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Title

Utility of Magnetic Resonance Imaging (MRI) in Diagnosing and Monitoring Enthesitis in Patients with Spondyloarthritis: an OMERACT Systematic Literature Review

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None

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Running head

MRI enthesitis in SpA

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Abstract

Objectives: A systematic literature review was performed to document published MRI lesion definitions and scoring systems for enthesitis in SpA. **Methods:** PubMed, EMBase and Cochrane library databases were searched for original publications involving adult SpA patients undergoing MRI of axial/peripheral joints. Selected articles were assessed for quality using a standardised assessment tool and metric indices. **Results:** Considering the heterogeneous nature, quality and outcome measures of studies, statistical data pooling was considered inappropriate. A qualitative narrative of results was undertaken based on study designs. **Conclusions:** Lack of a comprehensive, validated score warrants additional research to develop an MRI enthesitis scoring system.

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Introduction

Enthesitis, inflammation at the insertion site of tendon, ligament or joint capsule into bone, is considered to be a key pathological feature in spondyloarthritis (SpA) and psoriatic arthritis (PsA). ¹ Compared to conventional assessment of enthesitis using clinical scores, MRI detects both soft tissue and intra-osseous abnormalities in active enthesitis, potentially aiding early diagnosis and outcome measurement in SpA and PsA. ² With the advent of treat-to-target concept and novel therapies, objective and sensitive monitoring of response of enthesitis to therapy is desirable, and a validated

MRI scoring system would be a useful adjunct to clinical practice as well as providing additional information as an outcome measure in clinical trials.

The Outcome Measures in Rheumatology (OMERACT) MRI in Inflammatory Arthritis Working Group undertook a systematic literature review (SLR) to describe the MRI variables, definitions and scoring systems used to diagnose and monitor enthesitis in SpA. We assessed the quality and reported psychometric qualities, including validity, reliability and responsiveness, of original publications, in order to understand if there were a need for a novel MRI scoring system for enthesitis in SpA. ^{3,4}

Methods

Selection criteria and search strategies: We searched Medline, EMBase and Cochrane Library databases from their inception till February 2018 for original publications involving adult patients (>18 years) with SpA in whom MRI of axial or peripheral joints had been performed using a high-field magnet ($\geq 1.5T$), to assess enthesitis. Exclusion criteria included studies on enthesitis related to other conditions including degenerative, trauma-related, and inflammatory diseases other than SpA. The search strategy was designed to select cross-sectional, case-control, randomised controlled and non-randomised studies in English language containing at least one term from each of the following search blocks: 1) Spondyloarthritis, spondylarthritis, psoriatic arthritis or ankylosing spondylitis. 2) Enthesopathy, enthesitis or entheses. 3) Magnetic resonance imaging or MRI. The selected studies were evaluated for definitions of MRI enthesitis lesions, quality of studies using a standardised assessment tool and for their metric qualities.

Selection of studies and data extraction: Two reviewers (AJM and SK) independently selected the studies, systematically screened the titles and abstracts, applying inclusion and exclusion criteria. Selected articles were retrieved in full, and the same reviewers assessed each article for its eligibility. Disagreements between the reviewers on article selection were resolved by discussion. Data were extracted to a standardised form. Any discordance in opinion was resolved by consensus and involvement of a third reviewer (MØ). The data extraction sheet contained the following information: author, year of publication, study design, study population, number of participants, intervention, comparator, MRI field strength, sequences used, MRI sites used for evaluating enthesitis, definitions of MRI inflammatory and structural enthesitis, and scoring system used. (Table 1)

Quality assessment of selected studies: A standardised tool (Appendix) for assessment of quality of the analysed studies based on a set of 12 predefined criteria addressing the following components: study population, enthesitis imaging feature, outcome of interest, study design and analysis and data presentation, was developed and assessed in a binary mode (yes/no). Concepts from review of quality assessment tools in systematic reviews of observational studies were adapted for developing these criteria.⁵ Quality was reported on a scale of 0-12, with higher scores indicating better quality. Included studies that scored <3 on the scale were excluded from the final analysis.

Psychometric properties of included studies: Each selected article was analysed and assessed in order to determine whether it satisfied certain aspects of validity. The following metric qualities were evaluated: face and content validity, construct validity, criterion validity and discriminant validity (reliability and responsiveness) (Table 2).

Statistical Analysis: Details of the studies were reported with descriptive statistics such as frequencies and percentages for categorical data and mean and SD for continuous data. Due to variability in studies, meta-analysis could not be performed.

Results

Literature search:

The study selection process is depicted in a PRISMA flow diagram (Figure 1).

Study characteristics: Attributes of the included studies are summarised in Table 1.

The majority of included studies were of cross-sectional design (20; 51%).^{2, 6-24} Eight case-control,²⁵⁻³² six cohort,³³⁻³⁸ three randomized controlled trials,³⁹⁻⁴¹ and two other longitudinal studies.^{42,43} were included. Study populations involved SpA in 22, AS in 7, PsA in 9 studies and chronic low back pain in 1 study. Totally, 1534 (range: 8 - 127) individuals in different groups were evaluated for MRI enthesitis in all the studies together. Peripheral enthesitis were evaluated in 24 (62%),^{7,10,11,15-29,34,38} axial enthesitis in 8 studies,^{6,8,12-14,,36,42,43} and enthesitis at both sites using whole body MRI in 7 studies.^{2,9,30,33,37,40,41,} Both T1-weighted (T1w) and T2w fat suppressed or its comparable sequences were included in all the studies. Comparison with other methods of evaluating enthesitis (ultrasonography and clinical assessment) was described in 10 studies,^{7,9-11,18,30-32,35,36,} while 5 studies compared different MRI sequences to assess enthesitis.^{6,13,14,25,42} Only 4 studies compared efficacy of MRI against a gold standard.^{11,13,35,42,}

Qualitative assessment of enthesitis at different regions was used in 82% of studies. Only eight studies mentioned a semi-quantitative or quantitative MRI scoring system.^{2,14,16,17,19,25,39,40,} No studies described a validated, comprehensive MRI

scoring system measuring all the aspects of enthesitis in any region. The majority of studies defined inflammatory enthesitis as enhancement of ligaments, increased signal intensity, perientheseal increased signal intensity, adjacent bone marrow edema, soft tissue signal around ligaments or tendons, thickening of ligaments, capsulitis in sacroiliac joints, extracapsular soft tissue enhancement, Achilles tendon diameter of bone marrow edema, perientheseal fluid and/or tendinitis in T1w post-gadolinium or short tau inversion recovery (STIR) sequences. Enteseal structural damage defined by few studies include bone erosions, enthesophytes, focal signal intensity changes and calcaneal spur in T1w-sequences. ^{2,7,16,25,27-29,32}

Quality assessment of included studies: Quality scores assessed using a standardised tool are provided in Table 2. With one exception, all 38 studies met the minimal quality requirement score of 4. High quality scores (10-12) were present in only 2 studies,^{2,40} while the remaining 36 studies had moderate quality scores (5-9).

Assessment of psychometric properties: Table 2 describes psychometric properties of the selected studies. Face validity was assessed in 33 (87%) studies; content validity in 19 (50%) studies, and construct validity of MRI as related to ultrasonography and clinical examination in 5 (13%) and 6 (16%) studies, respectively. Five studies reported construct validity of different MRI sequences in relation to each other. ^{6,13,14,25,42} Criterion validity of MRI in relation to histology was described only by Tan et al.²² Reliability of MRI in detecting enthesitis using various scoring methods was reported by 26 (68%) studies in which images were evaluated by two independent readers who were blinded to clinical outcomes. Responsiveness of various MRI enthesitis scores was reported in 6 (18%) studies, of which three showed statistically significant changes ($p < 0.05$). ^{37,40,41}

Discussion

Axial and peripheral enthesitis constitute a core feature of SpA and PsA. The OMERACT PsA core domain set includes enthesitis, which makes it mandatory to be assessed in all clinical trials and observational studies.⁴⁴ MRI allows sensitive assessment of enthesitis in clinical trials. We have critically evaluated the published literature for available methods of evaluating enthesitis using MRI in SpA and PsA patients, and we identified notable limitations regarding standardisation of MRI enthesitis definitions across studies and validity of available semi-quantitative scores as outcome measures. The findings suggest there is no currently available reliable and validated MRI scoring system for enthesitis. Many studies have included definitions of MRI lesions suggestive of enthesitis,^{2,7,9,10,18,23,24,28,29,33,34,37,39,40} but definitions differ, hindering direct comparison of the available methods. A fifth of the selected studies described a semi-quantitative scoring system, albeit without standardisation and lack of internal validity, as all were developed based on expert opinion.

Poor content validity of reported scoring methods was another limitation of the literature. Most studies have focused on assessing inflammatory aspects of enthesitis, and not the structural variables which denote chronic, irreversible changes. MRI inflammatory lesions are amenable to change and responsive to therapy. Wide variation in the enthesal sites to be assessed adds to the challenge in standardisation. Lack of a standardised definition to define the borders of enthesitis makes it difficult to differentiate it from other inflammatory variables, like synovitis and tenosynovitis, thus increasing the variability of scores in each study.

Construct validity was evaluated in relation to ultrasonography and clinical examination. Most of the studies showed a poor correlation between MRI and ultrasonography. This again emphasises the lack of standardised definitions of MRI enthesitis lesions. Limited information exists regarding criterion validity as only one study which compared MRI with histology. Lack of significant responsiveness of available qualitative and semi-quantitative MRI enthesitis scores suggest limited utility as outcome measures in clinical trials.

The above-mentioned limitations and the lack of validated, generally accepted MRI enthesitis assessment systems warrant the development of a reliable and feasible MRI enthesitis scoring system, to increase the utility of MRI as an outcome measure in SpA and PsA clinical trials.

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