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**Whole-body MRI in inflammatory arthritis - Systematic literature review and first steps towards standardization and an OMERACT scoring system**

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**Whole-body MRI in inflammatory arthritis – Systematic literature review and first steps towards standardization and an OMERACT scoring system**

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#### **Running footline**

Whole-body MRI in arthritis

## ABSTRACT

**Aim:** Whole-body MRI (WBMRI) is a relatively new technique which potentially enables 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 WBMRI in inflammatory arthritis.

**Methods:** A SLR was initially performed, searching for whole-body MRI studies in arthritis/osteoarthritis/spondyloarthritis/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 WBMRI in inflammatory arthritides were developed with further iteration at the Working Group meetings at OMERACT 13.

**Results:** The SLR identified 10 relevant original articles (7 cross-sectional/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 area, 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 multi-reader exercises.

**Conclusion:** These first steps in developing an OMERACT WBMRI scoring system for use in inflammatory arthritides offer a framework for further testing and refinement.

## **INTRODUCTION**

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 utility of MRI in clinical research, and the OMERACT rheumatoid arthritis (RA) MRI score (RAMRIS)(1-6) 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 recently been developed and validated(7-10). The group has also developed and validated a psoriatic arthritis (PsA) MRI scoring method (PsAMRIS)(11-13), and the Assessment of SpondyloArthritis International Society (ASAS)/OMERACT working group has validated scoring methods for assessing inflammation in sacroiliac joints(14) and 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 (WBMRI) is a relatively new technique currently used as a screening tool for evaluating multifocal bone lesions in diseases such as multiple myeloma. WBMRI allows assessment of the entire body in one examination in less than an hour, and thereby can potentially provide a global assessment of the inflammatory status of an arthritis patient(16-25). This may improve the utility of MRI in AS, RA, and particularly PsA, which presents 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.

In order to develop this tool according to OMERACT Filter 2 as an applicable measurement instrument for the relevant pathophysiological domain of inflammation (26), we performed a systematic literature review to establish the current status of WBMRI 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 WBMRI in inflammatory arthritis. This new work, which has not been published before, provides the first international consensus report on WBMRI and a useful novel framework for further development of WBMRI as an outcome measure in inflammatory arthritides.

## **METHODS.**

### **Literature review**

A systematic literature review was undertaken. The population of interest was patients with arthritis and/or enthesitis, the intervention whole-body 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 (PICOS). A literature search was done by one author (KGH) on January 19, 2016, using Medline searching for “whole body MRI” AND (“arthritis” OR “osteoarthritis” OR “spondyloarthritis” OR “enthesitis”)” yielded 43 results. One article in press and not yet indexed in Pubmed was added. A flow diagram, made in accordance with the PRISMA guidelines ([www.equator-network.org/reporting-guidelines/prisma/](http://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 WBMRI technique left 18 articles. Finally, 8 articles focusing only on the axial skeleton were excluded(27-34), leaving 10 articles which used WBMRI 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)([www.quadas.org](http://www.quadas.org)).

### **Consensus process**

Members of the OMERACT MRI in Arthritis Working Group and other researchers who had previously worked with WBMRI participated in a one-day meeting in Berlin, January 21, 2016. At this meeting, the literature search was presented and discussed, followed by presentations by all groups who had previously published WBMRI data from patients with inflammatory arthritides. This was followed by a discussion of challenges in developing and applying WBMRI 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 email communications and meetings at the OMERACT conference in Whistler, Canada, May 2016.

## **RESULTS**

### **Literature review**

Characteristics of the 10 publications that used the WBMRI 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 WBMRI-visualization of peripheral synovitis, effusion, osteitis, enthesitis and, to a limited extent, bone erosions. Four studies included Reproducibility data (Table 1).

### **Initial focus area**

It was decided initially to focus 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;35-37), 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**

It was decided to focus on joints and entheses and that these should both be assessed separately for inflammation in the soft tissues and inflammation in the bone (Appendix).

### **Definition of key pathologies**

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

### **Selection of anatomical locations for assessment**

It was agreed that no peripheral joints should be excluded before reader exercises, with exception of the elbow joints, which based on the experience of the group are 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 were chosen by consensus (Appendix). The most informative imaging plane for the specific region was also taken into account, since generally only one 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 (STIR) or T2-weighted fat-suppressed (T2FS) sequences, and/or a fat suppressed T1-weighted sequence after intravenous gadolinium-contrast injection (T1-postGd). A T1-weighted sequence before contrast injection (T1-preGd) was not considered mandatory for assessing inflammation, but due to its high anatomical resolution, availability of a T1-preGd 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). 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, 2: severe inflammation.

Total scores would be calculated for each of the following: a. Joints – synovitis; b. joints – osteitis; c. entheses – soft tissue inflammation; d. entheses – osteitis. It was also decided to calculate composite scores (joint inflammation index: a+b, enthesal inflammation index: c+d, and total peripheral inflammation index: a+b+c+d).

## **DISCUSSION**

This report describes the first international consensus effort regarding the use of WBMRI in different arthritides. A literature review, an MR-image review, and discussion among physicians experienced in WBMRI and/or developing MRI scoring systems led to consensus on important pathologies and locations for assessment, MRI-definitions of these, core MRI sequences and imaging planes, and a preliminary scoring system. Future data are likely to modify these decisions, and the preliminary nature of the decisions was fully acknowledged by the group. Nevertheless, the group felt that the present work formed a useful framework for further development of WBMRI 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 follow-up in clinical trials, and not assessable without contrast injection and higher WBMRI-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. It was 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 WBMRI 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 one 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 the present initiative was that the most groups identified by the literature search as experienced in WBMRI in arthritis were represented in the consensus discussions. Limitations include that only one investigator searched one database, and extracted data. Searching in more databases and a broader search strategy could have diminished the risk of missed articles.

In conclusion, WBMRI offers significant potential as a measure of the total inflammatory burden in patients with arthritides. The present manuscript describes the first steps in developing an OMERACT WBMRI scoring system, and provides a useful framework for the further development of WBMRI as an outcome measure in inflammatory arthritides.

For Peer Review

**Text boxes:**

Text box 1: New work presented in this manuscript:

- A systematic literature review of WBMRI examination in arthritides
- Selection of key pathologies for assessment by WBMRI in arthritides
- Development of preliminary definitions of the key pathologies
- Selection of anatomical locations for assessment
- Selection of recommended MRI sequences and planes for WBMRI
- Development of a preliminary assessment (scoring) system for WBMRI

For Peer Review

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**Table 1: Characteristics of publications on WBMRI of the extremities, retrieved by the literature search**

First author	Year	Journal	Disease	Patients	Controls	Sites	Inflammatory lesions	Structural lesions	Manufacturer	Field strength	Gd	Sequences	Planes	Duration	TP (week)	Readers	Read setup	Reproducibility
Song IH	2011	Ann Rheum Dis	axSpA	76	None	27	enthesitis	ND	Siemens	1.5T	No	T1, STIR	cor, sag	65 mins.	0, 24 & 48	2	consensus	ND
Weckbach S	2011	Eur J Radiol	PsA	30	None	15	osteitis, effusion, synovitis, enthesitis	erosions, destruction	Siemens	1.5T	yes	STIR, dynT1*, VIBE	Cor	45 mins.	0	2	consensus	ND
Althoff CE	2013	Ann Rheum Dis	axSpA	75	None	J:12; E:30	effusion/synovitis, enthesitis	erosions	Siemens	1.5T	No	T1, STIR	cor, sag	65 mins.	0	2	consensus	ND
Karpitscka M	2013	Eur Radiol	AS	10	None	NA	synovitis, enthesitis	ND	Siemens	1.5T	yes	T1, STIR, T1fs/Gd	cor	-	0, 26 & 52	2	independent	NA
Schanz S	2013	Eur Radiol	SSc	18	None	NA	fasciitis, myositis, tenosynovitis, BME	ND	Siemens	1.5T	yes	STIR, T1**, T1/Gd**	cor	30 mins.	0	2	independent	inter-reader, kappa: 0.8–1.0
Axelsen MB	2014	Rheumatology	RA	20	None	J:76; E:30	Synovitis, enthesitis	erosions	Philips	3T	yes	T1, STIR, T1/Gd	cor, ax	60 mins.	0	1	ND	intra-reader agreement rate 85–100%



Mackie SL	2015	Ann Rheum Dis	PMR	22	16 (RA)	10	extracapsular PMR pattern	ND	Siemens	3T	yes	T2fs, Dixon-VIBE	ax, 3D-Reco	19 mins.	0	2	consensus	ND
Poggenborg RP	2015	Ann Rheum Dis	PsA, axSpA	36	12	35	enthesitis	ND	Philips	3T	yes	T1, STIR, T1fs/Gd	cor, ax	61 mins.	0	1	ND	intra-reader ICC: 0.58/0.85
Poggenborg RP	2015	Rheumatology	PsA, axSpA	36	12	76	synovitis, BME	erosions	Philips	3T	yes	T1, STIR, T1fs/Gd	cor, ax	61 mins.	Baseline	1	ND	intra-reader ICC: 0.31–1.0
Althoff CE	2016	J Rheumatol	axSpA	41	None	21	enthesitis	ND	Siemens	1.5T	No	T1, STIR	cor, sag	65 mins.	baseline, year 2 & 3	2	consensus	ND

AS: ankylosing spondylitis; ax: axial; AxSpa: axial spondyloarthritis; BME: bone marrow edema; cor: coronal; dyn: dynamic; E: entheses; Gd: gadolinium contrast, FS: fat suppression ICC: intraclass correlation coefficient, J: joints; NA: not available, ND: not done; PMR: polymyalgia rheumatic; PsA: psoriatic arthritis, RA: rheumatoid arthritis; sag: sagittal; STIR: short tau inversion recovery, T: tesla; TP: time point for MRI examination; VIBE: volumetric interpolated breath-hold examination, WBMRI: whole-body magnetic resonance imaging

**APPENDIX: Preliminary OMERACT WBMRI assessment system of inflammation in inflammatory arthritides.****Initial Focus Area**

Assessing inflammation in the extremities

**Selection of Key Pathologies**

Inflammation in joints:

- Soft tissues (synovitis)
- Bone (osteitis)

Inflammation at entheses (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.<sup>1</sup>

*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: Enteseal soft tissue inflammation

Procedure: If T1-postGd images are available, enteseal soft tissues should be assessed according to option a. If only STIR/T2FS images are available, enteseal soft tissues should be assessed according to option b.

Definitions:

- Option a: Definition of enteseal soft tissue inflammation, based on T1-postGd images: Above-normal post-gadolinium enhancement of enteseal soft tissues on T1-weighted images.
- Option b. Definition of enteseal soft tissue inflammation, based on STIR/T2FS images:

High signal intensity of the enteseal 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 enteseal 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 enteseal 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<sup>2</sup>
- Knee: Axial (+ if possible sagittal<sup>2</sup>)
- 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)<sup>3</sup>

- For each selected entheses, soft tissue inflammation (c) and osteitis (d) are scored separately (0-2)

- Individual scores: 0: None, 1: Mild-moderate, 2: severe<sup>4</sup>

- Sum scores: joint inflammation index: a+b, enteseal inflammation index: c+d, total peripheral inflammation index: a+b+c+d.

<sup>1</sup>Enhancing synovitis on T1-postGD may appear with low signal on STIR/T2FS, presumably because of high collagen content.

<sup>2</sup>Additional sagittal plane needed for adequate assessment of patellar and quadriceps tendon insertions. Additional coronal plane improves hip joint assessment

<sup>3</sup>When only STIR/T2wFS is available, the assessment will cover synovitis and effusion.

<sup>4</sup>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.

**Figure 1: Flow Diagram for the Systematic Literature Review, in accordance with the PRISMA statement.**

