRI might also differ. This revealed that an abnormal MRI for tenosynovitis was only associated with RA-development in patients with oligoarthritis. Of the 83 UA-patients that presented with oligoarthritis, 15 (18%) developed RA. In these patients the PPV

of MRI was 36% and the NPV was 98%. The outcome DMARD-initiation revealed similar findings.
The findings of this study suggest that MRI can contribute to the early identification of UA-patients that go on to develop RA. Although an abnormal MRI did not yield high risk for RA development, the absence of MRI-detected inflammation made progression to RA highly unlikely.

Discussion and future prospects

Diagnostic use of MRI
With the knowledge that early aggressive treatment in RA prevents joint damage and increases the chance of achieving remission on the one hand and overtreatment of patients on the other hand there is a need for adequate diagnostic tools in patients presenting with recent onset arthritis. Using MRI to depict inflammation in the hand and foot, we observed that tenosynovitis was of most diagnostic value (compared to synovitis and BME). Still, when using MRI as a diagnostic test to identify which UA-patients develop RA, the posttest odds only slightly improved compared to the pretest odds. The biggest improvement was seen in UA-patients that presented with 2-4 swollen joints. MRI especially had a high negative predictive value, i.e. in the absence of MRI-inflammation in the MCP, wrist and MTP joints RA-development in UA patients was rare.
Remarkably, BME was not associated with the development of RA in early UA patients. This finding might seem contradictory to previous studies and even our own study which show clear associations between BME and the development of erosions in RA patients.[7–10,12] The development of articular bone erosions is a hallmark of RA and histological studies have shown that BME lesions in RA patients reflect inflammatory infiltrates in the subcortical bone, which could be involved with the development of erosions.[31–33] However, UA patients that go on to develop RA are a different group of patients than patients with (longstanding) RA. These patients are in an early phase of disease in which erosive joint damage is not (yet) present and BME might be less specific for the development of erosions and thus less specific for RA-development. The MRI-finding of BME can indeed be caused by inflammatory causes, but can also occur with other underlying processes (trauma, degenerative, vascular, infectious, neoplastic, metabolic and neurological)[34] and has also been found in symptom-free controls.[22,35] Similarly to BME, the presence of MRI-erosions was also of limited value to discriminate between UA patients that developed RA and those that did not.
Tenosynovitis has a high sensitivity for the development of RA in UA-patients and interestingly it has also been shown that tenosynovitis is most predictive for development of clinically apparent arthritis in patients presenting with clinically suspected arthralgia.[36] However, although it has been shown that tenosynovitis is seldom in healthy controls,[22] the specificity of tenosynovitis is limited. We and others have shown that tenosynovitis is not only prevalent in RA patients, but also in other inflammatory arthritides.[37]
To truly evaluate a diagnostic test, the clinical consequences need to be taken into account. Does the test improve certainty of the presence or absence of a disease? Does it change the decision to initiate treatment or refrain from treatment? Does it lead to earlier initiation of DMARD-therapy than without the test? And most

importantly: does the use of the test improve disease outcome? The results of our study showed that MRI changed the post-test odds most in UA-patients that presented with 2-4 clinically inflamed joints. Still, our study was an observatory study. A diagnostic trial should be performed to study whether adding MRI to the diagnostic process truly improves the outcome for patients presenting with UA and of course whether this is cost-efficient.
For diagnostic purposes in clinical practice, US might be a more interesting imaging modality than MRI. It is cheaper than MRI, has logistical advantages over MRI and can also be used to detect synovitis and tenosynovitis. However, it is more operator dependent. The interpretation of US examinations performed by others and the comparison US examinations at multiple time points can be more complicated than when using MRI. Previous studies have shown that the sensitivity of ultrasound to detect inflammation is only slightly lower than contrast enhanced MRI.[6,38,39] Future research is needed to assess the diagnostic value of ultrasound in this setting, because similar questions as for the value of MRI also hold up for US.

Monitoring disease activity
With the improvement in treatment of RA, the current goal is not only to prevent joint damage but also to achieve (DMARD-free) clinical remission. To achieve this treat-to-target strategy is recommended: the adaption of therapy based on regular assessment of clinical disease activity.[40] Although there is no gold standard to measure disease activity in RA, several composite measures have been developed as surrogate measures for disease activity. Most of these composite scores contain a measure for the number of clinically involved joints. Because MRI and ultrasound are more sensitive to detect inflammation than physical examination it has been suggested that the use of these imaging modalities could be beneficial in the monitoring of disease activity.[41] Several studies have shown that ultrasound detected inflammation in patients in remission predicts clinical flare and progressive radiographic damage.[42–45] Moreover, it has been proposed that aiming for imaging remission in addition to composite measures might lead to better outcome of patients.
Recently the results of the TASER and ARTIC studies have been published, these studies compared a clinically monitored step-up treat-to-target strategy with a combination of clinically and ultrasound monitored step-up treat-to-target strategy in early arthritis patients.[46,47] Both studies showed a good response to treatment in both study arms, but the addition of US to disease monitoring did not lead to an improvement in outcome measures, despite more aggressive treatment in the ultrasound monitored group. This suggests that intensifying treatment based on inflammatory findings on ultrasound in the absence of clinical inflammation does not lead to better disease outcome and might even lead to overtreatment.
Whereas the additional value of imaging in step-up treat-to-target seems to be of limited help, some studies have shown that the presence of joint inflammation on imaging has predictive value to identify RA patients in clinical remission that are not able to stop or taper biological treatment without getting a relapse.[48,49] With more patients achieving clinical remission, side-effects and high costs of some DMARD-treatments, proper identification of patients who are able to taper or stop DMARD-therapy is a very interesting research topic.
Still, it is important to keep in mind that RA is an autoimmune disease and clinically detected joint inflammation or MRI-detected inflammatory findings are symptoms.

Although it is important to treat joint inflammation, the absence of joint inflammation (both clinical and subclinical) does not guarantee that the autoimmune processes related to RA are contained. Ideally (the disruption in) the immune system would be followed up and DMARD-therapy would be aimed to achieve new homeostasis of the immune system. By increasing our understanding of the pathogenesis of RA, new ways to observe disease activity might arise.

Other prospects for future research

We did some interesting MRI findings which could be explored further and might help in our understanding of RA.

First of all, the anatomical locations most often showing inflammatory features on MRI in symptom free controls were similar to those in arthritis patients (e.g. synovitis at the second and third MC-joint). These locations also had higher inflammation scores (i.e. more severe inflammation) most often. It could support the hypothesis that mechanical strains play a role in starting an inflammatory response in RA. A possible explanation for why RA patients develop joint complaints and healthy individuals do not could be that in healthy individuals this response is regulated and asymptomatic, where in RA this might lead to symptomatic joint inflammation and possibly even to joint destruction. A better understanding of why some joints/tendons/bones are more often involved in RA than others might help further unravel the pathophysiology of RA.

Secondly, inflammation at the extensor tendons at the MCP joints was an interesting finding because these tendons lack a synovial sheath at the level of the MCP joints and thus the ability to develop tenosynovitis. The inflammatory findings around these tendons could be explained by periarthritis or secondary to the swelling of the underlying joint. However, in some patients the extensor tendons were also involved without underlying synovitis. Interestingly, this was only seen in patients with RA, this could be some rest inflammation or inflammatory involvement of tendons. Further exploration could give more insight in some of the pathophysiological process of RA.

Furthermore, most studies have focused on erosions, bone marrow edema, synovitis and tenosynovitis in the wrist and MCP-joints; the features that are represented in the RA MRI scoring system (RAMRIS), the only validated scoring system.[4,5] The RAMRIS has recently been updated and a recent systematic literature review has shown its validity for the use in clinical trials.[50,51] However, RAMRIS has some disadvantages and there are other joints, MRI findings and MRI techniques that can be studied (more extensively).

RAMRIS is a semi-quantitative scoring method and has its limitations. For example, with RAMRIS the location of an erosion within a specific bone is not assessed (e.g. in the central portion of the joint, the margins of the joint or away from the joint). Also, the assessment of inflammatory findings with RAMRIS could be hampered by a floor effect: there is a broad range of inflammatory findings that fall under a RAMRIS score of “1” (e.g. BME in 1% of the scored bone is scored similarly as BME in 32% of the bone) and scores of “2” or higher are uncommon. It is likely that in clinical practice MR scans would be assessed more qualitatively, leading to different interpretation of the MR findings. However, it is hard to use qualitative assessment of MRIs for research purposes because of limitations to the comparability and reproducibility of these findings.

Most studies have assessed the wrist and MCP joints; we have also studied the MTP joints. Recently there have also been studies in which whole-body MRI has been performed.[52,53] It is not yet clear which joints should be scanned, which, of course, also greatly depends for which purpose an MRI would be performed (e.g. diagnostic, disease monitoring, etc.). MRI findings like enthesitis, cartilage damage and bursitis were not scored in our studies and also other have only limitedly studied these findings. Furthermore, there also are MRI techniques that are not included in the RAMRIS which could prove useful for the assessment of inflammatory arthritides (e.g. dynamic contrast enhancement and diffusion weighted imaging). Finally, there are now also (semi)-automated quantification methods which can assist in the interpretation of MRI findings and can help assess the value of MRI.[54,55]

The knowledge on the use of MRI could be improved by using MRI to study clinically inflamed joints in RA patients and study the changes of these joints over time. This might learn us more on which findings on MRI are associated with inflammatory arthritis or, more specific, RA. The additive value of MRI to other (clinical) findings in the field of RA probably lies in the detection of inflammation or aspects of inflammation that cannot be detected otherwise. However, these inflammatory findings can be subtle, especially in early phases of disease, and differentiating which findings are related to RA and which findings are related to other processes (i.e. trauma, overuse, degeneration) can be problematic. Inflammatory MRI findings are also seen in symptom-free controls.[22] We have already shown that including the findings in symptom-free controls improves the specificity of MRI. Studying the MRI findings in clinically inflamed joints could further improve the interpretation of MRI findings.
Additionally, the application of MRI in early arthritis patients could also improve if we succeed in further unraveling the pathophysiology of RA. When the disease processes of RA are better understood, it might be possible to perform MR examination focused on more specific findings.

In conclusion, over the past few decades the field of rheumatology has changed dramatically. With 1) the growing realization of the importance of early treatment of RA patients and thus of the importance of early recognition of RA patients and 2) new treatment options which can prevent joint destruction in most patients and make low disease activity and even remission realistic goals, there is a necessity for adequate tools to assess inflammatory and structural changes caused by RA. The studies in this thesis have assessed MRI findings in the important study population of patients with new onset arthritis and have shown that MRI provides valuable information.
Still, the additional value of MRI to other findings should be sorted out further. Future studies will need to show whether the information added by MRI is useful in clinical practice. It will have to be shown whether the information of MRI in trials is relevant in addition to the other observed parameters. It is not yet clear how MRI findings should influence clinical decision making and whether this would lead to better disease outcome for patients. For example, (the extent of) inflammation is detected more sensitively by MRI than physical examination; yet, it is not clear how this additional information should affect treatment. More aggressive treatment could lead to improved disease outcome, but also to overtreatment. In clinical trials,

MRI might help to detect smaller differences between treatment arms, but it should be kept in mind that these small differences might not be clinically relevant.

References

1 Egsmose EL et al. *Clin Rheumatol* 2015;34:1187–94.
2 Nikolaus S et al. *Arthritis Care Res* 2013;65:1128–46.
3 Hewlett S et al. *Rheumatology* 2011;50:1004–6.
4 Østergaard M et al. *J Rheumatol* 2003;30:1385–6.
5 Haavardsholm EA et al. *Ann Rheum Dis* 2007;66:1216–20.
6 Wakefield RJ et al. *Arthritis Care Res* 2007;57:1158–1164.
7 McQueen FM et al. *Arthritis Rheum* 2003;48:1814–27.
8 Haavardsholm EA et al. *Ann Rheum Dis* 2008;67:794–800.
9 Palosaari K et al. *Rheumatology* 2006;45:1542–8.
10 Hetland ML et al. *Ann Rheum Dis* 2009;68:384–90.
11 Mundwiler ML et al. *Arthritis Res Ther* 2009;11:R94.
12 Gandjbakhch F et al. *Ann Rheum Dis* 2011;70:2159–62.
13 Lisbona MP et al. *J Rheumatol* Published Online First: 1 July 2014.
14 Bøyesen P et al. *Ann Rheum Dis* 2011;70:176–9.
15 Døhn UM et al. *Ann Rheum Dis* 2011;70:252–8.
16 Hetland ML et al. *Ann Rheum Dis* 2010;69:1789–95.
17 Conaghan PG et al. *Arthritis Rheum* 2003;48:64–71.
18 Bøyesen P et al. *Ann Rheum Dis* 2011;70:428–33.
19 Baker JF et al. *Ann Rheum Dis* Published Online First: 31 July 2013.
20 Baker JF et al. *Arthritis Rheumatol* 2014;66:794–802.
21 Couderc M et al. *Ann Rheum Dis* 2015;74:222–222.
22 Mangnus L et al. *Arthritis Rheumatol* 2016;68:2593–602.
23 Aletaha D et al. *Arthritis Rheum* 2010;62:2569–81.
24 Quinn MA et al. *Rheumatology* 2001;40:1211–20.
25 van der Linden MPM et al. *Arthritis Rheum* 2010;62:3537–46.
26 Combe B et al. *Ann Rheum Dis* 2007;66:34–45.
27 Krabben A et al. *Ann Rheum Dis* 2012;71:238–41.
28 Krabben A et al. *Rheumatology* 2013;52:1265–70.
29 Tamai M et al. *Ann Rheum Dis* 2014;73:2219–20.
30 Arnett FC et al. *Arthritis Rheum* 1988;31:315–24.
31 Dalbeth N et al. *Ann Rheum Dis* 2009;68:279–82.
32 McQueen FM et al. *Ann Rheum Dis* 2007;66:1581–7.
33 Jimenez-Boj E et al. *Arthritis Rheum* 2007;56:1118–24.
34 Patel S. *Rheumatology* 2014;53:785–92.
35 Olech E et al. *J Rheumatol* 2010;37:265–74.
36 van Steenbergen HW et al. *Ann Rheum Dis* 2015;:annrheumdis-2015-208138.
37 Boutry N et al. *Eur J Radiol* 2009;71:217–24.
38 Navalho M et al. *J Rheumatol* 2013;40:1282–92.
39 Backhaus M et al. *Arthritis Rheum* 1999;42:1232–1245.
40 Smolen JS et al. *Ann Rheum Dis* 2016;75:3–15.
41 Colebatch AN et al. *Ann Rheum Dis* Published Online First: 21 March 2013.
42 Saleem B et al. *Ann Rheum Dis* 2012;71:1316–21.
43 Peluso G et al. *Ann Rheum Dis* 2011;70:172–5.
44 Scirè CA et al. *Rheumatology* 2009;48:1092–7.
45 Brown AK et al. *Arthritis Rheum* 2008;58:2958–67.
46 Haavardsholm EA et al. *BMJ* 2016;354:i4205.
47 Dale J et al. *Ann Rheum Dis* 2016;:annrheumdis-2015-208941.
48 Naredo E et al. *Rheumatology* 2015;54:1408–14.

49 Iwamoto T et al. *Arthritis Care Res* 2014;66:1576–81.
50 Woodworth TG et al. *Rheumatology* 2017;56:1177–88.
51 Østergaard M et al. *J Rheumatol* 2017;44:1706–12.
52 Axelsen MB et al. *Scand J Rheumatol* 2017;46:253–62.
53 Axelsen MB et al. *Rheumatology* Published Online First: 3 January 2014.
54 Aizenberg E et al. *Magn Reson Med* Published Online First: 7 May 2017.
55 Rastogi A et al. *Eur J Radiol* 2013;82:1286–91.

Nederlandse Samenvatting

10

Reumatoïde artritis
Reumatoïde artritis (RA) is een chronische ontstekingsziekte die zich vooral kenmerkt door de ontsteking van de gewrichten (artritis). Deze ontstekingen worden veroorzaakt door een auto-immuun reactie en betreffen meestal de kleine gewrichten van de handen en voeten. Ongeveer 0,5-1% van de westerse bevolking heeft RA en vrouwen hebben 3 keer vaker RA dan mannen.

Naast de ontsteking van de kleine gewrichten van de handen en voeten kunnen ook andere, grotere, gewrichten ontstoken zijn. Vaak hebben patiënten ook last van stijfheid van de gewrichten in de ochtend en moeheid. Wanneer RA niet (adequaat) wordt behandeld leidt de chronische ontsteking tot blijvende, invaliderende beschadigingen aan de gewrichten. RA geeft een verhoogd risico op hart- en vaatziekten en kan zich ook in de longen presenteren. De presentatie en het beloop van RA varieert sterk tussen patiënten, waarschijnlijk is RA niet één ziekte, maar een verzameling van verschillende ziekteprocessen met een min of meer gelijke klinische presentatie.

In de laatste decennia zijn er grote verbeteringen in de behandeling van RA geweest. We weten nu dat vroege behandeling met zogenoemde “disease modifying anti-rheumatic drugs” (DMARDs) de prognose van RA sterk verbeterd: patiënten krijgen minder vaak blijvende schade aan de gewrichten en steeds meer patiënten kunnen in remissie treden (hebben geen klachten meer). Sommige patiënten kunnen zelfs volledig stoppen met medicatie.

Voor het vroeg starten met behandeling is het ook nodig om RA-patiënten in een zo vroeg mogelijk stadium te identificeren. Daarom is het diagnosticeren (voor behandeling) en classificeren (voor wetenschappelijk onderzoek) de afgelopen jaren ook veranderd.

Diagnose en classificatie
Er bestaat niet één test of een combinatie van testen die als gouden standaard gebruikt kan worden voor de diagnose RA. In de kliniek stelt een reumatoloog de diagnose op basis van het combineren van anamnese, lichamelijk onderzoek, bloedtests en beeldvormend onderzoek (bijvoorbeeld röntgenfoto’s en echo). Voor wetenschappelijk onderzoek wordt gebruik gemaakt van classificatie criteria om relatief homogene patiëntenpopulaties te krijgen zodat de resultaten van verschillende studies beter te vergelijken zijn.

De eerste classificatie criteria voor RA stammen uit 1956 en werden in 1958 gereviseerd. Door nieuwe inzichten in RA en in andere vormen van artritis werden in 1987 nieuwe criteria ontwikkeld. De 1987 criteria waren er vooral op gericht om meer specifiek te zijn dan de voorgaande criteria, zodat minder patiënten met andere diagnoses voldeden aan de classificatie criteria voor RA. Ze waren er vooral op gericht om patiënten met gevorderde RA te kunnen onderscheiden van andere reumatologische diagnoses en hier worden ze nog steeds voor gebruikt.

Een nadeel van de 1987 criteria is echter dat, hoewel patiënten met gevorderde RA goed geclassificeerd worden, de identificatie van patiënten in vroege stadia van RA te wensen over laat. Met het ontdekken van de voordelen op het beloop van RA van vroege behandeling was er ook meer vraag naar verder klinische onderzoeken

naar de vroege stadia van RA. Daarvoor waren er ook classificatie criteria nodig die patiënten in een eerder ziekte stadium konden classificeren. Hiervoor zijn de 2010 ACR/EULAR classificatie criteria ontwikkeld. De 1987 en 2010 criteria worden vergeleken in tabel 1. De belangrijkste veranderingen waren dat bevindingen die vooral voorkomen bij gevorderde ziekte zoals reuma nodules of radiografische erosies geen deel meer uitmaakten van de criteria en dat acute fase eiwitten (CRP en BSE) en ACPA (anti-gecitrullineerde eiwit antilichamen) werden toegevoegd.

Tabel 1 Vergelijking van de 1987 en 2010 classificatie criteria

1987 ACR criteria	2010 ACR/EULAR criteria	Punten
● Ochtend stijfheid >1 uur	● Gewricht betrokkenheid	
● Artritis in ≥3 gewrichten	◦ 1 groot gewricht	0
● Artritis van de hand gewrichten	◦ 2-10 grote gewrichten	1
● Symmetrische artritis	◦ 1-3 kleine gewrichten	2
● Reuma nodules	◦ 4-10 kleine gewrichten	3
● Serum reumafactor	◦ >10 kleine gewrichten	5
● Radiografische veranderingen	● Serologische tests	
	◦ Negatieve RF en ACPA	0
	◦ Zwak positieve RF/ACPA	2
	◦ Sterk positieve RF/ACPA	3
	● Acute fase eiwitten	
	◦ Normale CRP en BSE	0
	◦ Verhoogde CRP/BSE	1
	● Symptoomduur	
	◦ <6 weken	0
	◦ ≥6 weken	1
Voor de classificatie van RA moeten tenminste 4 van de 7 criteria positief zijn.	Tenminste 6 van de 10 punten zijn nodig voor classificatie van RA	

RF, Reuma Factor. ACPA, anti-citrullinated peptide antibodies. CRP, c-reactive protein. BSE, bezinkingsnelheid erytrocyten. Populatie waarop de 2010 criteria toe te passen zijn: patienten met tenminste 1 gewricht met klinische synovitis waarbij de synovitis niet door een andere ziekte beter verklaard wordt.

Studies hebben inderdaad laten zien dat de 2010 criteria een hogere sensitiviteit hebben (d.w.z. meer patiënten met RA zo classificeren) dan de 1987 criteria ten koste van een kleine afname van de specificiteit (d.w.z. iets vaker patiënten die geen RA hebben toch zo classificeren). Dat doel lijkt dus gerealiseerd. Het is wel belangrijk om in gedachten te houden dat met het gebruik van nieuwe classificatie criteria andere studiepopulaties worden geselecteerd. In de 2010 criteria wordt bijvoorbeeld de aanwezigheid van met RA geassocieerde antilichamen (RF en ACPA) zwaarder meegewogen; dit maakt het verschil tussen RA met aanwezigheid van die auto-antilichamen (seropositief) en RA zonder aanwezigheid van die auto-antilichamen (seronegatief) groter. Terwijl seropositieve patiënten met RA kunnen worden geclassificeerd met artritis van 1 klein gewricht, hebben seronegatieve patiënten artritis in meer dan 10 gewrichten nodig om geclassificeerd te worden als RA.

Er is ook een groep patiënten met inflammatoire artritis die bij de eerste presentatie niet als RA of een andere vorm van artritis kan worden geclassificeerd; deze patiënten hebben ongedifferentieerde artritis (UA). Hoewel bij de meerderheid van deze patiënten de artritis spontaan verdwijnt, ontwikkelen sommige van deze patiënten alsnog RA tijdens de follow-up. Dit maakt UA-patiënten een interessante populatie om te bestuderen, want idealiter zou je de UA-patiënten die doorgaan om RA te ontwikkelen zo vroeg mogelijk identificeren.

Het gebruik van de classificatie criteria uit 1987 of 2010 resulteert ook in een andere populatie van patiënten met UA (hierna 1987UA en 2010UA). Eén van de belangrijke verschillen is de aanwezigheid van ACPA bij deze patiënten. Studies in 1987UA hebben aangetoond dat ACPA een sterke voorspeller is voor het ontwikkelen van RA. Omdat ACPA daarna is opgenomen in de 2010 criteria en daarin zwaar wordt gewogen, bestaat 2010UA voornamelijk uit seronegatieve patiënten. Ook andere voorspellende factoren voor RA-ontwikkeling in 1987UA zijn minder discriminerend voor patiënten met 2010UA. Toch laten studies zien dat tot 25% van de 2010UA-patiënten nog steeds RA ontwikkelen tijdens de follow-up. Een deel van het werk in dit proefschrift richtte zich op het gebruik van MRI (magnetic resonance imaging) om deze patiënten te identificeren.

Beeldvorming in RA

Beeldvorming van de gewrichten wordt in RA voor verschillende doeleinden gebruikt: diagnose, prognose, ziektemonitoring en als uitkomstmaat in trials. Hoewel röntgenfoto's van de handen en voeten nog steeds de meest gebruikte beeldvormingsmodaliteit zijn op het gebied van RA, worden MRI en echografie (US) in toenemende mate gebruikt. Röntgenfoto's tonen structurele schade aan botten, inclusief erosies en vernauwing van gewrichtsruimte. MRI en US visualiseren echter ook inflammatoire veranderingen van de weke delen zoals synovitis en tenosynovitis, daarnaast zijn ze ook sensitiever voor de detectie van kleine erosies.

Met de erkenning van het belang van vroege initiatie van DMARD-behandeling, en dus ook vroegtijdige identificatie van RA-patiënten en de aanwezigheid van weinig of geen radiologische schade in vroege ziektestadia, zijn MRI en US als beeldvormingsmodaliteiten van toenemend belang. Bovendien is erosieve gewrichtsdestructie bij RA aanzienlijk verminderd vanwege de verbeteringen in de behandeling van RA. In klinische onderzoeken is er tegenwoordig zeer weinig toename van radiografische gewrichtsschade in de verschillende behandelingsarmen, waardoor het gebruik van de uitkomstmaat toename van gewrichtsschade wordt gehinderd. Daarom zijn beeldvormingsmodaliteiten die ontstekingslaesies kunnen weergeven, in plaats van de gevolgen van inflammatoire laesies, op de lange termijn interessant voor de vergelijking van behandelingsarmen in klinische onderzoeken.

Een uniek kenmerk van MRI is het vermogen om beenmergveranderingen te detecteren die worden beschreven als beenmergoedeem (BME) of osteïtis. In gevorderde RA is histologisch aangetoond dat vet in het beenmerg wordt vervangen door inflammatoir cellulair infiltraat in BME-laesies op MRI. Inflammatoire veranderingen op MRI zoals synovitis, tenosynovitis, maar vooral

BME, zijn in eerder onderzoek sterke voorspellers gebleken voor de ontwikkeling van erosieve schade.

Hoewel het gebruik van MRI en US al wordt aanbevolen voor de eerder genoemde doeleinden door de imagingrichtlijnen van EULAR, is het bewijsniveau voor deze aanbevelingen laag. Verder onderzoek is nodig om onze kennis over het gebruik van MRI bij inflammatoire artritis te vergroten.

Samenvatting van dit proefschrift

Dit proefschrift richt zich hoofdzakelijk op het verder uitzoeken van de waarde van MRI bij vroege (reumatoïde) artritis. Alle studies in dit proefschrift zijn uitgevoerd in de populatie van de Leiden Early Arthritis Clinic (EAC). Dit observationele cohort is in 1993 gestart toen men zich toenemend bewust werd van het belang om zo vroeg mogelijk te starten met DMARDS bij patiënten met reumatoïde artritis. De EAC bevat achtereenvolgens geïncludeerde patiënten die zich presenteren op de reumatologie-polikliniek van het Leids Universitair Medisch Centrum met artritis bevestigd door lichamelijk onderzoek en daarbij een symptoomduur van minder dan 2 jaar hebben. Deze polikliniek reumatologie voorziet een gebied van> 400.000 inwoners. Bij deze patiënten werden vragenlijsten, uitgebreide klinische informatie en serummonsters verzameld. Het cohort heeft geen behandelingsprotocol en patiënten krijgen reguliere reumatologische zorg. Patiënten worden gevolgd tot ontslag uit de polikliniek. Sinds 2010 werd er ook een MRI van de hand- en voetgewrichten uitgevoerd bij alle daarvoor instemmende patiënten. MRI ontsteking en erosieve schade worden beoordeeld met behulp van het RA MRI-scoresysteem (RAMRIS).

De oorspronkelijke RAMRIS-methode bevatte scores voor erosies, BME en synovitis. Later werd een aanvullend scoresysteem voor tenosynovitis ter hoogte van de pols- en MCP-gewrichten ontwikkeld. De prevalentie, onderscheidende waarde en prognostische waarde van MRI-gedetecteerde tenosynovitis bij vroege artritis was echter nog maar beperkt bestudeerd. In Hoofdstuk 2 hebben we tenosynovitis bij de pols- en MCP-gewrichten bestudeerd met deze methode. Wij onderzochten de prevalentie van tenosynovitis bij de presentatie op de polikliniek van 178 patiënten van de EAC. Verder onderzochten we of patiënten met RA vaker tenosynovitis hadden dan patiënten met andere vormen van artritis en of de aanwezigheid van tenosynovitis is geassocieerd met een slechtere prognose van RA. We hebben niet alleen gekeken of een patiënt wel of geen tenosynovitis had, maar ook de afzonderlijke peesgroepen geanalyseerd.
De prevalentie van MRI-gedetecteerde tenosynovitis was hoog (65% van de patiënten met vroege artritis had tenosynovitis). De prevalentie was significant hoger bij RA-patiënten dan bij andere patiënten met vroege artritis (75% versus 59%). De meeste afzonderlijk gescoorde peeslocaties waren echter niet specifiek voor RA, maar ook aangedaan bij patiënten met andere artritiden. Pezen die wel vaker waren betrokken bij RA-patiënten waren de flexor-pezen bij MCP 5, de extensorpezen bij MCP 2 en 4, en de pezen in de pols extensor compartimenten I, II en IV. Desondanks was de discriminerende waarde van tenosynovitis op deze specifieke locaties beperkt: de specificiteit was hoog (> 90%), maar de sensitiviteit was laag (<20%). Dit betekent dat de meerderheid van RA-patiënten op een van

deze locaties geen tenosynovitis had, maar dat tenosynovitis op deze locaties bij niet RA patiënten niet vaak voorkwam.
Synovitis (ontsteking van het gewrichtskapsel) naast de aangedane pezen werd waargenomen bij 70-100% van de aangedane pezen. De meerderheid van de locaties van tenosynovitis die geassocieerd zijn met RA, waren ook geassocieerd met RA gecorrigeerd voor lokale synovitis. De associatie tussen tenosynovitis en RA lijkt dus niet te worden veroorzaakt door onderliggende synovitis. De ernst van tenosynovitis was niet significant geassocieerd met ernstigere RA (radiografische toename van erosieve gewrichtsschade of ACPA-positiviteit). Een interessante observatie bij RA was dat hoewel de extensor pezen geen synoviale peesschede op het niveau van de MCP-gewrichten hebben, we wel ontsteking rond deze pezen vonden. Een eerdere studie noemde dit periextensor ontsteking. Het zou moeilijk kunnen zijn om synovitis en periextensor ontsteking te onderscheiden en de vraag kan worden gesteld of periextensor ontsteking eigenlijk geen synovitis van het onderliggende gewicht betreft. Interessant is dat we periextensor-ontsteking ook vonden zonder synovitis van het specifieke MCP-gewricht. Hoewel de aantallen klein waren, vonden we dit alleen bij patiënten met RA. Het kan een effect van RA op ander weefsel suggereren dan het tenosynovium, bijvoorbeeld een direct effect op de pezen.
Deze studie heeft aangetoond dat tenosynovitis een veelvoorkomende bevinding is bij vroege (reumatoïde) artritis en dat de aanwezigheid van MRI-gedetecteerde tenosynovitis enig diagnostisch nut kan hebben. We waren niet in staat om een relatie aan te tonen met meer radiografische gewrichtsschade. Toch kan tenosynovitis pijn, bewegingsverlies en (grip) zwakte veroorzaken wat toch invaliderend kan zijn voor patiënten. Daarom kan de aanwezigheid van MRI gedetecteerde tenosynovitis van belang zijn in vroege RA.

MRI heeft potentieel ook een prototypische waarde. Het was al aangetoond dat patiënten met hoge BME- en synovitisscores meer erosieve schade ontwikkelen tijdens de follow-up. Tot nu toe werd dit echter bestudeerd op patiëntniveau, d.w.z. de totale BME-, synovitis- en erosiescores van een patiënt. In Hoofdstuk 3 hebben we BME- en synovitis-laesies op botniveau beoordeeld, d.w.z. we hebben per bot beoordeeld of BME in dat bot of synovitis rond dat bot (lokale synovitis) aanwezig was en of er tijdens de follow-up toename was van erosieve schade in dat bot. We gebruikten patiënten waarbij MRI op drie tijdstippen was uitgevoerd: bij inclusie in de EAC, na 4 maanden en na 12 maanden follow-up. Dit stelde ons in staat om niet alleen de associatie tussen baseline-bevindingen en toename van erosieve schade te bestuderen, maar ook om het beloop van BME- en synovitis-laesies te bestuderen en of het beloop van deze laesies geassocieerd was met toename van erosieve schade.
De aanwezigheid van BME en de aanwezigheid van lokale synovitis bij aanvang waren geassocieerd met toename van erosieve schade in dat bot na follow-up in univariabele analyses. Omdat BME en synovitis vaak tegelijkertijd voorkomen, zijn gestratificeerde analyses en multivariabele “generalized estimating equation” (GEE) analyses uitgevoerd. In deze analyses was BME bij baseline nog steeds geassocieerd met toename van erosieve schade, maar bij correctie voor BME was de associatie van synovitis met toename van erosieve schade zwakker of verloren. De follow-up MRI’s toonden aan dat het beloop van BME en lokale synovitis vergelijkbaar waren: deze waren meestal op elk tijdstip aanwezig of afwezig.

Laesies verschenen of verdwenen minder vaak en slechts zeer zelden verdwenen laesies en verschenen later weer (of andersom). Dit suggereert dat deze inflammatoire laesies niet veel fluctueren. Om het verband tussen het beloop van BME en synovitis en toename van erosieve schade te bepalen, werd het aantal MRI-scans waarbij BME of lokale synovitis aanwezig was bepaald voor elk bot (als BME bijvoorbeeld op alle 3 MRI-tijdspunten in een bepaald bot aanwezig was, was de belasting van BME voor dit bot 3). GEE-analyses toonden aan dat zowel hogere BME belasting, als synovitis belasting univariabel geassocieerd waren met erosieve progressie. Multivariabele analyses met zowel BME als synovitis belasting toonden echter aan dat alleen BME onafhankelijk geassocieerd was met toename van erosieve schade. Aanwezigheid van BME op 2 of 3 tijdpunten was sterk geassocieerd met toename van erosieve schade (OR> 55). Hoewel het absolute aantal botten met BME op alle drie de tijdstippen met toename van erosieve schade niet erg hoog was (15%), toonde deze studie aan dat persisterende BME voorspellend is voor toename van erosieve schade in hetzelfde bot.
Hoewel je niet zo maar assumpties met betrekking tot de pathogenese van boterosies op basis van dit onderzoek alleen kan maken, zouden de bevindingen echter kunnen passen bij de hypothese dat synovitis van een gewricht leidt tot ontsteking van het bot, te zien op MRI als BME, wat weer kan leiden tot erosieve botveranderingen. Dit zou kunnen verklaren waarom synovitis univariabel geassocieerd is met toename van erosieve schade, maar deze associatie verliest wanneer gecorrigeerd wordt voor de aanwezigheid van BME. Toename van erosieve schade kwam zelden voor bij afwezigheid van BME. Het zou interessant zijn om de aanwezigheid van BME als een prognostische factor verder te bestuderen. BME zou een rol kunnen spelen bij de keuze van behandeling. Dit zou kunnen leiden tot meer gepersonaliseerde geneeskunde.

De waarde van MRI bij de diagnostisering van RA werd beoordeeld in Hoofdstuk 4 en Hoofdstuk 5. Omdat een vroege start van de behandeling de kans op een betere ziekte-uitkomst vergroot, is vroege identificatie van patiënten met RA belangrijk. De 2010 ACR/EULAR classificatie criteria voor RA zijn ontwikkeld om de vroege identificatie van RA-patiënten te verbeteren. Toch kan een deel van de RA-patiënten niet worden geclassificeerd bij de eerste presentatie. Tot 25% van de patiënten met UA (artritis die niet kan worden geclassificeerd volgens de 2010 RA classificatie criteria of als een andere ziekte) gaan RA ontwikkelen. MRI zou van waarde kunnen zijn om deze patiënten vroegtijdig te identificeren.
In Hoofdstuk 4 werd de toevoeging van MRI bevindingen in de pols- en MCP-gewrichten aan de 2010-criteria, zoals beschreven door Tamai et al., gerepliceerd en geëvalueerd. Tamai et al. onderzochten of MRI-bevindingen de diagnostische prestaties van de classificatiecriteria uit 2010 verbeterden bij 166 patiënten met vroege artritis die niet voldeden aan de 1987 classificatie criteria voor RA of criteria voor andere reumatologische aandoeningen (1987UA). Twee uitkomstmaten werden gebruikt voor het ontwikkelen van RA tijdens de follow-up: binnen een jaar aan de criteria van 1987 voldoen en de start van behandeling met DMARDs binnen een jaar. De testkarakteristieken van alleen voldoen aan de 2010-criteria werden vergeleken met de testkarakteristieken van of voldoen aan de 2010-criteria of de aanwezigheid van specifieke MRI-bevindingen. Hun meest interessante bevinding was de toevoeging van de aanwezigheid van BME aan de 2010-criteria, dit toonde een toename in sensitiviteit, negatief voorspellende

waarde (NPV) en nauwkeurigheid. Hierbij was er echter wel een afname van de specificiteit en positief voorspellende waarde (PPV). In onze studie leidde de toevoeging van MRI-gedetecteerde BME aan de 2010-criteria ook tot een toename van de sensitiviteit en NPV. Dit ging echter gepaard met een aanzienlijke afname van de specificiteit en PPV. Over het algemeen leidde dit niet tot een toename van de nauwkeurigheid. Onze resultaten suggereerden dat het gebruik van MRI voor diagnostische doeleinden bij patiënten die niet voldoen aan de 1987 classificatie criteria, met deze methode, van beperkte diagnostische waarde is. Bovendien zijn met de gebruikte methoden de resultaten sterk afhankelijk van de prevalentie van RA in de studiepopulatie en is het vooral belangrijk hoe foutpositieve en foutnegatieve testresultaten worden gewogen.

In hoofdstuk 5 kozen we voor een andere benadering: we wilden de waarde van MRI bepalen om die artritis patiënten te identificeren die zich presenteren met UA, maar later RA ontwikkelen. Eerdere studies hadden enkele belangrijke beperkingen die de klinische toepassing belemmerden. De meeste studies werden uitgevoerd vóór de introductie van de 2010-criteria in relatief kleine populaties met selectiecriteria die ertoe hadden geleid dat een onderzoekspopulatie niet leek op de dagelijkse praktijk. Daarom voerden wij ons onderzoek uit in de grote onderzoekspopulatie van de EAC met behulp van alle achtereenvolgens geïncludeerde patiënten (n = 589). Eerdere studies hebben aangetoond dat het moeilijk is om verschillende vormen van artritis te onderscheiden met MRI. Wij hadden de hypothese dat foutpositieve MRI-bevindingen zouden kunnen worden verminderd door de MRI-bevindingen in symptoomvrije controles als een referentie te gebruiken voor het definiëren van een abnormale MRI. Bij symptoomvrije controles kwam in een eerdere studie van onze groep namelijk ook vrij veel laaggradige ontsteking op MRI voor; vooral bij oudere proefpersonen en op bepaalde (voorkeurs)locaties. We gebruikten in dit onderzoek twee uitkomstmaten: binnen het eerste jaar van de follow-up voldoen aan de criteria uit 1987 en initiatie van DMARD-therapie binnen het eerste jaar.
Eerst hebben we de discriminerende waarde van MRI onderzocht door patiënten die zich presenteerden met classificeerbare RA te vergelijken met symptoomvrije controles en patiënten die zich met andere artritiden presenteerden. We observeerden dat patiënten met andere artritiden dan RA ook hoge MRI-inflammatiescores hadden. In vergelijking met BME en synovitis onderscheidde tenosynovitis het beste tussen patiënten die zich presenteerden met classificeerbare RA en symptoomvrije controles en patiënten die zich presenteerden met andere artritiden.
Daarna onderzochten we de waarde van een abnormale MRI in de klinisch relevante groep patiënten: de 201 die zich presenteerden met UA. Na 1 jaar follow-up voldeden 29 (14%) UA patiënten aan de RA-criteria van 1987 (RA-ontwikkeling) en bij 75 (37%) UA patiënten werd gestart met een behandeling met DMARDs. Een abnormale MRI op basis van welk type ontsteking dan ook was geassocieerd met RA-ontwikkeling. Van de individuele ontstekingstypen waren synovitis en tenosynovitis geassocieerd met RA-ontwikkeling, maar BME niet. UA-patiënten hadden vaak een abnormale MRI voor verschillende soorten ontstekingen. Alleen een abnormale MRI voor tenosynovitis werd geassocieerd met de ontwikkeling van RA, gecorrigeerd voor andere typen van ontsteking. Ook na correctie voor leeftijd, het aantal gezwollen gewrichten en CRP was een

abnormale MRI voor tenosynovitis significant geassocieerd met RA-ontwikkeling. Het beoordelen van de testkarakteristieken van een abnormale MRI voor tenosynovitis liet een PPV van 25% en een NPV van 95% zien. Dus 95% van de UA-patiënten met een normale MRI voor tenosynovitis ontwikkelt geen RA en 25% van de UA-patiënten met een abnormale MRI voor tenosynovitis ontwikkelde wel RA.

Als laatste hebben we ook de testkarakteristieken onderzocht van een abnormale MRI voor tenosynovitis bij UA-patiënten met mono-, oligo- of polyartritis (1, 2-4 of >4 ontstoken gewrichten). Omdat de differentiaal diagnose bij deze patiënten kan verschillen, kan de waarde van MRI hier ook verschillen. Dit toonde aan dat een abnormale MRI voor tenosynovitis alleen geassocieerd was met RA-ontwikkeling bij patiënten met oligoartritis. Van de 83 UA-patiënten die zich met oligoartritis presenteerden, ontwikkelde 15 (18%) RA. Bij deze patiënten was de PPV van MRI 36% en de NPV 98%.
De uitkomst DMARD-initiatie onthulde soortgelijke bevindingen.
De bevindingen van deze studie suggereren dat MRI kan bijdragen aan de vroege identificatie van UA-patiënten die RA ontwikkelen. Hoewel een abnormale MRI geen super hoog risico op de ontwikkeling van RA geeft, was bij afwezigheid van inflammatie op MRI ontwikkeling van RA hoogst onwaarschijnlijk.

Omdat MRI een zeer gevoelige beeldvormende modaliteit is, zou MRI ook een rol kunnen spelen bij de beoordeling van de ziekteactiviteit bij RA-patiënten.
Er is geen gouden standaard om ziekteactiviteit te meten. Eerder werden radiografische toename van erosieve schade en klinische besluitvorming gebruikt als surrogaatmaten om klinische samengestelde scores te ontwikkelen voor de bepaling van ziekteactiviteit en hierop de therapie aan te passen. In Hoofdstuk 6 gebruikten we de gegevens van patiënten die bij inclusie in de EAC al RA hadden om nieuwe ziekteactiviteitscores te repliceren die waren ontwikkeld door correlatie met MRI-bevindingen.
De nieuwe ziekteactiviteitscores van Baker et al. werden ontwikkeld met behulp van onderzoekspopulaties uit 2 verschillende klinische onderzoeken. In de eerste populatie (GO-BEFORE studie) werden MRI-gedetecteerde synovitis en BME gebruikt om gemodificeerde ziekteactiviteit scores (M-DAS) te ontwikkelen. Dit werd gedaan door de regressiecoëfficiënten van de gecorrigeerde voorspellers van MRI-synovitis te gebruiken. Deze voorspellers werden geselecteerd uit andere veel gebruikte componenten van andere ziekteactiviteitscores (de DAS28-ESR, DAS28-CRP, SDAI en CDAI). De tweede populatie (GO-FORWARD studie) werd gebruikt om de M-DAS te valideren en om te beoordelen of de M-DAS de predictie van toename van erosieve schade verbeterde. De M-DAS correleerden sterker met MRI-gedetecteerde synovitis dan de andere veel gebruikte ziekteactiviteitscores (DAS28-ESR, DAS28-CRP, SDAI en CDAI). Verder waren de M-DAS ook sterker geassocieerd met toename van erosieve schade in het eerste jaar. Echter, replicatie in de RA patiënten van de EAC toonde geen sterkere associatie van de verschillende M-DAS ten opzichte van de standaardscores (DAS28-ESR, DAS28-CRP, SDAI en CDAI) met MRI-gedetecteerde synovitis, MRI-gedetecteerde BME of radiografische progressie. Verder correleerden zowel de standaard als de gemodificeerde ziekteactiviteitscores slechts matig tot zwak met MRI-bevindingen en voorspelde ze radiografische progressie slecht, vergelijkbaar met de

bevindingen in de studie van Baker et al. Deze bevindingen zijn illustratief voor de moeilijkheid om de ziekteactiviteit te bepalen en verschillende ziektemetingen met elkaar te vergelijken. Een andere replicatie van deze studie in het Franse vroege artritiscohort ESPOIR vond ook geen verschil tussen M-DAS en DAS. Niettemin zou ook het gebruik van verschillende studiepopulaties hier een rol kunnen spelen. Verder onderzoek is nodig om te achterhalen of MRI kan worden gebruikt om de beoordeling van ziekteactiviteit te verbeteren (en eventuele therapeutische keuzes op te baseren).

In 193 gezonde, symptoomvrije controles hadden we eerder aangetoond dat de MRI-gedetecteerde ontsteking toeneemt met de leeftijd. In Hoofdstuk 7 bestudeerden we het effect van leeftijd op MRI-gedetecteerde ontsteking bij alle 589 vroege artritispatiënten en in een subgroep van 229 die bij presentatie voldeden aan de 2010 ACR/EULAR-classificatiecriteria. Vervolgens hebben we onderzocht of het effect van leeftijd op MRI inflammatie bij artritis patiënten anders was dan dat bij gezonde controles. Tenslotte hebben we de meest aangedane anatomische locaties vergeleken bij RA patiënten in verschillende leeftijdscategorieën.
Zowel bij alle patiënten met vroege artritis als bij alleen patiënten met RA was de totale MRI-ontstekingsscore hoger bij patiënten die zich op hogere leeftijd presenteerden. Het effect van leeftijd bij presentatie op de totale ontstekingsscore bij alle patiënten met vroege artritis en bij RA-patiënten was vergelijkbaar met het effect van leeftijd gevonden bij symptoomvrije controles (3% toename per jaar). Hoewel het leeftijdseffect vergelijkbaar was, was de totale MRI-ontstekingsscore bij alle vroege artritispatiënten en RA-patiënten hoger (respectievelijk 2,6 en 3,7 keer hoger). Een vergelijking van de anatomische lokalisaties van inflammatie bij RA-patiënten die zich presenteerde in verschillende leeftijdscategorieën (<40 jaar, 40-60 jaar en> 60 jaar) toonde dat op hogere leeftijd meer verschillende locaties waren aangedaan. De locaties die het vaakst ontstoken waren, waren echter vergelijkbaar op jongere en oudere leeftijd (bijvoorbeeld synovitis op MCP 2 of BME in de eerste rij carpalia).
De bevindingen van deze studie suggereren dat er een algemeen effect van leeftijd op MRI-ontsteking is dat niet specifiek voor ziekte is, d.w.z. het effect bij patiënten met artritis is vergelijkbaar met dat bij symptoomvrije controles. Verder waren de meest betrokken anatomische locaties vergelijkbaar bij RA-patiënten die zich presenteren op verschillende leeftijden. Interessant is dat deze locaties ook het vaakst zijn aangetast bij symptoomvrije controles. Deze studie onderstreepte het belang van het meenemen van de leeftijd bij de interpretatie van MRI bevindingen.

De EAC is gestart in 1993. Bij de start van de EAC, maar ook in de jaren na de start, werd het belang van vroege behandeling van vroege artritispatiënten extra onder de aandacht gebracht door campagnes en richtlijnen in de eerste lijn (zoals huisartsen). In Hoofdstuk 8 hebben we onderzocht of RA-patiënten inderdaad met een kortere symptoomduur werden geïdentificeerd in de loop van het bestaan van de EAC en of dit gepaard ging met minder ernstige RA bij de eerste presentatie op de polikliniek. We zagen dat patiënten eerder werden geïdentificeerd en dat dit gepaard ging met minder ernstige ontsteking (minder aangetaste gewrichten en lagere waarden van acute fase eiwitten in het bloed). De ernst van de door de patiënt gemelde uitkomstmaten (“patient reported outcome measures”, PROMs:

vermoeidheid, pijn, ochtendstijfheid en ziekteactiviteit) namen in dezelfde periode echter geleidelijk toe. Deze bevindingen lijken paradoxaal: waarom neemt de ernst van PROMs toe, terwijl patiënten zich met minder ontsteking presenteren? Blijkbaar zijn deze PROMs multidimensionaal: er zijn niet alleen inflammatoire, maar ook psychosociale factoren bij betrokken. Dit wordt ook door andere onderzoeken aangetoond: er is bijvoorbeeld aangetoond dat vermoeidheid slechts beperkt verklaard wordt door inflammatoire variabelen, maar sterk gecorreleerd is met variabelen zoals pijn. Vermoedelijk weerspiegelt de toename van de ernst van PROMs een algemene toename van de maatschappelijke sociale druk, waarbij kleinere gezondheidsproblemen ervaren kunnen worden als meer invaliderend. Ook kunnen hogere gezondheidsverwachtingen leiden tot een verschuiving van het referentiekader van patiënten bij het rapporteren van PROM's. De bevindingen in deze studie brengen mogelijke moeilijkheden aan het licht bij het vergelijken van (verschillen in) PROMs tussen verschillende studiepopulaties; niet alleen bij het vergelijken van populaties uit verschillende landen, maar ook bij het vergelijken van populaties uit dezelfde landen maar uit verschillende tijdsperioden.

Conclusies

In de afgelopen decennia is de reumatologie drastisch veranderd. Met 1) het groeiende besef van het belang van vroege behandeling van RA patiënten en dus ook het belang van de vroege identificatie van RA patiënten en 2) nieuwe behandelopties die gewrichtsdestructie bij de meeste patiënten kan voorkomen en welke lage ziekte activiteit en zelfs remissie realistische behandeldoelen maken, zijn er instrumenten nodig die inflammatoire en structurele veranderingen veroorzaakt door RA adequaat kunnen beoordelen. De studies in dit proefschrift hebben de MRI-bevindingen in de belangrijke onderzoekspopulatie van patiënten met vroege artritis onderzocht en hebben aangetoond dat MRI waardevolle informatie verschaft

Toch moet de toegevoegde waarde van MRI ten opzichte van andere instrumenten verder worden onderzocht. Toekomstige studies zullen moeten aantonen of de informatie toegevoegd door MRI nuttig is in de klinische praktijk. Er zal moeten worden aangetoond of MRI bevindingen relevant zijn naast (of in plaats van) andere bevindingen. Het is nu nog niet duidelijk hoe MRI-bevindingen de klinische besluitvorming zouden moeten beïnvloeden en of dit zou leiden tot een betere ziekte-uitkomst voor patiënten. MRI detecteert (de mate van) ontsteking bijvoorbeeld gevoeliger dan lichamelijk onderzoek; toch is het nog niet duidelijk hoe deze aanvullende informatie de behandeling zou moeten beïnvloeden. Meer agressieve behandeling kan leiden tot een beter ziekte beloop, maar ook tot overbehandeling zonder een beter beloop. In klinische onderzoeken kan MRI helpen om kleinere verschillen tussen behandelingsarmen te detecteren, maar er moet rekening mee worden gehouden dat deze kleine verschillen mogelijk niet klinisch relevant zijn.

Curriculum vitae

De auteur van dit proefschrift werd geboren op 26 december 1987 in Leiden. In 2006 behaalde hij zijn gymnasium diploma aan het Christelijk Gymnasium Utrecht en startte hij zijn studie geneeskunde aan Universiteit Leiden. Tijdens zijn studie werkte hij als onderzoeksstudent bij de kinder maag-darm-lever ziekte in het LUMC. Tijdens zijn wetenschapsstage deed hij onderzoek naar “alternative open reading frames on the insulin mRNA”. Zijn keuze co-schappen liep hij op de afdelingen radiologie van het MCH Westeinde en het LUMC. Zijn semi-artsstage liep hij op de afdeling kindergeneeskunde van het Diaconessenhuis. In juni 2013 behaalde hij het artsexamen.

In juli 2013 startte hij met zijn promotieonderzoek op de afdeling Reumatologie in het LUMC onder begeleiding van Prof. Dr. A.H.M. van der Helm-van Mil, Prof. Dr. T.W.J. Huizinga en Dr. Reijnierse (afdeling radiologie). Het onderzoek richtte zich op het gebruik van MRI bij vroege artritis patiënten, de resultaten van dit onderzoek staan beschreven in dit proefschrift.

Sinds augustus 2016 is hij in opleiding tot radioloog in het HagaZiekenhuis.

List of publications

Mangnus, L., van Steenbergen, H.W., Nieuwenhuis, W.P., Reijnierse, M., van der Helm-van Mil, A.H.M., 2018. Moderate use of alcohol is associated with lower levels of C reactive protein but not with less severe joint inflammation: a cross-sectional study in early RA and healthy volunteers. RMD Open 4, e000577. https://doi.org/10.1136/rmdopen-2017-000577

Boeters, D.M., Nieuwenhuis, W.P., van Steenbergen, H.W., Reijnierse, M., Landewe, R.B.M., van der Helm-van Mil, A.H.M., 2018. Are MRI-detected erosions specific for RA? A large explorative cross-sectional study. Ann Rheum Dis 77, 861–868. https://doi.org/10.1136/annrheumdis-2017-212252

Aizenberg, E., Roex, E.A.H., Nieuwenhuis, W.P., Mangnus, L., van der Helm-van Mil, A.H.M., Reijnierse, M., Bloem, J.L., Lelieveldt, B.P.F., Stoel, B.C., 2018. Automatic quantification of bone marrow edema on MRI of the wrist in patients with early arthritis: A feasibility study. Magn Reson Med 79, 1127–1134. https://doi.org/10.1002/mrm.26712

Nieuwenhuis, W.P., van Steenbergen, H.W., Mangnus, L., Newsum, E.C., Bloem, J.L., Huizinga, T.W.J., le Cessie, S., Reijnierse, M., van der Helm-van Mil, A.H.M., 2017. Evaluation of the diagnostic accuracy of hand and foot MRI for early Rheumatoid Arthritis. Rheumatology (Oxford) 56, 1367–1377. https://doi.org/10.1093/rheumatology/kex167

Boer, A.C., Burgers, L.E., Mangnus, L., Ten Brinck, R.M., Nieuwenhuis, W.P., van Steenbergen, H.W., Reijnierse, M., Huizinga, T.W.J., van der Helm van Mil, A.H.M., 2017. Using a reference when defining an abnormal MRI reduces false-positive MRI results-a longitudinal study in two cohorts at risk for rheumatoid arthritis. Rheumatology (Oxford) 56, 1700–1706. https://doi.org/10.1093/rheumatology/kex235

Nieuwenhuis, W.P., van Steenbergen, H.W., Stomp, W., Stijnen, T., Huizinga, T.W.J., Bloem, J.L., van der Heijde, D., Reijnierse, M., van der Helm-van Mil, A.H.M., 2016c. The Course of Bone Marrow Edema in Early Undifferentiated Arthritis and Rheumatoid Arthritis: A Longitudinal Magnetic Resonance Imaging Study at Bone Level. Arthritis Rheumatol 68, 1080–1088. https://doi.org/10.1002/art.39550

Nieuwenhuis, W.P., Mangnus, L., van Steenbergen, H.W., Newsum, E.C., Huizinga, T.W.J., Reijnierse, M., van der Helm-van Mil, A.H.M., 2016b. Older age is associated with more MRI-detected inflammation in hand and foot joints. Rheumatology (Oxford) 55, 2212–2219. https://doi.org/10.1093/rheumatology/kew335

Nieuwenhuis, W.P., de Wit, M.P., Boonen, A., van der Helm-van Mil, A.H., 2016a. Changes in the clinical presentation of patients with rheumatoid arthritis from the early 1990s to the years 2010: earlier identification but more severe patient reported outcomes. Ann Rheum Dis 75, 2054–2056. https://doi.org/10.1136/annrheumdis-2016-209949

Mangnus, L., Nieuwenhuis, W.P., van Steenbergen, H.W., Huizinga, T.W.J., Reijnierse, M., van der Helm-van Mil, A.H.M., 2016. Body mass index and extent of MRI-detected inflammation: opposite effects in rheumatoid arthritis versus other arthritides and asymptomatic persons. Arthritis Res Ther 18, 245. https://doi.org/10.1186/s13075-016-1146-3

Burgers, L.E., Nieuwenhuis, W.P., van Steenbergen, H.W., Newsum, E.C., Huizinga, T.W.J., Reijnierse, M., le Cessie, S., van der Helm-van Mil, A.H.M., 2016. Magnetic resonance imaging-detected inflammation is associated with functional disability in early arthritis-results of a cross-sectional study. Rheumatology (Oxford) 55, 2167–2175. https://doi.org/10.1093/rheumatology/kew334

Boeters, D.M., Nieuwenhuis, W.P., Verheul, M.K., Newsum, E.C., Reijnierse, M., Toes, R.E.M., Trouw, L.A., van der Helm-van Mil, A.H.M., 2016. MRI-detected osteitis is not associated with the presence or level of ACPA alone, but with the combined presence of ACPA and RF. Arthritis Res Ther 18, 179. https://doi.org/10.1186/s13075-016-1076-0

Nieuwenhuis, W.P., Reijnierse, M., van der Helm-van Mil, A.H., 2015b. Does adding the presence of MRI detected bone marrow oedema improve the accuracy of the 2010 EULAR/ACR criteria for rheumatoid arthritis? Ann Rheum Dis 74, e29. https://doi.org/10.1136/annrheumdis-2014-206930

Nieuwenhuis, W.P., Krabben, A., Stomp, W., Huizinga, T.W.J., van der Heijde, D., Bloem, J.L., van der Helm-van Mil, A.H.M., Reijnierse, M., 2015a. Evaluation of magnetic resonance imaging-detected tenosynovitis in the hand and wrist in early arthritis. Arthritis Rheumatol 67, 869–876. https://doi.org/10.1002/art.39000

Nieuwenhuis, W.P., van Nies, J.A.B., Reijnierse, M., van der Heijde, D., van der Helm-Van Mil, A.H.M., 2014. Is the modified disease activity score superior to the disease activity score in early arthritis and rheumatoid arthritis? Comment on the article by Baker et al. Arthritis Rheumatol 66, 3244–3245. https://doi.org/10.1002/art.38807

Nieuwenhuis, W.P., Kneepkens, C.M.F., Houwen, R.H.J., de Beer, H.J.A., Mulder, C.J., Mearin, M.L., 2010. [Guideline 'Coeliac disease and dermatitis herpetiformis']. Ned Tijdschr Geneeskd 154, A1904.

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