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The forefoot in early rheumatoid arthritis: Anatomy, imaging and clinical aspects

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Chapter 2

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*Validity of the Rheumatoid Arthritis
Magnetic Resonance Imaging Score applied
to the forefeet using the OMERACT Filter:
a systematic literature review*

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Abstract

Objective: Magnetic Resonance Imaging(MRI) depicts inflammation and structural damage in Rheumatoid Arthritis(RA). The validity of MRI-scoring of wrist- and metacarpophalangeal-joints according to the RA MRI score(RAMRIS) has been demonstrated. The Outcomes in Rheumatology Clinical Trials(OMERACT) RAMRIS Working Group recently called for validation of the RAMRIS of the metatarsophalangeal(MTP)-joints. Therefore, a systematic literature review was performed to test if the RAMRIS applied to the MTP-joints meets the OMERACT Filter of Truth, Discrimination and Feasibility.

Methods: Medical literature databases up to January 2018 were systematically reviewed for studies reporting on RAMRIS applied to MRI of the MTP-joints in RA. To be included, an article had to contain at least one MRI-feature (synovitis, bone marrow edema (BME), tenosynovitis, erosion, joint space narrowing (JSN)) and one item from the OMERACT Filter: Truth (face, content and construct validity), Discrimination (test-retest reliability, ability to discriminate in trials, longitudinal construct validity, and thresholds of meaning) and Feasibility.

Results: Of the 749 retrieved studies, 13 were included, of which 9 provided data on construct validity, 4 on discrimination (3 on reliability, 2 on longitudinal construct validity and 1 on ability to discriminate in trials) and none on feasibility. Construct validity was suggested for BME and erosions, but lacking for synovitis, tenosynovitis and JSN. Data for discrimination remain to be developed for all outcomes.

Conclusion: According to the OMERACT Filter, the validity of the RAMRIS of the forefeet is insufficient in different aspects. A research agenda was determined.

Introduction

In rheumatoid arthritis (RA), conventional radiographs are traditionally used to assess structural damage as an outcome measure for the efficacy of treatment in trials. However, radiographs do not assess disease activity, and with improving treatment strategies structural damage has become less common.(1) Therefore, in recent years magnetic resonance imaging (MRI) is increasingly used in studies, as it detects damage with greater sensitivity than radiography, and in addition provides information about joint inflammation.

As part of The Outcomes in Rheumatology Clinical Trials (OMERACT), an RA MRI Working Group was set up that developed an RA MRI scoring system (RAMRIS) to standardise MRI-scoring for research-purposes.(2) This working group prioritised the wrist and metacarpophalangeal-(MCP)-joints due to their frequent involvement in RA and the large amount of MRI data on these joints.(2) However, studies in early RA have revealed MRI findings to be as prevalent in the metatarsophalangeal-(MTP)-joints as in the MCPs and wrists.(3-5) In addition, radiographic studies have shown that erosive change occurs more commonly in the feet than in the hands, and also earlier.(6-8) The RAMRIS has not been described for the MTPs by the working group. There seems to be a paradox between the notion that the feet are commonly affected in RA, and the priority given to MRI studies of hands over feet. The MRI in arthritis working group has recognized this, as their recently published updated recommendations call for validation of the existing RAMRIS in other joints than the hands, such as the MTPs.(9)

The OMERACT-group has developed a Filter that provides guidelines for the development and validation of outcome measures for use in clinical trials.(10-12) This systematic literature review set out to assess whether the existing RAMRIS, when applied to the MTP-joints in RA patients, meets the OMERACT Filter 2.1 of Truth, Discrimination and Feasibility. More specifically it was aimed to answer the question if there is currently enough evidence to conclude that applying the RAMRIS to MRI-scoring of the MTP-joints is a valid outcome measure in the assessment of joint inflammation and structural damage in RA, and subsequently to identify a research agenda for OMERACT criteria that still require studying for the MTP-joints.

Methods

Identification of studies

In cooperation with a medical librarian (JWS), a systematic literature search was performed to obtain all manuscripts reporting on studies that perform MRI of the MTP-joints in RA patients. Medical literature databases (PubMed, Embase, Web of Science, COCHRANE, Emcare, Academic Search Premier and ScienceDirect) were searched up to January 2018, using all variations of the following key words: 'foot', 'rheumatoid arthritis', and 'magnetic resonance imaging' (see Supplementary File for the exact search strings). Animal studies, reviews, abstracts and letters to the editor and in languages other than English were excluded from the search.

Inclusion criteria

All retrieved titles were screened, if deemed relevant abstracts were reviewed and finally full text articles were read by one reviewer (YJD). A random sample of 75 titles (10% of the titles identified by the literature search) was also reviewed by a second reviewer (AHM), resulting in a similar selection of titles. Therefore further extraction was done by a single reviewer. In case of uncertainties in the reviewing process by the single reviewer, these were discussed and solved by consensus with AHM. Retrieved studies that reported on diseases other than RA, that were not scored according to the RAMRIS applied to the foot, or that did not analyse data of the MTP-joints separately were excluded.

Studies reporting on the RAMRIS-measures in the MTP-joints in RA patients were evaluated and categorized according to the following OMERACT Filter items: Truth (subdivided into face, content and construct), Discrimination (subdivided into test-retest reliability, ability to discriminate in randomised controlled trials (RCTs)/ comparative studies, longitudinal construct validity and thresholds of meaning) and Feasibility, of which a detailed description is provided elsewhere.(10,12) Face and content validity of the Truth aspect were not part of the systematic literature search, as they are considered subjective measures and in the past have been assessed by consensus.(10) Hence the assumption was made that MRI captures the intended pathophysiologic feature for synovitis, bone marrow edema, erosions and joint space narrowing. For face and content validity of tenosynovitis on the other hand, anatomic atlases were explored to study whether the tendons have a sheath, and thus whether MRI is able to capture this intended pathophysiologic feature. Per OMERACT-item a PICO (participants, interventions, comparisons, outcomes) was made, this resulted in the following inclusion criteria per OMERACT-item:

- Construct validity was evaluated in studies comparing one or more RAMRIS-features to conventional radiography, ultrasound, computed tomography, histology, physical examination and symptoms. Both cross-sectional and longitudinal studies were included.
- Test-retest reliability was evaluated in studies comparing one or more RAMRIS-features in the same patients, either by the same performer over time or by different performers at the same time point. Both cross-sectional and longitudinal studies were included.
- Ability to discriminate in randomised controlled trials (RCT)/comparative studies (sensitivity to change) was evaluated in studies that measured change of one or more RAMRIS-features over time, either in randomised controlled trials (RCTs) if available, or from non-randomised studies or cohorts.
- Longitudinal construct validity (responsiveness) was evaluated in studies that measured change in one or more RAMRIS-features compared to change in other instruments like conventional radiography, ultrasound, computed tomography, histology, physical examination and symptoms. This differs from 'Construct validity' by the fact that it includes MRI at different time points rather than at one point in time.
- Thresholds of meaning was evaluated in studies that rate patients with a certain response to therapy (eg, minimum important difference or patient acceptable symptom state) as measured by a change in one or more RAMRIS-features.
- Feasibility was evaluated in studies describing the cost, patient and responder burden, equipment needs, sensitivity of content and overall ease of use of one or more RAMRIS-features. Both cross-sectional and longitudinal studies were included.

Studies that fulfilled the requirements for at least one of these items were included in this review.

After screening and including, next the articles were weighted by two reviewers (YJD and AHM) according to predefined criteria. First, to select MRI-data with high quality, the MRI had to be performed on ≥ 1.5 Tesla(T) MRI and to use gadolinium contrast-enhancement (CE) for synovitis and tenosynovitis. Second, the results were further weighted by the presence of replication studies. For the final conclusion, the validity of an OMERACT criterion was considered to be suggested if there were ≥ 2 studies with high-quality MRI-data of which $\geq 2/3^{\text{rd}}$ had a uniform

conclusion (meaning that the associations found in the studies point in the same direction of either a positive or a negative/absence of any association), this type of validity was categorized as '++' or '--' depending on the directionality of the effect. If only 1 article was available with regards to the type of validity, then according to the direction of the association it was categorized as '+' or '-', and the conclusion was drawn that limited data possibly suggested the validity to be present but more studies were needed for a more definite conclusion. If the high-quality MRI-articles were not uniform in their conclusion, or if articles were available but the MRI-data was not deemed to be of high quality, then it was categorized as '+/-', meaning data was available but insufficient for a conclusion. If there were no articles available at all then it was categorized as '?', meaning that there was no data available.

The MRI-features studied were synovitis, bone marrow edema (BME) and tenosynovitis as measures of inflammation, and erosions and joint space narrowing (JSN) as measures of structural damage. An updated RAMRIS has recently been published that now besides synovitis, BME and erosions also includes tenosynovitis and JSN.(9) Considering the short time interval between this systematic literature search and the publication of this updated RAMRIS definition, the systematic search included not only the updated RAMRIS, but also the old RAMRIS-definition for synovitis, BME and erosions, for tenosynovitis the score according to Haavardsholm et al, and for JSN the score that was proposed by Ostergaard.(2,13,14)

Statistical analyses

Due to the heterogeneity of the studies and the difference in outcome measures that were used it was not possible to perform a meta-analysis. Therefore, we chose to perform a descriptive review.

Results

Literature flow

After removing duplicate references, 749 unique references were identified (Figure 1). After reviewing 115 abstracts and 41 full-text articles, 13 articles were included in the review. Of the included studies, 9 fulfilled the inclusion criteria for evaluation of the construct aspect of Truth(15-23), 4 on Discrimination (of which 3 on test-retest reliability(5,24,25), 2 on longitudinal construct validity (5,25) and 1 on the ability to discriminate (26)), and none for Feasibility.

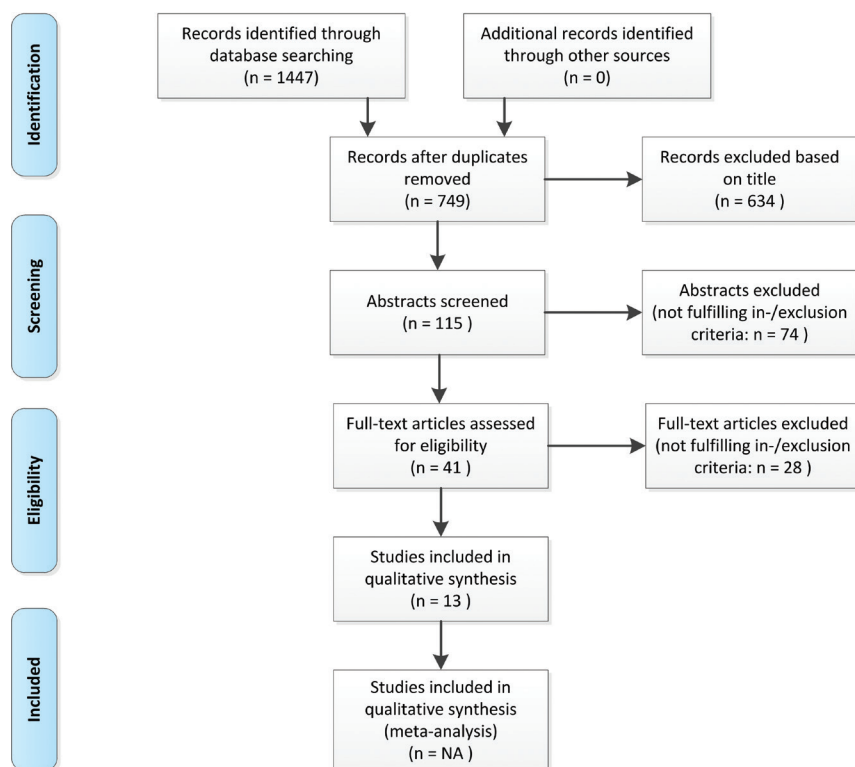


Figure 1. Overview of literature research. NA: not applicable.

Study characteristics

The 13 included studies are depicted in Tables 1–3, grouped according to the category of the OMERACT Filter that is addressed: Table 1 addresses articles on construct (aspect of Truth), Table 2 on test-retest reliability (aspect of Discrimination), and Table 3 on longitudinal construct validity and clinical trial discrimination (also aspects of Discrimination). These tables also depict the studies that fulfilled the inclusion criteria but were considered to have lower MRI-quality as described in the methods, and that thus were not part of the final conclusions drawn. Overall, the studies included a small number of patients, with a median number of 39. There were no randomised controlled trials, 9 studies were cross-sectional, and 4 longitudinal. MRI was most often performed on a 1.5T scanner (n=7).

The OMERACT Filter was applied to each MRI-measure separately. These results will be discussed per MRI-feature and are summarized in Table 4.

Synovitis

The RAMRIS defines MRI-detected synovitis as an area in the synovial compartment that shows above-normal post-gadolinium enhancement of a thickness greater than the width of the normal synovium.(2) As specified in the methods, face and content validity for MRI-detected synovitis were considered to be evident ('++' in Table 4).

Regarding construct validity, 3 studies were deemed to have MRI-data of high quality.(16,20,22) Synovitis was associated with plantar plate pathology, which represents a failure of the ligamentous system and displacement of the plantar plates of the forefoot leading to malformation.(22) When patients were followed for up to 24 months, MRI-detected synovitis was not associated with radiographic damage.(20) Correlations were found between MRI-detected synovitis in MTP-1 and a decrease in movement of the same joint.(16) Although this is a positive correlation, the outcome of decreased range of motion in MTP-1 is not typical for RA, but is affected in for instance osteoarthritis. Therefore this study was not considered in the final conclusion. Overall, 1 out of 2 studies found a positive association, therefore no uniform conclusion can be drawn on construct validity for MRI-detected synovitis ('+/-' in Table 4).

Test-retest reliability has been confirmed in one study that has shown excellent inter- and intrareader reliability for scoring synovitis ('+').(24) For longitudinal construct validity and the ability to discriminate in trials the two studies available did not meet the quality criteria for MRI ('+/-').(5,26) There were no data regarding thresholds of meaning or feasibility ('?').

Bone marrow edema

Also referred to as osteitis, BME is defined as a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content.(2) Again, face and content validity were deemed present ('++').

Construct validity was examined in six studies that met the quality criteria for the MRI-protocol.(15,18-22) MRI-detected BME was associated with clinical swelling, with pain and CRP and with plantar plate pathology.(18,19,22) When MRI-detected BME in MTP-joints was assessed histologically, it was associated with the severity of osteitis.(19) One study found an association for BME with the development of MRI-detected erosions a year later, and reported that erosions were unlikely to develop in the absence of BME.(20) Two studies did not find an association

of BME with Disease Activity Score of 28 joints (DAS-28), Health Assessment Questionnaire (HAQ) or walking disability.(15,21) Overall, 4 out of 6 studies found a positive association, therefore the evidence suggested construct validity to be present ('++').

Test-retest reliability has been investigated in one study that proved good inter- and intrareader reliability ('+').(24) For the ability of MRI to discriminate in trials and for longitudinal construct validity only studies of lower quality were available ('+/-'). (5,26) There was no data on thresholds of meaning or feasibility ('?').

Tenosynovitis

Tenosynovitis is defined as tendon sheath fluid, sheath thickening and enhancement after intravenous contrast injection seen in two consecutive axial slices.(13) Thus for face and content validity it is essential for the imaged tendon to have a sheath. The anatomy books that were consulted, gave contradicting information. Regarding the extensor tendons some portrayed a sheath to be absent, but other anatomic atlases did not portray the extensor tendons at the MTP-region. At the flexor tendons of the MTP-joints some resources portrayed a sheath to be present, some did not or in some cases the region of interest was not depicted.(27-30) Thus it remains unclear whether a sheath is present around the tendons, and if so what its' exact localization is. This is relevant, as it questions the nature of the inflammation observed. Thus, face and content validity of tenosynovitis at the level of MTP-joints was absent ('?'). In addition, no studies concerning tenosynovitis at the MTP-joints have been performed to date ('?' for all OMERACT-elements).

Erosions

MRI-detected bone erosions are defined as a sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics visible in two planes with a cortical break in at least one plane.(2) Face and content validity for erosions were assumed to be present ('++').

Five studies that met the criteria for the MRI-protocol were assessed for construct validity.(15,16,20-22) MRI-detected erosions were associated with plantar plate pathology and with decreased movement of MTP-1.(16,22).

Table 1. Summary of previous studies on 'Truth': Construct

Reference	N	Population	MRI-feature					MRI	CE	Method	Outcome
Clinical parameters											
			SYN	BME	TS	ERO	JSN				
Rondina, 2017 (21)	55	RA	+	+	-	+	-	15T	?	To evaluate the correlation between DAS28 and HAQ with MRI of the feet. MRI-protocol is not specified.	There is no correlation between synovitis, BME, erosions and DAS28 and HAQ. Patients in DAS28-remission still had inflammation on MRI.
Burgers, 2016 (15)	206	Early RA ^a	+	+	-	+	-	15T	-	To compare MRI-detected inflammation with functional disability.	There was no association with walking disability for synovitis (p=0.68), BME (0.83) or erosions (0.59).
Krabben, 2013 (18)	66	Early RA ^a	+	+	-	-	-	15T	-	To assess the concordance of inflammation on MRI with physical examination.	Synovitis and BME were associated with clinical swelling (OR2.0 and 1.4 respectively). Of all swollen MTP-joint 23% had MRI-detected synovitis and 21% BME.
Dubbeldam, 2013 (16)	25	RA	+	-	-	+	-	15T	+	To explore the relationship between clinical pathology and gait kinematics, in the forefoot MRI was performed of MTP-1.	An increase in erosion- and synovitis-score of MTP-1 correlated with less MTP-1 dorsiflexion at preswing (95%CI of -0.86 to -0.40 for erosions and -0.82 to -0.30 for synovitis).
Duer-Jensen, 2011 (11)	116	UA	-	+	-	+	-	0.6 and 1.0T	-	To determine the prognostic value of baseline MRI in UA patients that progress to RA.	BME is associated with future development of RA, as it is found in 14.8% of patients who develop RA, vs. 3.4% who did not. Erosions were present equally in both groups (18.5 vs 18.2%).

Histology											
McQueen, 2007 (19)	11	Longstanding RA	+	+	-	+	-	1.5T	+	To histologically examine resected bone samples from patients undergoing orthopaedic surgery. MRI was performed prior to resection.	MRI-detected BME was associated with histological presence and severity of osteitis, pain and CRP. Association of MRI-detected synovitis with histology was not examined.
Other imaging											
Siddle, 2012 (22)	24	RA	+	+	-	+	-	3T	+	To examine the relationship between plantar plate pathology on MRI and the RAMRIS of MTP 2-5.	Plantar plate pathology was associated with synovitis, BME and erosions, in MTP 4 and 5 in particular.
Mundwiler, 2009 (20)	50	Early RA	+	+	-	+	-	1.5T	+	To determine whether MRI BME progresses to MRI erosion, and whether MRI erosion progresses to erosions on radiographs, by MRI at baseline and after 6 months, and radiographs at baseline, and after 6, 12 and 24 months.	For BME PPV was 0.50 and NPV 0.99 to predict MRI-detected erosions after 1 year, for MRI-detected erosions PPV was 0.10 and NPV 0.995 to predict radiographic erosions after 1 year Synovitis was not associated with radiographic damage.
Szkudlarek, 2004 (23)	40	RA	+	-	-	+	-	1.0T	+	To compare MRI radiography, US and physical examination.	MRI and US are more sensitive than radiography and clinical examination: Erosions were detected by MRI in 20 patients, US in 26 and radiographs in 11. Synovitis by MRI in 31 patients, US in 36, and clinical examination 20.

^a Study performed in a cohort of unselected early arthritis patients, sensitivity analyses were performed on patients with RA according to the 2010 criteria; results of the sensitivity analyses are shown. MRI: magnetic resonance imaging; SYN: synovitis; BME: bone marrow edema; TS: tenosynovitis; ERO: erosions; JSN, joint space narrowing; CE: gadolinium contrast-enhancement; T: Tesla; RA: rheumatoid arthritis; UA: undifferentiated arthritis; MTP: metatarsophalangeal joint; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; US: ultrasound; CRP: C-reactive protein; PPV: positive predictive value. NPV: negative predictive value.

Table 2. Summary of previous studies on ‘Discrimination’: test-retest reliability

Reference	N	Population	MRI	CE	Reading	Reliability per MRI-feature					Conclusion
						SYN	BME	TS	ERO	JSN	Foot
Baan, 2015 (24)	29	RA	1.5T	+	Inter Intra	0.94 0.85	0.77 0.70	-	0.95 0.89	-	-
Elbjerg, 2005 (25)	35	RA	0.2T	?	SDD	-	-	-	1.36	-	-
Sewerin, 2014 (5)	26	Early RA	0.2T	+	SDD	1.29	0.87	-	0.87	-	1.81

MRI: magnetic resonance imaging; CE: gadolinium contrast-enhancement; SYN, synovitis; BME, bone marrow edema; TS, tenosynovitis; ERO, erosions; JSN, joint space narrowing; RA: rheumatoid arthritis; T: Tesla; Inter: inter-reader reliability; intra: intra-reader reliability (assessed by quadratic-weighted κ scores); MTP: metatarsophalangeal joint; MCP: metacarpophalangeal joint; SDD: smallest detectable difference; RAMRIS; RA MRI score.

Table 3. Summary of previous studies on 'Discrimination': longitudinal construct validity and clinical trial discrimination

Reference	N	Population	MRI-feature				MRI	CE	Method	Outcome	
Longitudinal construct validity											
Ejbjerg, 2005 (25)	35	RA	-	-	-	+	-	0.2T	?	To compare MRI-detected erosions to radiography with respect to sensitivity to change after one year.	Progression of erosions was detected by MRI of MTPs in 14 patients, as opposed to 9 by radiography of hands and feet. However, when changes greater than SDD were considered this was 4 and 5 patients respectively.
Sewerin, 2014 (5)	26	Early RA	+	+	-	+	-	0.2T	+	To study MRI prior and after 6 months of methotrexate monotherapy.	A decrease in synovitis and BME correlated to a change in DAS28, this correlation was not found for change in erosions.
Clinical trial discrimination											
Buchbender, 2013 (26)	39 early RA	RA and RA	+	+	-	+	-	0.2-3T	+	To assess patterns of inflammation and changes under therapy by MRI at baseline and after 8 months follow-up.	A change in BME was seen in 77% of MTP-joints, synovitis in 59%, erosions in 68%.

MRI: magnetic resonance imaging; CE: gadolinium contrast-enhancement; SYN, synovitis; BME, bone marrow edema; TS, tenosynovitis; ERO, erosions; JSN, joint space narrowing; RA, rheumatoid arthritis; T: Tesla; MTP: metatarsophalangeal joint; SDD: smallest detectable difference.

Table 4. Validity of MRI measures of the forefeet in their assessment of inflammation and structural damage in RA

A: Presence of type of validity given for every MRI-measure					
Type of validity	Inflammation			Structural damage	
	SYN	BME	TS	ERO	JSN
Truth					
Face	++	++	?	++	++
Content	++	++	?	++	++
Construct	+/-	++	?	++	?
Discrimination					
Test-retest reliability	+	+	?	+	?
Longitudinal construct validity	+/-	+/-	?	+/-	?
Clinical Trial Discrimination	+/-	+/-	?	+/-	?
Thresholds of meaning	?	?	?	?	?
Feasibility	?	?	?	?	?
B: Criteria handled for the interpretation of data					
Category	Definition		Criteria for conclusion		
++	Validity suggested for a positive association between MRI-measure and outcome		≥2 studies, ≥2/3rd have a uniform conclusion, and all of the following: MRI ≥1.5T CE for SYN and TS		
+	Validity possibly suggested for a positive association between MRI-measure and outcome		1 study with a positive association, and all of the following: MRI ≥1.5T CE for SYN and TS		
+/-	Insufficient data for a conclusion		Studies are available, but one of the following: No uniform conclusion MRI on <1.5T No CE for SYN and TS		

-	Validity possibly suggested for a negative association between MRI-measure and outcome	1 study with a negative association, and all of the following: MRI ≥1.5T CE for SYN and TS
- -	Validity suggested for a negative association between MRI-measure and outcome	≥2 studies, ≥2/3rd have a uniform conclusion, and all of the following: MRI ≥1.5T CE for SYN and TS
?	No data available	No studies available

*uniform conclusion: studies pointing in the same direction (either positive or negative) with regards to the association for the MRI-measurement with the outcome. SYN, synovitis; BME, bone marrow edema; TS, tenosynovitis; ERO, erosions; JSN, joint space narrowing; MRI: magnetic resonance imaging; T: Tesla; CE: gadolinium contrast-enhancement.

Also, MRI-detected erosions were associated with the development of radiographic erosions one year later, and in the absence of MRI-detected erosions radiographic erosions were unlikely to occur.(20) Two studies showed no correlation of MRI-detected erosions with DAS-28, HAQ or with walking disability.(15,21) Overall, 3 out of 5 studies found a positive association, therefore the evidence suggested construct validity to be present ('++').

With regards to Discrimination, reliability was excellent in one study showing high inter- and intrareader reliability ('+').(24) For longitudinal construct validity and ability to discriminate the found studies did not meet the criteria on the MRI-protocol ('+/-').(5,25,26) Thresholds of meaning and feasibility have not been studied ('?').

Joint space narrowing

JSN is defined as reduced joint space width compared to normal, as assessed in a slice perpendicular to the joint surface.(14) There is no reason to believe that face and content validity for JSN in the forefeet are not applicable ('++'). As of yet there are no studies on JSN in the forefeet in RA, therefore further validation is required ('?').

Discussion

This is the first SLR to assess the status of the development or application of the RAMRIS for the feet. From the limited evidence available, a foot RAMRIS-score would be useful to evaluate the impact of inflammation and damage in the feet on long term outcomes. Based on the results, as presented in table 4, construct validity is suggested for BME and erosions, but lacking for synovitis, tenosynovitis and JSN. Data for discrimination remain to be developed. A research agenda was formulated for the further evaluation of the validity of MRI of the forefoot, as presented in Table 5.

In contrast to previous OMERACT Filters, Filter 2.1 that was applied in this review does not distinguish between construct and criterion validity. Criterion validity assumes that the comparator instrument is a 'gold standard', for example histology for MRI-detected BME.(12) In addition, previous studies have subdivided criterion validity further into concurrent validity and predictive validity, where concurrent validity assumed that the comparator instrument is a gold standard, and predictive validity looked at a later status of for example a radiographic or functional outcome.(31) For the current study all these different types of measures were taken together as 'construct'. As a result, there were sufficient studies to conclude that construct validity was present BME and erosions. However, when one for example looks at only predictive validity, data is actually insufficient to draw conclusions on this aspect, as only 1 of the 9 studies included in construct looked at the predictive value.(20) This was taken into consideration when formulating the research agenda. Determining the possible added value of MRI of the MTP-joints to that of MRI of the wrist and MCPs, and assessing the value of MRI of MTP-1 are also subjects for future research.

When studying the predictive accuracy of forefoot MRI in future studies, it might be relevant to include data from healthy controls in the definition of disease-related MRI-features. Previous studies demonstrated that inclusion of information obtained from symptom-free persons from the general population increased the specificity and accuracy of MRI and that this finding also applies to the use of MRI of the MTP-joints.(32,33)

An updated version of the RAMRIS was recently published that now includes a definition of JSN and tenosynovitis to previous versions in addition to the previous version that only included BME, synovitis and erosions. For tenosynovitis the

updated RAMRIS shows subtle differences compared to the score developed by Haavardsholm et al that is generally used in MRI of wrist and MCPs.(9,13) No validity data on the updated RAMRIS are published to date. However, as the definition of synovitis, BME and erosions did not change, it is assumed that the observed results are also valid for the updated RAMRIS. No conclusions on the validity of tenosynovitis and JSN in the forefeet according to the older definitions or according to the updated RAMRIS could be drawn as there were no data available. Besides adding tenosynovitis and JSN, the updated RAMRIS also included novel recommendations on the scan-protocol, such as a slice thickness of $\leq 2\text{mm}$ in high quality MRI units. However it also states that the recommendations are not intended to be exclusive, but rather to provide common standards. In this review the quality of the MRI-protocol was only weighted regarding field strength and contrast-enhancement, more thorough details such as slice thickness and plane of scanning were not included in the evaluation.

The 13 included studies were heterogeneous in various aspects, such as the scan-protocols that were used and the type of RA-patients that were included (early versus established RA). Most studies mention the use of a coil, varying from dedicated extremity coils (19) to knee or wrist coils.(17) While most studies scanned all MTP-joints, some made a selection.(16,20,22) Not all studies used contrast-enhancement, potentially decreasing the reliability of synovitis scores.(34) Different field strengths were used, with a wide range of 0.2–3T, of which 1.5T was most common. Lower field MRI $< 1.5\text{T}$ generates lower imaging quality, which may influence the interpretability of the data. Therefore, for the final conclusions of this study, included studies were weighted depending on the use of contrast-enhancement for synovitis, an MRI field strength of $\geq 1.5\text{T}$ and the presence of replication studies. The importance of the presence of replication studies is underlined by the small number of patients included in the studies.

Although these weighing criteria (summarized in Table 4) are arbitrary, they served to give a more critical appraisal of the data and enhance the interpretability of the results. Future studies should focus on ACR core set measures for their outcomes to make comparison of studies more attainable. Finally, studies showing a negative correlation could potentially have remained unpublished leading to a reporting bias that may have affected the results of this review.

In conclusion, although for synovitis, tenosynovitis and JSN data was lacking, for MRI-detected BME and erosions, truth of the RAMRIS of the forefeet were

Table 5. Research agenda for the further validation of MRI of the forefeet

Evaluate whether MRI of the MTP-joints performs better than MRI of the MCPs and wrists in predicting radiographic and/or functional outcomes, and if it could be used solely
Study whether MRI of the MTP-joints has additional value to MRI of the MCPs and wrists in predicting radiographic and/or functional outcomes
Assessing the value of MRI of MTP-1
Determine the longitudinal construct validity, clinical trial discrimination and thresholds of meaning for all MRI measures
Evaluate the feasibility for all MRI measures
Assess the anatomy of sheaths of tendons adjacent to MTP-joints for face and content validity
Assess the association with clinical parameters for tenosynovitis and JSN for construct validity
Assess the predictive value of all MRI features with radiographic and/or functional outcomes
Assess the test-retest reliability of tenosynovitis and joint space narrowing and replicate this for synovitis, bone marrow edema and erosions
Assessment of validity in early RA versus established RA

MTP: metatarsophalangeal joint; JSN: joint space narrowing; MRI: magnetic resonance imaging; MCP: metacarpophalangeal joint.

suggested by the data. In contrast, studies on discrimination and on feasibility are needed or require validation. Thus, the validity of applying the RAMRIS to the forefeet still is insufficient on different aspects. Awareness of the gaps in the OMERACT Filter criteria prior to including MRI of the MTP-joints in the RAMRIS and its implementation in trials is essential for optimal interpretation of results obtained.

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Supplementary data

Supplementary methods are available at *RMD Open* online.

