Title

Utility of Magnetic Resonance Imaging in Diagnosis and Monitoring Enthesitis in Patients with Spondyloarthritis: an OMERACT Systematic Literature Review

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Key indexing terms

Enthesopathy, Magnetic resonance imaging, Spondyloarthropathy, Inflammation, OMERACT

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Source of financial support

This project has not received any outside funding

Conflicts of interest

None

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Running head

MRI enthesitis in SpA

Word count

1466/1500

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.

Word count: 100

PROSPERO registration number: CRD42018090537

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 (≥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 enthesis. 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. Entheseal 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 entheseal 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.

Acknowledgements

AJB and PGC are supported in part through the UK National Institute for 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 1: Flow diagram of article selection (PRISMA)

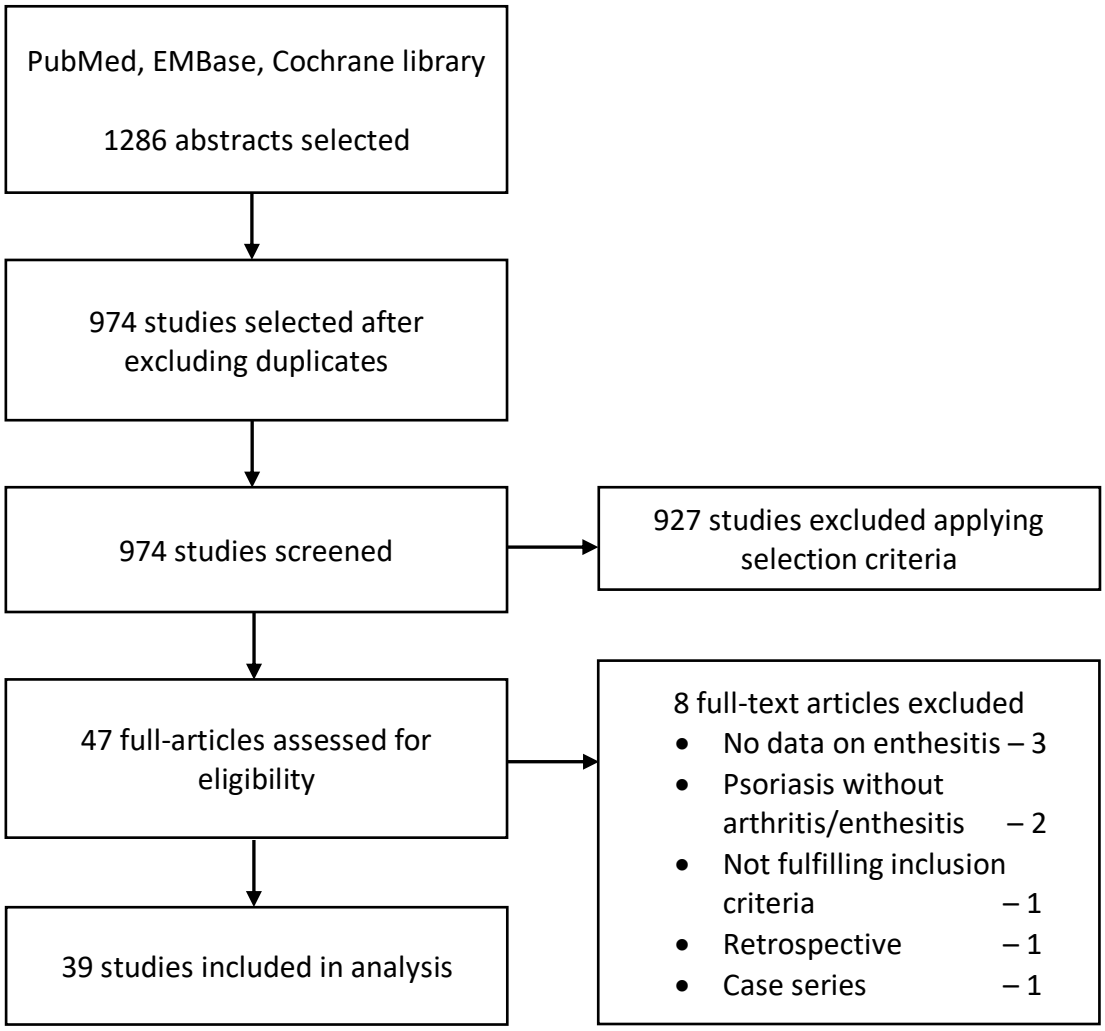

Table 1: Characteristics of included studies

Author/Year of publication	Study population	Number of participants	Intervention	Comparator	MRI field strength	Sequences	MRI sites	Scoring systems
Cross sectional studies								
Fournie 1997	AS fulfilling Amor criteria and PsA based on seronegative joint disease with psoriasis	8 (5; 3)	MRI	NA	NA	T1W Gd	Anterior chest wall	Qualitative
McGonagle 2002	SpA with plantar fasciitis; Mechanically induced plantar fasciitis	28 (17; 11)	MRI	NA	0.5; 1.5	T1W; SPIR	Plantar fascia	Semi quantitative
Olivieri 2002	SpA with dactylitis	6	MRI	NA	1.5	T1W; T2W FS; GRE-T2W	Finger tendon insertions	Semi quantitative
Tan 2006	DIP joint PsA; DIP joint OA; Healthy subjects	30 (10; 10; 10)	MRI	NA	1.5	T1W; T2W FS; PD; 3DGE; T1W FS Gd	DIP joints	Qualitative
McQueen 2007	PsA	10	MRI	NA	0.6	T1W; T1W Gd; STIR	2nd-5th finger	Semi quantitative
Tan 2007	DIP joint PsA; DIP joint OA; Healthy subjects	30 (10; 10; 10)	MRI	NA	1.5	T1W; T2W FS; PD; 3DGE; T1W FS Gd	DIP joints	Qualitative
Marzo-Ortega 2009	SpA; RA	20 (10; 10)	MRI	NA	1.5	T1W; DCE-MRI; SPIR FS Gd	MCP joints	Qualitative
Maksymowicz 2010	SpA or suspected SpA	35	MRI T1W FS Gd	MRI T2W FS	1.5	T1W; T1W FS; T2W FS; T1W FS Gd	Enthesitis of SIJ ligaments	Semi quantitative
Feydy 2012	SpA; Controls hospitalized low-back pain	75 (51; 24)	MRI	NA	1.5	T1W; STIR	Heel enthesitis	Qualitative
Althoff 2013	SpA	75	MRI	NA	1.5	T1W; STIR	Whole-body	Qualitative
Aydin 2013	SpA with swollen knee	21	MRI	US	1.5	T1W; T2 SPIR; TI SPIR; TI SPIR Gd	Knee entheses	Qualitative
Braum 2013	Suspected inflammatory joint disease	69	MRI	Clinical	1.5	T1W; T1W FS Gd; STIR	Collateral ligaments of finger joints	Qualitative
Paramarta 2014	Knee or ankle arthritis: SpA; RA; crystal arthritis	41 (13; 20; 8)	MRI	NA	1.5	T1W; T2W FS; STIR; T1W FS Gd	Knee and ankle entheses	Qualitative
Ramirez 2014	Greater trochanter pain: SpA/RA/no inflammatory disease	40	MRI	NA	1.5	T1W; T2W FS	Greater femoral trochanter	Qualitative

Poggenborg 2015	PsA; SpA; Healthy subjects	48 (18; 18; 12)	MRI	NA	3	T1W; STIR	Whole-body	Semi quantitative
Tan 2015	PsA with dactylitis; Healthy subjects	22 (12; 10)	MRI	NA	1.5	T2W FS; T1W; TSE; T1W FS Gd	Fingers/toes	Qualitative
Agten 2016	Suspected SpA	68	MRI T1W Gd	MRI STIR	1.5; 3.0	T1W FS Gd; STIR	T12-S1 interspinous and supraspinous ligaments	Qualitative
Giraudo 2016	Suspected SpA	106	MRI T2W; MRI PD	T1W Gd	3	T2W; PD; T1W; T1W FS Gd	SIJ anterior and posterior ligaments	Qualitative
Aivazoglou 2017	SpA	16	MRI	NA	1.5	T1W FS; T1W FS Gd; STIR	Enthesitis of SIJ ligaments	Qualitative
Maldonado 2017	SpA	40	MRI	US; CR	1.5	T1W; T1W FS Gd; T2W FS or STIR	Achilles tendon insertion; Plantar fascia	Qualitative
Case control studies								
Olivieri 1998	SpA fulfilling Amor's criteria and showing severe Achilles enthesitis	19 pathologic 9 normal tendons	MRI	US	0.5	T1W, PD, T2W	Ankle	Qualitative
Lambert 2004	AS; Healthy subjects	111 (17; 94)	MRI	NA	1.5	T1W; T2W; PD; T2W FS or STIR	Shoulder	Qualitative
Erdem 2005	AS; Healthy subjects	33 (23; 10)	MRI	NA	1.5	T1W; T2W; STIR	Heel enthesitis	Qualitative
Wiell 2007	PsA; RA; Healthy subjects	25 (15; 5; 5)	MRI	US	0.6	T1W; STIR; T1W Gd	Fingers/toes	Qualitative
Emad 2010	PsA/AS/ReA/IBD/Skin psoriasis; Healthy subjects	76 (56; 20)	MRI	NA	1.5	T1W; T1W Gd	Knee entheses	Qualitative
Weckbach 2011	PsA	30	MRI	Clinical	1.5	STIR, VIBE; VIBE Gd	Whole-body	Qualitative
Wiell 2013	SpA; non-SpA; Healthy subjects	37 (12; 15; 10)	MRI	US	0.6	T1W; STIR; T1W Gd	Achilles tendon and enthesis	Qualitative
Chen 2018	PsA; Healthy subjects	16 (9; 7)	MRI 3D UTE Cones	MRI T1W	3	3D UTE Cones; T1W	Achilles tendon	Quantitaiv e
Cohort studies								

Godfrin 2004	Entheseal pain at multiple sites	33	MRI	Clinical	1.5	T1W; T2W; T1W FS Gd and/or STIR	Not described	Qualitative
Eshed 2008	SpA with hindfoot pain	27	MRI	NA	0.2; 1.5	T1W; STIR; T1W FS Gd; T1W GRE FS	Heel enthesitis	Qualitative
Karpitscha 2013	AS	10	MRI	NA	1.5	T1W; STIR	Whole-body	Qualitative
Zhen-Guo 2013	AS	58	MRI	CR; Clinical	1.5	T2W; T1W; STIR; T1W FS Gd	Hip	Qualitative
Althof f2016	SpA	41	MRI	Clinical	1.5	T1W; STIR	Whole-body	Qualitative
Marzo-Ortega 2001	SpA	10	MRI	NA	1.5	T1W; T2W FS; T1W FS Gd	Depending on symptoms of each patient	Qualitative
Tan 2004	AS fulfilling modified NY criteria	9	MRI	NA	1.5	T1TSE, STIR	SIJ and spine	Semi quantitative
de Hooge 2013	Chronic back pain	127	MRI T1W FS Gd	MRI STIR	1.5	T1W; T1W FS Gd; STIR	SIJ enthesitis/ capsulitis	Qualitative
Randomised controlled trials								
Dougados 2010	SpA with heel enthesitis	24	MRI	NA	Not reported	T1W; STIR	Heel enthesitis	Quantitaive
Song 2011	SpA	76	MRI	NA	1.5	T1W; STIR	Whole-body	Qualitative
Krabbe 2018	SpA	49	MRI	NA	3	T1W; STIR	Whole-body	Semi quantitative

* AS – ankylosing spondylitis, SpA – spondyloarthritis, PsA – psoriatic arthritis, RA – rheumatoid arthritis, OA – osteoarthritis, MCP – metacarpophalangeal joint, DIP – distal interphalangeal joint, SIJ – sacroiliac joints, T1W – T1 weighted, T2W – T2 weighted, Gd – gadolinium, FS – fat suppressed, SPIR – spectral pre-saturation with inversion recovery, GRE – gradient recalled echo, PD – proton density, 3D-GE – 3D gradient echo, STIR – short tau inversion recovery, DCE – dynamic contrast enhanced, TSE – turbo spin echo, VIBE – volumetric interpolated breath-hold sequence, UTE – quantitative ultrashort echo time, US – ultrasound, CR – conventional radiograph

Table 2: Psychometric properties and quality scores of selected studies (n = 38)

Author/Year of publication	Face validity*	Content validity*	Construct validity*	Criterion validity*	Reliability*	Responsiveness*	QUALITY SCORING
Cross sectional studies							
McGonagle 2002	YES	YES	NO	NO	YES	NO	9
Olivieri 2002	YES	NO	NO	NO	NO	NO	7
Tan 2006	YES	NO	NO	NO	YES	NO	7
McQueen 2007	YES	YES	NO	NO	YES	NO	8
Tan 2007	NO	NO	NO	YES	NO	NO	5
Marzo-Ortega 2009	NO	NO	NO	NO	YES	NO	7
Maksymowicz 2010	NO	NO	NO	NO	NO	NO	6
Althoff 2013	YES	YES	NO	NO	YES	NO	7
Aydin 2013	YES	YES	YES	NO	YES	NO	8
Braum 2013	YES	YES	YES	NO	NO	NO	7
Ramirez 2014	YES	NO	NO	NO	NO	NO	8
Paramarta 2014	YES	YES	NO	NO	YES	NO	7
Poggenborg 2015	YES	YES	YES	NO	YES	NO	10
Tan 2015	YES	YES	NO	NO	YES	NO	7
Giraudo 2016	YES	NO	NO	NO	YES	NO	7
Agten 2016	NO	NO	YES	NO	YES	NO	8

Maldonado 2017	YES	YES	YES	NO	YES	NO	7
Aivazoglou 2017	YES	NO	YES	NO	NO	NO	7
Case control studies							
Olivieri 1998	YES	YES	YES	NO	NO	NO	6
Lambert 2004	YES	YES	NO	NO	YES	NO	6
Erdem 2005	YES	YES	NO	NO	YES	NO	5
Wiell 2007	YES	NO	NO	NO	NO	NO	8
Emad 2010	YES	NO	NO	NO	YES	NO	6
Weckbach 2011	YES	NO	YES	NO	YES	NO	7
Feydy 2012	YES	NO	NO	NO	YES	NO	8
Wiell 2013	YES	YES	YES	NO	YES	NO	9
Chen 2018	YES	YES	YES	NO	NO	NO	6
Cohort studies							
Godfrin 2004	YES	NO	YES	NO	YES	NO	6
Eshed 2008	YES	YES	NO	NO	YES	NO	6
Zhen-Guo 2013	YES	NO	YES	NO	YES	NO	9
Karpitschka 2013	YES	YES	YES	NO	YES	YES	9
Althoff 2016	YES	YES	NO	NO	YES	NO	8
Marzo-Ortega 2001	YES	YES	YES	NO	YES	YES	8

Tan 2004	YES	NO	NO	NO	NO	YES	8
de Hooge 2013	YES	NO	YES	NO	NO	YES	9
Randomised controlled trials							
Dougados 2010	NO	NO	NO	NO	NO	NO	7
Song 2011	YES	NO	NO	NO	YES	YES	9
Krabbe 2018	YES	YES	NO	NO	YES	YES	11

*Face validity was defined as expert opinion on the credibility of scoring system used in each article to measure enthesitis. Content validity estimated the reliability of the scoring system used in each study to measure the full spectrum of outcome - inflammatory and structural changes. Construct validity was achieved when MRI evaluation of enthesitis correlated with the following concepts of enthesitis: 1) clinical assessment of enthesitis using a validated enthesitis score (e.g., MASES), 2) ultrasound or radiographic assessment of enthesitis sites, and/or 3) comparison of different sequences of MRI in assessing enthesitis. Criterion validity was achieved when MRI evaluation of enthesitis correlated with a gold standard (e.g., histology). Reliability was defined in studies mentioning inter-rater reliability measures of scoring consistency between and within MRI readers, e.g. inter/intra-class correlation coefficients (ICCs) or kappa statistics. Responsiveness was achieved in studies documenting statistically significant changes in relation to treatment introduction or change.