Whole-body Magnetic Resonance Imaging in Inflammatory Arthritis: Systematic Literature Review and First Steps Toward Standardization and an OMERACT Scoring System

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ABSTRACT. ***Objective.*** Whole-body magnetic resonance imaging (WB-MRI) is a relatively new technique that can enable assessment of the overall inflammatory status of people with arthritis, but standards for image acquisition, definitions of key pathologies, and a quantification system are required. Our aim was to perform a systematic literature review (SLR) and to develop consensus definitions of key pathologies, anatomical locations for assessment, a set of MRI sequences and imaging planes for the different body regions, and a preliminary scoring system for WB-MRI in inflammatory arthritis.

Methods. An SLR was initially performed, searching for WB-MRI studies in arthritis, osteoarthritis, spondyloarthritis, or enthesitis. These results were presented to a meeting of the MRI in Arthritis Working Group together with an MR image review. Following this, preliminary standards for WB-MRI in inflammatory arthritides were developed with further iteration at the Working Group meetings at the Outcome Measures in Rheumatology (OMERACT) 2016.

Results. The SLR identified 10 relevant original articles (7 cross-sectional and 3 longitudinal, mostly focusing on synovitis and/or enthesitis in spondyloarthritis, 4 with reproducibility data). The Working Group decided on inflammation in peripheral joints and entheses as primary focus areas, and then developed consensus MRI definitions for these pathologies, selected anatomical locations for assessment, agreed on a core set of MRI sequences and imaging planes for the different regions, and proposed a preliminary scoring system. It was decided to test and further develop the system by iterative multireader exercises.

Conclusion. These first steps in developing an OMERACT WB-MRI scoring system for use in inflammatory arthritides offer a framework for further testing and refinement. (J Rheumatol First Release June 15 2017; doi:10.3899/jrheum.161114)

Key Indexing Terms:
MAGNETIC RESONANCE IMAGING OMERACT ARTHRITIS SYNOVITIS ENTHESITIS

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Magnetic resonance imaging (MRI) is now frequently used as an outcome measure in rheumatology clinical trials. By objectively assessing both disease activity and structural damage, MRI has provided new insights into disease pathogenesis and treatment response. The Outcome Measures in Rheumatology (OMERACT) MRI Working Group has been instrumental in advancing the use of MRI in clinical research, and the OMERACT rheumatoid arthritis (RA) MRI score (RAMRIS)[1,2,3,4,5,6] for evaluating bone erosion, osteitis (bone marrow edema), and synovitis in RA, is now the standard method used in clinical trials. Further, supplementary RAMRIS joint space narrowing and tenosynovitis scores have been developed and validated[7,8,9,10]. The group has also developed and validated a psoriatic arthritis (PsA) MRI scoring method (PsAMRIS)[11,12,13], and the Assessment of Spondyloarthritis international Society/OMERACT working group has validated scoring methods for assessing inflammation in sacroiliac joints[14] and the spine[15] in patients with ankylosing spondylitis (AS).

A disadvantage of conventional MRI is the limited anatomical area that is assessed in a typical examination. Whole-body MRI (WB-MRI) is a relatively new technique currently used as a screening tool for evaluating multifocal bone lesions in diseases such as multiple myeloma. WB-MRI allows assessment of the entire body in 1 examination in less than an hour, and thereby can potentially provide a global assessment of the inflammatory status of a patient with arthritis[16–25]. This may improve the utility of MRI in AS, RA, and particularly PsA, which present with varying patterns of arthritis, enthesitis, spondylitis, and/or dactylitis. However, standards for image acquisition and definitions of key pathologies need to be established, and a system for quantification needs to be developed and validated.

To develop this tool according to the OMERACT Filter 2 as an applicable measurement instrument for the relevant pathophysiological domain of inflammation[26], we performed a systematic literature review (SLR) to establish the current status of WB-MRI in imaging of peripheral joints. Thereafter based on published data and review of MR images, we decided on consensus definitions of key pathologies, anatomical locations for assessment, a set of MRI sequences and imaging planes for the different regions of the body, and a preliminary scoring system for WB-MRI in inflammatory arthritis. Our new work, which has not been published before, provides the first international consensus report on WB-MRI and a useful novel framework for further development of WB-MRI as an outcome measure in inflammatory arthritides.

MATERIALS AND METHODS

Literature review. An SLR was undertaken. The population of interest was patients with arthritis and/or enthesitis, and the intervention was WB-MRI. A control group was not mandatory. The outcomes included lesions observed and intra/interreader agreement, and the study design should either be cross-sectional or longitudinal original studies. A literature search was done by 1 author (KGH) on January 19, 2016, using Medline and searching for "whole body MRI" AND ("arthritis" OR "osteoarthritis" OR "spondyloarthritis" OR "enthesitis"); it yielded 43 results. One article in press and not yet indexed in PubMed was added. A flow diagram, made in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (www.equator-network.org/reporting-guidelines/prisma), is provided in Figure 1. After manually excluding non-English articles, review papers, and case reports, 22 articles remained. Manual exclusion of papers not truly applying the WB-MRI technique left 18 articles. Finally, 8 articles focusing only on the axial skeleton were excluded[27,28,29,30,31,32,33,34], leaving 10 articles that used WB-MRI for assessment of the extremities (Table 1)[16–25]. The QUADAS-2 tool was used to assess risk of bias and concerns for applicability (Supplementary Figure 1, available with the online version of this article; www.quadas.org).

Consensus process. Members of the OMERACT MRI in Arthritis Working Group and other researchers who had previously worked with WB-MRI participated in a 1-day meeting in Berlin, Germany, on January 21, 2016. At this meeting, the literature search was presented and discussed, followed by presentations by all groups who had previously published WB-MRI data from patients with inflammatory arthritides. This was followed by a discussion of challenges in developing and applying WB-MRI as an outcome measure, and of the following predefined topics: initial focus area, selection of key pathologies to assess, MRI definitions of key pathologies, selection of anatomical locations for assessment, core MRI sequences and imaging planes, and development of a preliminary assessment system. These issues were further discussed and refined during e-mail communications and meetings at the OMERACT conference in Whistler, British Columbia, Canada, in May 2016.

RESULTS

Literature review. Characteristics of the 10 publications that used the WB-MRI technique to assess the extremities, with or without additional examination of the axial skeleton, are provided in Table 1[16–25]. The manuscripts described 7 cross-sectional and 3 longitudinal studies, mainly in SpA/PsA. They reported WB-MRI visualization of peripheral synovitis, effusion, osteitis, enthesitis, and to a limited extent, bone erosions. Four studies included reproducibility data (Table 1).

Initial focus area. Our study initially focused on assessment of inflammation, as opposed to damage, in the extremities. Inflammation was chosen because total inflammatory load was considered to be clinically most important, and because the requirements for spatial resolution were believed to be less challenging than those for assessing bone erosion. Much standardization has been done in axial SpA/AS[14,15,35,36,37], and the extremities were prioritized because consensus scoring systems exist only for a limited number of regions (mainly hand and wrist joints).

Selection of key pathologies. Our study focused on joints and entheses, and that these should both be assessed separately for inflammation in the soft tissues and inflammation in the bone (Appendix 1).

Definition of key pathologies. With previously published OMERACT MRI definitions used as a starting point, definitions of the joint and entheseal pathologies were developed (Appendix 1), taking into account the MRI sequences available.

Selection of anatomical locations for assessment. It was agreed that no peripheral joints should be excluded before

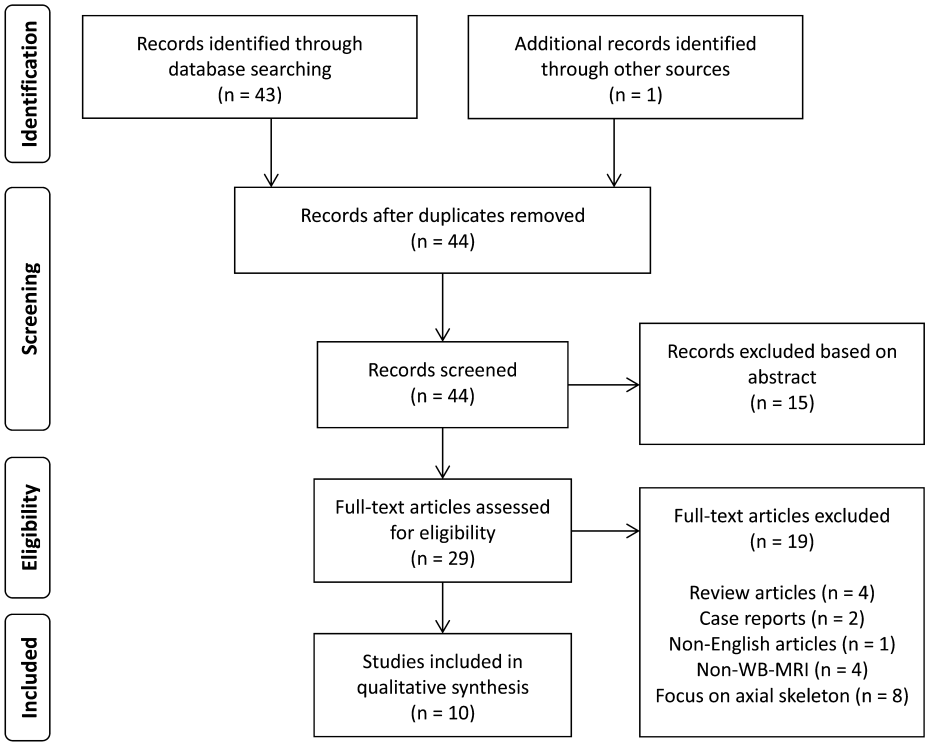

Figure 1. Flow diagram for the systematic literature review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. WB-MRI: whole-body magnetic resonance imaging.

reader exercises, with the exception of the elbow joints, which based on the experience of the group were always located outside the field of view because of peripheral positioning in the MRI bore.

Since there is a large number of entheses in the body, a choice of which entheses to examine had to be made, for feasibility. The selection was based on existing clinical enthesitis indices and the ability of MRI to visualize those specific anatomical locations. A questionnaire was circulated to all participating groups, and from this a preliminary set of entheses to be assessed in reading exercises was chosen by consensus (Appendix 1). The most informative imaging plane for the specific region was also taken into account because generally only 1 plane could be selected per region for feasibility reasons.

MRI sequences and planes. For evaluating inflammation, it was considered crucial to have either a short-tau inversion recovery or T2-weighted fat-suppressed sequences, and/or a fat-suppressed T1-weighted sequence after intravenous gadolinium (Gd)-contrast injection. A T1-weighted sequence before contrast injection (T1-pre-Gd) was not considered mandatory for assessing inflammation, but because of its high anatomical resolution, availability of a T1-pre-Gd facilitates exact anatomical localization of imaging pathologies. If structural damage is to be assessed, it is crucial to include T1-pre-Gd.

The recommended imaging plane depends on the anatomical region (Appendix 1). The planes were selected with the aim of optimally presenting the most common and important pathologies in the individual regions.

Assessment (scoring) system. It was decided that all assessed pathologies in all selected joints and entheses would be scored 0–2 as follows: 0 = no inflammation, 1 = mild/moderate inflammation, and 2 = severe inflammation.

Total scores would be calculated for each of the following: (a) joints – synovitis, (b) joints – osteitis, (c) entheses – soft tissue inflammation, and (d) entheses – osteitis. Composite scores would also be calculated (joint inflammation index = a + b, entheseal inflammation index = c + d, and total peripheral inflammation index = a + b + c + d).

DISCUSSION

Our report describes the first international consensus effort regarding the use of WB-MRI in different arthritides. A literature review, an MR image review, and discussion among physicians experienced in WB-MRI and/or developing MRI scoring systems led to consensus on important pathologies and locations for assessment, MRI definitions of these pathologies, core MRI sequences and imaging planes, and a preliminary scoring system. Future data are likely to modify these decisions, and the preliminary design of the decisions was fully acknowledged by the group. Nevertheless, the

Table 1. Characteristics of publications on WB-MRI of the extremities retrieved by the literature search.

Study	Disease	Patients, n	Controls, n	Sites	Inflammatory Lesions	Structural Lesions	Manufacturer	Field Strength	Gd	Sequences	Planes	Duration, Min	TP, Week	Readers, n	Read Setup	Reproducibility
Song, *et al*[16]	axSpA	76	None	27	Enthesitis	ND	Siemens	1.5T	No	T1, STIR	Cor, sag	6	0, 24, 48	2	Consensus	ND
Weckbach, *et al*[17]	PsA	30	None	15	Osteitis, effusion, synovitis, enthesitis	Erosions, destruction	Siemens	1.5T	Yes	STIR, dynT1, VIBE	Cor	45	0	2	Consensus	ND
Althoff, *et al*[18]	axSpA	75	None	J: 12, E: 30	Effusion/ synovitis, enthesitis	Erosions	Siemens	1.5T	No	T1, STIR	Cor, sag	65	0	2	Consensus	ND
Karpitschka, *et al*[19]	AS	10	None	NA	Synovitis, enthesitis	ND	Siemens	1.5T	Yes	T1, STIR, T1FS/Gd	Cor	—	0, 26, 52	2	Independent	NA
Schanz, *et al*[20]	SSc	18	None	NA	Fasciitis, myositis, tenosynovitis, BME	ND	Siemens	1.5T	Yes	STIR, T1, T1/Gd	Cor	30	0	2	Independent	Interreader, κ 0.8–1.0
Axelsen, *et al*[21]	RA	20	None	J: 76, E: 30	Synovitis, enthesitis	Erosions	Philips	3T	Yes	T1, STIR, T1/Gd	Cor, ax	60	0	1	ND	Intrareader agreement rate 85–100%
Mackie, *et al*[22]	PMR	22	16 RA	10	Extracapsular PMR pattern	ND	Siemens	3T	Yes	T2FS, Dixon-VIBE	Ax, 3-D Reco	19	0	2	Consensus	ND
Poggenborg, *et al*[23]	PsA, axSpA	36	12	35	Enthesitis	ND	Philips	3T	Yes	T1, STIR, T1FS/Gd	Cor, ax	61	0	1	ND	Intrareader ICC: 0.58/0.85
Poggenborg, *et al*[24]	PsA, axSpA	36	12	76	Synovitis, BME	Erosions	Philips	3T	Yes	T1, STIR, T1FS/Gd	Cor, ax	61	Baseline	1	ND	Intrareader ICC: 0.31–1.0
Althoff, *et al*[25]	axSpA	41	None	21	Enthesitis	ND	Siemens	1.5T	No	T1, STIR	Cor, sag	65	Baseline, yrs 2 and 3	2	Consensus	ND

WB-MRI: whole-body magnetic resonance imaging; Gd: gadolinium contrast; TP: timepoint for MRI examination; axSpA: axial spondyloarthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; SSc: systemic sclerosis; RA: rheumatoid arthritis; PMR: polymyalgia rheumatica; J: joints; E: entheses; NA: not available; BME: bone marrow edema; ND: not done; T: tesla; STIR: short-tau inversion recovery; T1: T1-weighted images; T1/Gd: T1-weighted images after intravenous Gd contrast injection; Reco: reconstruction; dyn: dynamic; VIBE: volumetric interpolated breath-hold examination; FS: fat suppression; cor: coronal; sag: sagittal; ax: axial.

group felt that our present work formed a useful framework for the further development of WB-MRI as an outcome measure in inflammatory arthritides.

Joints and entheses were selected as the key pathologies for scoring. Pericapsular inflammation was discussed as a relevant manifestation in some joints, particularly in SpA, including PsA. However, the group felt that this disease feature was not suitable for followup in clinical trials, and not assessable without contrast injection and higher WB-MR image quality than currently available. The group, therefore, decided to exclude it. Similarly, bursitis, tenosynovitis, tendonitis, and dactylitis were excluded, although some of these may be considered in the future depending on technical developments and new information about the individual importance of such pathologies in the different diseases. We also decided not to distinguish large joints from small joints, until more information about this becomes available and data-driven conclusions can be made.

The use of WB-MRI is currently challenged by the examination time, which limits the image quality and spatial resolution attainable to significantly less than what can be achieved with conventional, single-location MRI. It also limits the number of imaging planes and pulse sequences. However, imaging speed is constantly improving[22], and probably this limitation will be less significant in the future.

The proposed assessment system is not designed for 1 specific disease, but rather is meant to be tested in iterative exercises in different inflammatory arthritides. After such exercises, separate scoring systems specifically designed for individual diseases, such as RA or PsA, may be developed.

The planned next step of the group will be an initial multireader exercise to test the feasibility and reproducibility of the assessment system, followed by data-driven modifications and improvements.

A strength of our present initiative was that most groups identified by the literature search as experienced in WB-MRI in arthritis were represented in the consensus discussions. Limitations include that only 1 investigator searched 1 database and extracted data. Searching in more databases and a broader search strategy could have diminished the risk of missed articles.

WB-MRI offers significant potential as a measure of the total inflammatory burden in patients with arthritides. Our present study describes the first steps in developing an OMERACT WB-MRI scoring system, and provides a useful framework for the further development of WB-MRI as an outcome measure in inflammatory arthritides.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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APPENDIX 1. Preliminary OMERACT WB-MRI assessment system of inflammation in inflammatory arthritides. OMERACT: Outcome Measures in Rheumatology; WB-MRI: whole-body magnetic resonance imaging; Gd: gadolinium contrast; STIR: short-tau inversion recovery; FS: fat suppression; RAMRIS: rheumatoid arthritis MRI score; PsAMRIS: psoriatic arthritis MRI scoring method.

Initial Focus Area
Assessing inflammation in the extremities
Selection of Key Pathologies
Inflammation in joints:
- Soft tissues (synovitis)
- Bone (osteitis)
Inflammation at enthesis (enthesitis):
- Soft tissue (soft tissue inflammation)
- Bone (osteitis)
Definitions of Key Pathologies
Joints: Synovitis
Procedure: If T1-postGd images are available, synovitis should be assessed according to option a. If only STIR/T2FS images are available: Synovitis/effusion should be assessed according to option b.
Definitions:
- Option a. Definition of synovitis, based on T1-postGd images: An area in the synovial compartment that shows above-normal post-gadolinium enhancement on T1-weighted images, of a thickness greater than the width of the normal joint capsule
- Option b. Definition of synovitis/effusion, based on STIR/T2FS images: (to be used if STIR/T2FS images, but not T1-postGd images, are available): An area in the synovial compartment that shows high signal intensity on T2-weighted fat- saturated or STIR images, of a thickness greater than the width of the normal joint capsule and joint fluid.[1]
Joints: Osteitis
Procedure: If STIR/T2FS images are available, assess bone edema according to option a. If only T1-postGd images are available: Assess intraosseous post-Gd enhancement according to option b.
Definitions:
- Option a: Definition of osteitis, based on STIR/T2FS images: A lesion within the trabecular bone, with ill- defined margins and high signal intensity on T2-weighted fat-saturated and STIR images ("bone marrow edema")
- Option b. Definition of osteitis, based on T1-postGd images): A lesion within the trabecular bone marrow, with ill- defined margins, which shows above-normal enhancement (signal intensity increase) on T1-weighted after iv. Gadolinium contrast injection ("bone marrow post-contrast enhancement")
Entheses: Entheseal soft tissue inflammation
Procedure: If T1-postGd images are available, entheseal soft tissues should be assessed according to option a. If only STIR/T2FS images are available, entheseal soft tissues should be assessed according to option b.
Definitions:
- Option a: Definition of entheseal soft tissue inflammation, based on T1-postGd images: Above-normal post-gadolinium enhancement of entheseal soft tissues on T1-weighted images.
- Option b. Definition of entheseal soft tissue inflammation, based on STIR/T2FS images:
High signal intensity of the entheseal soft tissues on T2-weighted fat-saturated or STIR images.

Entheses: osteitis
Procedure: If STIR/T2FS images are available, assess bone edema according to option a. If only T1-postGd images are available: Assess intraosseous post-Gd enhancement according to option b.
Definitions
- Option a: Definition of osteitis, based on STIR/T2FS images: A lesion within the entheseal bone marrow, with ill- defined margins and high signal intensity on T2-weighted fat-saturated and STIR images ("bone marrow edema").
- Option b. Definition of osteitis, based on T1-postGd images): A lesion within the entheseal bone marrow, with ill-defined margins, which shows above-normal enhancement (signal intensity increase) on T1-weighted after iv. Gadolinium contrast injection ("bone marrow post-contrast enhancement").
Anatomical Locations for Assessment
Joints:
- All peripheral joints, except the elbow.
- Joints of the chest wall: sternoclavicular joint, costosternal joints, manubriosternal joint
Entheses:
- Upper extremity: Insertion of supraspinatus tendon into humerus,
- Pelvis: Anterior superior iliac spine, posterior superior iliac spine, iliac crest (excluding the anterior and posterior superior iliac spines), ischial tuberosity, pubic symphysis.
- Lower extremities: greater trochanter of femur, medial femoral condyle, lateral femoral condyle, insertion of the quadriceps femoris tendon into patella, insertion of the patellar ligament into patella, insertion of the patellar ligament into the tibial tuberosity, insertion of the calcaneal (Achilles) tendon into calcaneus, insertion of the plantar aponeurosis into calcaneus.
MRI Sequences and Imaging Planes:
Recommended imaging planes:
- Spine: Sagittal
- Shoulder/anterior chest wall: Coronal
- Sacroiliac joints: Coronal oblique
- Wrist and hand: Coronal
- Pelvis: Axial[2]
- Knee: Axial (+ if possible sagittal[2])
- Ankle: Sagittal
- Feet: Axial (will provide coronal view of foot)
Recommended MRI sequences:
- T1-PostGd or alternatively STIR/T2FS,
- T1 without contrast (not mandatory if only inflammation is assessed)
Scoring System
- For each selected joint, synovitis (a) and osteitis (b) are scored separately (0-2)[3]
- For each selected enthesis, soft tissue inflammation (c) and osteitis (d) are scored separately (0–2)
- Individual scores: 0: None, 1: Mild-moderate, 2: severe[4]
- Sum scores: joint inflammation index: a + b, entheseal inflammation index: c + d, total peripheral inflammation index: a + b + c + d.

[1]Enhancing synovitis on T1-postGD may appear with low signal on STIR/T2FS, presumably because of high collagen content.
[2]Additional sagittal plane needed for adequate assessment of patellar and quadriceps tendon insertions. Additional coronal plane improves hip joint assessment
[3]When only STIR/T2wFS is available, the assessment will cover synovitis and effusion.
[4]A 0–2 score was agreed by the group at the Berlin meeting, since it was considered difficult to reliably score with more steps with the current image quality. Definitions of mild/moderate/severe are as described for RAMRIS/PsAMRIS[1,11]. At the OMERACT meeting participants in the Special Interest Group suggested using a 0–3 score (none, mild, moderate, severe), and this approach may also be tested.