

Title

Development and Validation of an OMERACT MRI Whole-Body Score for Inflammation in Peripheral Joints and Enteses in Inflammatory Arthritis (MRI-WIPE)

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Key indexing terms

Magnetic Resonance Imaging, Outcome Assessment (Health Care), Arthritis, OMERACT

Funding

S.K. received research grants from The Danish Rheumatism Association and Rigshospitalet.

Conflicts of interest

All authors have no conflicts of interest with regards to this article.

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Short running head

Whole-Body MRI Score

Abstract

Objective

To develop a whole-body MRI-scoring system for peripheral arthritis and enthesitis.

Methods

After consensus on definitions/locations of MRI pathologies, four multi-reader exercises were performed.

Eighty-three joints were scored 0-3 separately for synovitis and osteitis, thirty-three entheses 0-3 separately for soft tissue inflammation and osteitis.

Results

In the last exercise, reliability was moderate-good for musculoskeletal radiologists and rheumatologists with previously demonstrated good scoring proficiency. Median pairwise single-measure/average-measure ICCs were 0.67/0.80 for status scores and 0.69/0.82 for change scores; kappas ranged 0.35-0.77.

Conclusion

WBMRI scoring of peripheral arthritis and enthesitis is reliable which encourages further testing and refinement in clinical trials.

Introduction

Magnetic resonance imaging (MRI) allows objective assessment of inflammation in peripheral joints and entheses.(1–7) MRI scoring systems have until now focused on assessing parts of the musculoskeletal system in detail, e.g. the Rheumatoid Arthritis MRI Scoring System (RAMRIS), which is applied to wrist and metacarpophalangeal joints and adjacent tendon sheaths.(8–10) The interest in a whole-body MRI (WBMRI) approach is growing as modern MRI scanners permit whole-body scanning within an acceptable time frame (<1 hour), and future improvements in MRI hardware and pulse sequences are expected to improve scan time and image resolution further.

WBMRI of patients with inflammatory arthritis has mainly been investigated in small cross-sectional(2,5–7,11) or longitudinal studies.(3,4,12) To our knowledge two randomized, controlled trials have used WBMRI as an outcome measure, applying different assessment systems.(3,4) To increase homogeneity, validity and across-study comparability of WBMRI as outcome measure, the OMERACT MRI in Arthritis Working Group decided to develop a scoring system for inflammation of peripheral joints and entheses for use in future phase II/III studies which aim to objectively document the effect of an intervention on the inflammatory load in peripheral joints and entheses.

The objective was to develop an MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE) and to investigate its feasibility and reliability.

Methods

Development of the scoring system through iterative multi-reader scoring exercises

In 2016, the OMERACT MRI in Arthritis Working Group decided on inflammation in peripheral joints and entheses as primary focus for WBMRI development, and then agreed on consensus MRI definitions for arthritis and enthesitis, selected anatomical locations for assessment, and 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.(13–15)

In 2017-2018, 4 (3 cross-sectional and 1 longitudinal) web-based multireader exercises were performed, separated by online training and calibration meetings. Schematics for data recording the presence of lesions and their severity were drawn (S.K. and M.Ø.) (Figure 1). Subsequently, courtesy of CaRE Arthritis, a web-based schematic data entry interface was created (J.P.) and used together with a DICOM image viewer (Figure 2), to conduct entirely web-based scoring exercises. In Exercise 1, nine readers (1 radiologist, 8 rheumatologists) tested a draft scoring system in 2 axial spondyloarthritis (axSpA) patients. Results were

discussed, and the system was slightly modified. In Exercise 2, fourteen readers (3 radiologists, 11 rheumatologists) assessed 5 axSpA patients. Discrepant cases and potential difficulties in applying the scoring system were discussed online to obtain consensus, train inexperienced readers, and identify potential pitfalls.

In Exercise 3, MRIs of 8 patients (4 rheumatoid arthritis (RA), 4 psoriatic arthritis (PsA)) were scored by fourteen readers (4 radiologists, 10 rheumatologists). Because of widely variable agreement (minimal-good) between reader pairs, 2 online meetings were held to improve calibration before proceeding to Exercise 4, where MRIs at two time points of 6 axSpA patients who started TNF inhibitor treatment were assessed by ten readers (3 radiologists, 7 rheumatologists) blinded for chronology. In all exercises, readers were aware of the patient groups involved (SpA or RA), but not the diagnosis of individual cases.

Reader instructions containing definitions and image examples of normal findings (e.g. blood vessels) that could be mistaken for inflammation, and many examples of lesions with different grading were made available at www.copecare.dk and www.carearthritis.com. While Exercises 1-2 were solely used for qualitative training and understanding principles and pitfalls, for Exercises 3-4 reliability statistics (pairwise single measures and average measures intraclass correlation coefficients by absolute agreement for sum scores and squared weights Cohen's kappa for individual scores) were calculated.

Approval was obtained from the Regional Committee on Health Research Ethics, Region Hovedstaden, Denmark (H-1-2013-118), and patients provided written informed consent.

Scoring methodology

Inflammation in joints (arthritis) and at entheses (enthesitis) are both assessed separately for soft tissues (synovitis at joints, soft tissue inflammation at entheses) and bone (osteitis), see Østergaard et al (13) for exact MRI definitions.

Preferentially, synovitis and soft tissue inflammation are assessed on T1-post-Gd images and osteitis on Short Tau Inversion Recovery (STIR)/T2-Weighted Fat-Sat (T2FS) images, but if only STIR/T2FS is available, synovitis and soft tissue inflammation can be assessed based on this. Each component is scored on a semiquantitative scale of 0-3 (none/mild/moderate/severe), following the principles from the RAMRIS and PsAMRIS systems.(8)(16) In total, 83 peripheral joints and 33 entheses are assessed. The MRI-WIPE score is derived by adding all scores together, the total range is 0-738 (joints 0-537; entheses 0-201), see **Figure 2** and **Appendix** for details.

Results

Readers from 10 different countries across the globe participated. Exercises 1-2 were only used for initial learning, calibration and identification of pitfalls. In Exercise 3, agreement between readers varied from poor to good for the 4 lesion types and their sum scores (**Table 1**). Reliability varied between reader pairs depending on reader experience. When limiting the analysis to the 4 musculoskeletal radiologists, reliability improved to moderate-good.

The same pattern was observed in Exercise 4, where reliability was poor-good among all readers, but when restricted to the 3 musculoskeletal radiologists plus 3 rheumatologists with the better reliability in the previous exercise, reliability was moderate-good. Thus, among the more trained readers, grading seemed reliable. MRI-WIPE reading time for one MRI was not measured but estimated to be ≤ 60 minutes.

Responsiveness of the MRI-WIPE score was good during TNF inhibitor treatment (mean change score -6.3 , standard deviation 6.5 , and standardized response mean (SRM) 1.0). Average-measure ICCs based on two readers (status: 0.80 , change: 0.82) were higher than single-measure ICCs (status: 0.67 , change: 0.69)(Table 1). Using three readers, average-measure ICCs were higher (status: 0.86 , change: 0.86).

Discussion

Definitions of key MRI pathologies and a scoring system (MRI-WIPE, MRI Whole-Body Score for Inflammation in Peripheral Joints and Enteses in Inflammatory Arthritis) were agreed by consensus in the OMERACT MRI in Arthritis Working Group. The scoring system was developed in analogy with RAMRIS/PsAMRIS scoring systems but allows assessment of multiple peripheral joints and enteses and is not limited to one specific diagnosis in its current form. In small cross-sectional and longitudinal reading exercises, the system had moderate-good reliability for status scores and change scores, when limiting the analysis to readers who were musculoskeletal radiologists or had shown good proficiency of scoring in agreement with most readers in the previous exercises. Potentially, WBMRI could provide a high between-group discrimination in randomized controlled trials.(4) Thus, the scoring system appears promising for further validation and future use in randomized controlled trials.

A scan time of about 45 minutes for peripheral joints and enteses, and approximately 1 hour if axial joints were included, was acceptable to the included patients. Thus, the approach was feasible, although no formal survey of patient satisfaction or discomfort was undertaken.

Subsequent steps may include tailoring/exploring different joint combinations for different diseases (i.e. a modular approach, where only a selection of areas is imaged and scored, guided by the key questions in

individual studies), since diseases as RA, PsA and axial SpA have different patterns of joint and enthesis involvement. Exploring different weighting of components, as recently attempted with the RAMRIS system,(17) e.g. by putting less weight on small joints, may also be considered. Currently, WBMRI image quality is lowest in small joints, due to their size and limited image resolution (slice thickness 3-5 mm), but new MRI units and sequence types can provide better resolution.

Not all readers reached the same level of reliability, but several readers' experiences in reading certain areas were also minimal, and as expected this could not be resolved by a few training exercises. Due to the complex anatomy and many regions to score, it is essential to use appropriate equipment, i.e. 1-2 large high-resolution monitors, in an appropriately lit room, where images of the needed number of time points are visualized in an appropriate size without zooming. An online training and calibration module, potentially with a final test of the reader's proficiency compared to expert readers, is considered. Investigating alternative MRI sequences or scanning protocols may also be an option.

Rather few cases were included in the exercises, but for the purposes of development, it was considered more important to understand and discuss potential discrepancies and try to calibrate readers. Higher patient numbers would have increased the certainty of the calculated reliability measures.

The MRI-WIPE score appears to be particularly reliable to use if the average score of two or three readers is used in the final analysis of a study, compared to scores only based on one reader, as the average measure ICCs for 2 or 3 readers were substantially higher than single measure ICCs. With 3 readers, average measure ICCs for status scores were 0.86 and for change scores 0.86.

The MRI-WIPE score is promising, as scoring was reliable between readers with previous good scoring proficiency. The system needs further validation in larger, longitudinal studies, but in its current form it could be of interest in trials striving for global measures of inflammation in peripheral joints and entheses.

Acknowledgement

Thanks to CaRE Arthritis (www.carearthritis.com) for software development of the web-based scoring interface, use of the CaRE web-based DICOM viewer, and for help in organizing the WebEx online meetings. PGC is supported in part by the UK National Institute of Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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Figure legends

Figure 1. Data entry schematics and scoring ranges. Abbreviations: OST, osteitis; SYN, synovitis; STI, soft tissue inflammation. Shoulder/ACW (anterior chest wall): ACJ, acromioclavicular joint; SCJ, sternoclavicular joint; SST, supraspinatus tendon; CS, costosternal joint; MSJ, manubriosternal joint; Should, glenohumeral joint. Hands: DRU, distal radioulnar joint; RC, radiocarpal joint; IC-CMC, intercarpal and carpometacarpal joints; CMC, carpometacarpal joint; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal, DIP, distal interphalangeal. Pelvis: PSIS, posterior superior iliac spine; Iliac C, iliac crest; ASIS, anterior superior iliac spine; G troch, greater trochanter; Isch t, ischial tuberosity; Symph, pubic symphysis. Knees: QFTP, quadriceps femoris tendon insertion into patella; PTP, patellar tendon insertion into patella; PTTT, patellar tendon insertion into tibial tuberosity; MFC, medial femoral condyle; LFC, lateral femoral condyle; F-L, femur-lateral; F-M, femur-

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Figure 2. Web-based DICOM image viewer (provided courtesy of CaRE Arthritis at www.carearthritis.com). Short tau inversion recovery (STIR) images of the left shoulder region from the same patient at two time points (left side and middle) and the corresponding completed data entry schematics (right). White arrows: synovitis (score 3, severe) and osteitis (score 1, mild) of the left glenohumeral joint as assessed on the MRI images and entered in the corresponding data entry schematic.

Table 1. Inter-reader reliability.

	Number of patients	Type of score	MRI-WIPE (total score)	MRI-WIPE (subscore: osteitis, joints)	MRI-WIPE (subscore: synovitis, joints)	MRI-WIPE (subscore: osteitis, entheses)	MRI-WIPE (subscore: soft tissue inflammation, entheses)	ICC for sum scores (single measure)	ICC for sum scores (average measure)	Kappa at lesion-level (osteitis, joints)	Kappa at lesion-level (synovitis, joints)	Kappa at lesion-level (osteitis, entheses)	Kappa at lesion-level (soft tissue inflammation, entheses)
Exercise 3 - All 14 readers	8	Status scores	18.4 (10-32)	4.5 (2-9)	10.2 (5-21)	1.2 (0-3)	2.5 (1-5)	0.28 (-0.37-0.92)	0.44 (-1.18-0.96)	0.34 (0.05-0.74)	0.45 (0.21-0.71)	0.39 (0.00-1.00)	0.30 (-0.03-0.72)
Exercise 3 - 4 musculoskeletal radiologists†	8	Status scores	16.8 (5-39)	4.3 (0-10)	9.3 (3-28)	0.8 (0-2)	2.5 (1-5)	0.67 (0.30-0.87)	0.80 (0.46-0.93)	0.51 (0.32-0.59)	0.59 (0.52-0.71)	0.47 (0.00-1.00)	0.40 (0.24-0.61)
Exercise 4 - All 10 readers	6	Status scores	15.1 (8-28)	4.0 (1-8)	5.2 (2-13)	3.1 (1-7)	2.7 (0-4)	0.55 (-0.08-0.96)	0.71 (-0.17-0.98)	0.49 (-0.02-0.83)	0.54 (0.17-0.84)	0.54 (-0.02-0.89)	0.28 (-0.03-0.72)
(same as above)	6	Change scores	-5.2 (-10-3)	-1.3 (-3-1)	-1.2 (-5-2)	-1.8 (-5-0)	-0.8 (-3-1)	0.43 (-0.67-0.94)	0.60 (-4.0-0.97)	0.26 (-0.19-0.60)	0.22 (-0.12-0.69)	0.23 (-0.04-0.80)	0.14 (-0.09-0.66)
Exercise 4 - 3 musculoskeletal radiologists† + 3 rheumatologists‡	6	Status scores	13.2 (5-26)	3.3 (0-9)	5.1 (1-13)	2.4 (0-7)	2.3 (0-5)	0.67 (0.37-0.96)	0.80 (0.54-0.98)	0.64 (0.29-0.83)	0.67 (0.53-0.84)	0.77 (0.57-0.89)	0.44 (0.19-0.72)
(same as above)	6	Change scores	-6.3 (-14-2)	-1.8 (-4-1)	-1.9 (-7-1)	-1.7 (-5-0)	-1.0 (-4-0)	0.69 (0.27-0.94)	0.82 (0.43-0.97)	0.40 (-0.17-0.60)	0.40 (0.11-0.69)	0.42 (0.15-0.80)	0.35 (0.11-0.66)

Sum scores are mean (range) of the patients' scores (each patient's score is the average of the scores assigned to that patient). All ICC and kappa values are median (range) of estimates for all reader pairs [1 reader pair for 2 readers, 3 reader pairs for 3 readers, etc.]; ICC is two-way model, single measure/average measure (with k = 2 readers), by agreement; Cohen's kappa with squared weights.

Applied MRI sequences: T1 weighted pre-contrast images (Exercise 1-4), post-contrast T1-weighted images (Exercise 3) and STIR (Exercise 1-4). MRI-planes: Shoulder/anterior chest wall: coronal; Hands: coronal; Pelvis: coronal; Knees: sagittal; Feet: Sagittal of ankles and axial of feet (provides coronal view of feet). Readers: A.J.M., F.G., I.E.†, M.Ø.‡, P.B., S.J.P.‡ and S.K.‡ (all exercises); D.G. and W.P.M. (Exercises 1-3); M.S.S. and R.G.L.† (Exercises 2-4); R.P. (Exercises 2-3); L.J.† (Exercises 3-4); J.L.J.† and V.F. (Exercise 2); N.H.† (Exercise 3). † Musculoskeletal radiologists. ‡ Three rheumatologists with the better inter-reader reliability in previous scoring round. Abbreviations: ICC, Intra-class correlation coefficient; MRI-WIPE, MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE); STIR, short tau inversion recovery.

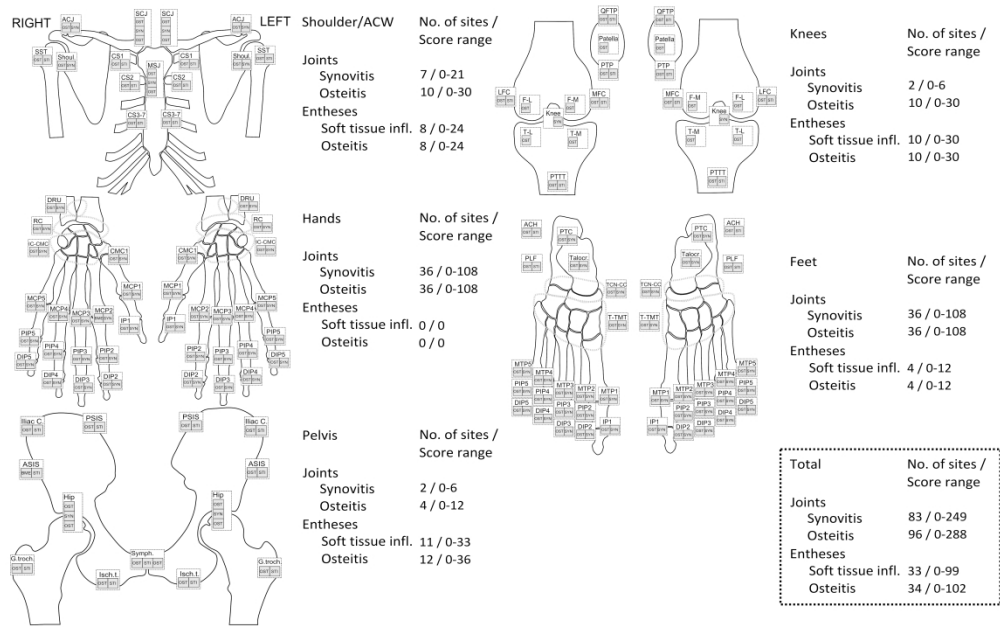


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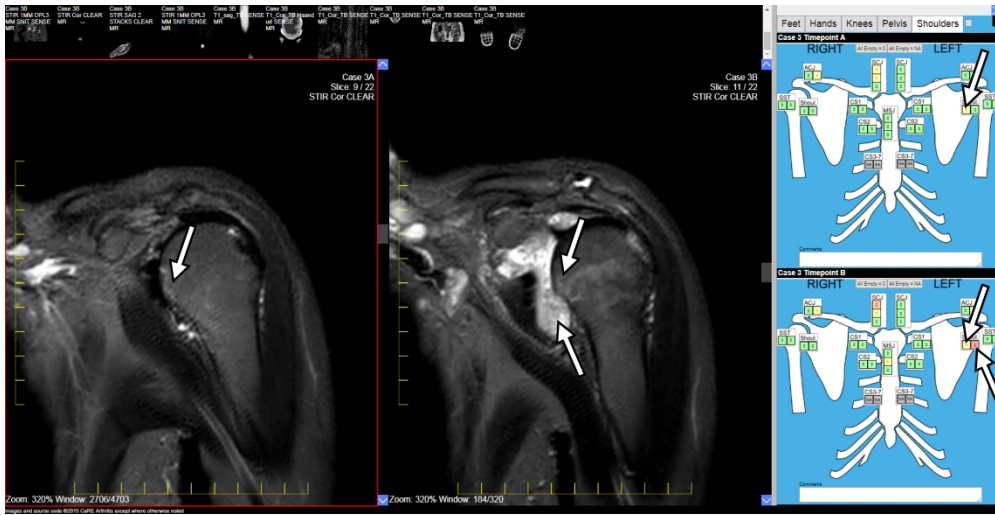


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