Psoriatic Arthritis Sonographic Enthesitis Instruments: A Systematic Review of the Literature

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ABSTRACT. ***Objective.*** As part of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) ultrasound working group, we performed a systematic review of the literature to assess the evidence and knowledge gaps in scoring instruments of enthesitis in psoriatic arthritis (PsA).

Methods. A systematic search of PubMed, EMBase, and Cochrane databases was performed. The search strategy was constructed to find original publications containing terms related to ultrasound, enthesitis, spondyloarthritis (SpA) or PsA. Data extraction focused on the properties of the sonographic enthesitis instruments used in each study following components of the Outcome Measures in Rheumatology (OMERACT) filter: feasibility, test-retest reliability, construct validity as related to clinical assessment of enthesitis, biomarkers of inflammation and imaging of enthesitis by other modalities, discriminative validity, and responsiveness to treatment.

Results. Fifty-one of 310 identified manuscripts were included. Only 1 scoring instrument of enthesitis was specifically developed and validated in patients with PsA. Only 18 (35%) of the studies involved patients with PsA, while the remaining studies focused on SpA. In PsA, construct validity was assessed using biomarkers and clinical examination in 1 (2%) and 11 (21.5%) of the studies, respectively, whereas no studies used imaging for the same purpose. Only 2 (4%) of the studies assessed discriminative validity in PsA. Responsiveness to treatment was assessed in 7 studies, none of which included patients with PsA.

Conclusion. Although sonographic enthesitis scoring instruments have been developed for SpA, only a few have been validated in PsA. None of them passed the OMERACT filter in patients with PsA. Additional research is required before endorsing a specific instrument for the assessment of enthesitis in patients with PsA. (J Rheumatol First Release July 15 2018; doi:10.3899/jrheum.171466)

Key Indexing Terms:
PSORIATIC ARTHRITIS ENTHESITIS SCORING INSTRUMENTS

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Dr. Eder is supported by a New Investigator Salary Grant from the Arthritis Society and the Canadian Association of Psoriasis Patients.

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Accepted for publication May 7, 2018.

Enthesitis, the inflammation of the insertion of tendon, ligament, and capsule into the bone, is a prominent feature of spondyloarthritis (SpA), including psoriatic arthritis (PsA). The evaluation of enthesitis is conventionally conducted by clinical examination, a method with significant limitations, including low sensitivity and specificity. Imaging modalities including ultrasound (US) and magnetic resonance imaging (MRI) have gained interest in enthesis evaluation. US can identify abnormalities at the enthesis in high fidelity and may assist with the diagnosis and management of patients with SpA[1].

In 2014, the Outcome Measures in Rheumatology (OMERACT) US special interest group reached a consensus regarding the sonographic elementary lesions defining SpA-related enthesitis. The following sonographic lesions at the enthesis were included: hypoechogenicity (loss of fibrillar architecture), thickening (compared to the body of the tendon), calcifications, enthesophytes (step-up of bony prominence), bone erosions (step-down with cortical break), and Doppler signal[2]. This was an important first step toward

ensuring a high degree of consistency across studies using US to assess enthesitis. However, while this exercise defined the concept of sonographic enthesitis at the level of any given enthesis, it did not address the issue of evaluating the extent of enthesitis at the patient level. In other words, it provided standard definitions for evaluating the presence of enthesitis at a specific site, such as Achilles tendon, but it did not provide a tool that can help the physician in quantifying the burden of entheseal involvement in a patient with PsA.

Several sonographic enthesitis instruments have been developed, mostly in patients with axial SpA (axSpA), to quantify the extent of enthesitis at the global patient level. Glasgow Ultrasound Enthesitis Scoring System (GUESS) assesses 5 entheseal sites in the lower extremities. The original GUESS does not include power Doppler vascularization[3]. The score developed by D'Agostino includes the assessment of sonographic enthesitis at 10 sites in the upper and lower extremity sites as in GUESS[4]. Sonographic Entheseal Index (SEI) involves the assessment of the same 5 entheseal sites as in GUESS but includes a distinction between chronic entheseal lesions, such as erosions and calcifications, and acute entheseal lesions, such as increased thickening and hypoechogenicity[5]. The Madrid Sonographic Enthesitis Index (MASEI) is a weighted score that assesses 6 entheseal sites. MASEI assigns higher scores to erosions, larger enthesophytes, and Doppler signal compared with other elementary lesions. The Belgrade Ultrasound Enthesitis Score (BUSES) evaluates 6 sites[6]. Lastly, Ultrasound composite scores for the assessment of inflammatory and structural pathologies in PsA (PsASon) score is not exclusively an entheseal score, albeit a composite score that also includes joints. This score includes only 2 sites, the common extensor tendon at the lateral epicondyle and the insertion of the distal patellar tendon[7].

The instruments described above have been increasingly used in studies evaluating entheseal abnormalities, though they may have some limitations. All but 1 were developed and validated in patients with predominantly axSpA, thus their validity in patients with PsA is unknown. Further, entheseal sites were chosen based on expert opinion and most of the included sites are in the lower extremities, which are more prone to mechanically related enthesopathies, especially in overweight patients[8]. Currently, there is limited information on the effect of confounding factors that are prevalent in patients with PsA, such as obesity and mechanical stress, on the performance of these scoring systems in psoriatic patients.

US could be used to quantify the extent of enthesitis for diagnostic purposes, patient management, and monitoring treatment response in clinical trials, observational studies, and clinical practice[9]. Implementing a treat-to-target approach in patients with PsA requires an accurate evaluation of disease activity in all core domains, including enthesitis. However, this purpose requires validated instruments (outcome measures) for patients with PsA. Therefore, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) US working group performed this systematic literature review (SLR) to evaluate the current evidence and knowledge gaps in instruments for the assessment of enthesitis in PsA.

Our aims in this SLR were first to describe the measurement properties of the available sonographic enthesitis instruments particularly used in patients with PsA; secondly, to evaluate the validity of the available scoring systems according to the OMERACT filter measurements[10]. Lastly, we aimed to critically appraise the quality of the studies on different scoring systems in PsA. The results of this SLR will inform GRAPPA about the validity of existing scoring systems for assessment of sonographic enthesitis in PsA and determine whether a new scoring system for the assessment of enthesitis is warranted.

MATERIALS AND METHODS

Literature review: Data sources and search strategies. We searched Medline, EMBase, and Cochrane Central Register databases from their inception (1966, 1980, and 1982, respectively) to January 3, 2017, using a strategy designed by an experienced medical librarian (MA) to find primary references. The search strategy was constructed to find publications containing at least 1 term from each of 3 search blocks: (1) The terms *psoriasis*, *psoriatic arthritis*, *spondyloarthritis*, *spondyloarthropathy*, or *ankylosing spondylitis*; (2) *Enthesitis*, *enthesopathy, enthesis,* or *entheses* and in addition to *tendon*, synonyms were included; (3) *Ultrasound, ultrasonography, sonography*, or *Doppler*. The search was limited to English publications in humans.

Studies selection. Titles and abstracts of articles were systematically screened by 2 reviewers (SBU and OE) regarding inclusion and exclusion criteria. Selected publications were retrieved in full, and 2 reviewers (SBU and OE) independently assessed them for eligibility. The final search was verified by a third author (LE). Additional papers were obtained by scanning the references of the selected articles. To be included in the systematic review, original studies needed to fulfill the following inclusion criteria: study design (case-control, cross-sectional, or cohort); population (studies that assessed patients with SpA, PsA, or psoriasis); outcome (studies that evaluated sonographic enthesitis at the patient level). Studies that evaluated only 1 entheseal site and those that used 3-D US were excluded.

Data extraction. Data were independently extracted by 2 authors (SBU and OE) according to a standardized form and summarized in tables. Discrepancies were resolved by consensus and involvement of a third author if needed (LE). For each study the following information was recorded: year of publication, study design, study population, sample size, the mean age, body mass index, disease duration, sex distribution, US machine, US settings, sonographic entheseal scoring system used, entheseal sites assessed, and sonographic elementary lesions assessed.

Appraisal of measurement properties of included studies. Feasibility was assessed as the time to complete the examination. Reliability (test-retest) was considered positive if common measures for interrater and intrarater reliability were measured and were found to be with moderate to high agreement [$\kappa > 0.4$ or intraclass correlation coefficient (ICC) > 0.6][11]. Construct validity was achieved when US evaluation of enthesitis significantly correlated with each the following 3 theoretical concepts of enthesitis: (1) clinical enthesitis as assessed on physical examination using an established clinical enthesitis score (e.g., Leeds Enthesitis Index); (2) laboratory biomarkers of inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); (3) other imaging modality assessing

enthesitis, such as radiographs or MRI. Responsiveness was evaluated by the ability of the instrument to measure change in response to an intervention (e.g., study drug) when a change has occurred (based on an external construct). Discriminant validity was considered positive if a strict cutoff was found to significantly distinguishing disease (e.g., PsA or SpA) from healthy controls.

Quality assessment of identified studies. The risk of bias and applicability were assessed using QUADAS-2[12]. This tool consists of 4 domains: patient selection, index test, reference standard, and flow and timing of the index test. Each domain assesses the risk of bias (e.g., patient selection, risk of bias related to the conduct or interpretation of the results of the external construct, and the index tests). In addition, the applicability regarding patients, external construct, and the index tests is assessed. In each domain, the risk of bias and the concerns regarding applicability are scored independently (low, high, or unclear). We illustrated the process as recommended in the Preferred Reporting Items for the Systematic Reviews and Meta-Analyses (PRISMA) statement[13].

RESULTS

Literature search. Figure 1 is a flowchart of the article selection. The initial literature search retrieved 310 abstracts. After an initial screening of abstracts, 118 full text manuscripts were chosen for further review. After reviewing the full text manuscripts, 67 publications were excluded for the following reasons: 33 evaluated only a single entheseal site, 12 were the wrong study type (e.g., review, case report), 9 studies did not provide sufficient data regarding the scoring system used, 6 had irrelevant study populations, 2 did not assess entheses, and for 5, full text was not available. A total of 51 studies were included in the manuscript[2,3,4,5,6,7,14-59].

Study characteristics. The characteristics of the studies are summarized in Table 1[3,4,5,6,7,14-59]. The study designs were 38 cross-sectional and 13 prospective cohort studies. The study population was divided as follows: 18 (35%) assessed patients with PsA, 17 (33%) assessed patients with SpA, 10 (19.6%) examined patients with ankylosing spondylitis (AS), 5 (9.8%) examined patients with psoriasis, and 1 assessed juvenile idiopathic arthritis. Some studies used scoring methods that were not previously validated, although often these scoring methods used entheseal sites and elementary lesions similar to those in validated scores. Therefore, we aggregated these studies along with the studies that used the formal validated instruments. The following sonographic entheseal scores or their modifications were used: 14 (27.4%) GUESS score, 9 (17.6%) MASEI, 6 (11.7%) for the score used by D'Agostino, 4 (7.8%) BUSES, 3 (5.8%) SEI, and 1 (2%) PsASon-score. The entheseal sites and the elementary lesions evaluated in the studies are presented in Table 2. Positioning of the patient during enthesis scanning, as described in the study protocols, was almost uniform. All scores (MASEI, GUESS, SEI, BUSES, PsASon) assessed the quadriceps tendon, proximal and distal patellar tendon while the knee is flexed, and the Achilles and plantar fascia while

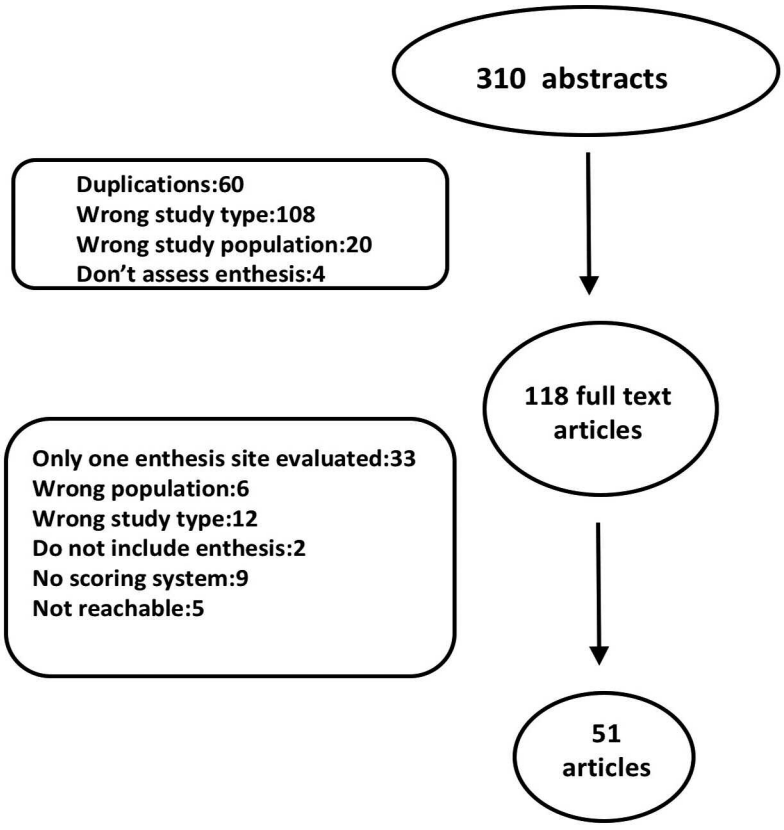

Figure 1. Flowchart of the article selection. "Not reachable" means full text was not available.

Table 1. Characteristics of the studies.

Year	Authors, Ref No.	Study Design	Population and Size	Age, yrs	BMI	Sex Ratio (M:F)	Disease Duration, yrs	US Machine Model	Purpose of Study
MASEI									
2016	Lackner[28]	Prospective	PsA 83	51.8	NA	1.56	7.5	MyLab Twice	Outcome
2015	Hamdy[36]	Cross sectional	Psoriasis 50	44.8	NA	1.38	8.7	Picus 4D	Diagnostic
2014	Husic[33]	Prospective	PsA 70	51.1	27	2.33	7	MyLab Twice	Diagnostic
2014	Eder[48]	Cross sectional	PsA 50	53.2	30.9	1.77	14.2	MyLab 70XVG	Diagnostic
2011	de Miguel[50]	Cross sectional	SpA 113	33.3	NA	0.95	0.91	Logiq 9 machine	Diagnostic
2009	Munoz-Fernandez[24]	Cross sectional	SpA 21	47.6	NA	0.85	NA	GE Logiq 5 Pro	Diagnostic
2009	de Miguel[51]	Cross sectional	SpA 25	44.8	NA	1.84	15	GE Logiq 5 Pro	Diagnostic
2016	Shenoy[17]	Cross sectional	JIA 30	16	NA	Males only	4	Esaote MyLab40	Diagnostic
2015	Acquacalda[59]	Prospective	Psoriasis, PsA 34	43.45	NA	1.42	15.9	MyLab 70 XVG	Diagnostic
GUESS									
2013	Hamdi[38]	Prospective	AS 60	36	NA	4	8.8	Philips HD11TM	Diagnostic
2013	Aydin[56]	Cross sectional	Psoriasis 42, PsA 58	47.4	26.2	1.23	18.4	Logiq E9 machine	Diagnostic
2011	Ruta[18]	Cross sectional	SpA 60	37	25	2.13	6.375	MyLab 60	Diagnostic
2011	Gutierrez[40]	Cross sectional	Psoriasis 45	NA	24.3	NA	NA	MyLab 70 XVG	Diagnostic
2008	Gisondi[41]	Cross sectional	Psoriasis 30	56.3	28.5	1.22	NA	ATL HDI 3000	Diagnostic
2007	Genc[42]	Prospective	RA 20, AS 16	42	26	0.63	8.5	Siemens, Sonoline Adara	Response to treatment
2006	Borman[53]	Cross sectional	SpA 44	39.9	NA	1.59	9	A Hitachi US device	Diagnostic
2005	Genc[43]	Cross sectional	RA 24	42.9	26	0.68	8.46	Siemens Sonoline Adara	Diagnostic
2002	Balint[3]	Cross sectional	SpA 35	48	NA	2.5	24.9	ATL HDI 3000	Diagnostic
2013	Bandinelli[54]	Cross sectional	PsA 92	51	NA	0.8	0.61	My Lab 70 XVG	Diagnostic
2016	Rovisco[20]	Cross sectional	IBD 76	NA	NA	NA	NA	MyLab 70XVG	Diagnostic
2016	Michelsen[26]	Cross sectional	PsA 141	52.4	28.3	1	9.5	Siemens Acuson S2000, GE logic E	Diagnostic
2012	Ash[57]	Cross sectional	Psoriasis 46	46.1	26.1	0.97	14.1	Logiq E9 ,Logiq 5	Diagnostic
2015	Ruta[19]	Prospective	SpA 34	31	NA	2.44	1	MyLab 70 XV	Response to treatment
SEI									
2011	Hamdi[37]	Cross sectional	AS 60	36	NA	4	8.8	Philips HD11TM	Diagnostic
2007	Alcalde[5]	Cross sectional	AS 44	43	NA	3.8	17	Toshiba Capasee	Diagnostic
2015	Hu[34]	Prospective	AS 41	27.7	NA	12.66	7.2	Aloka α5, Tokyo, Japan	Response to treatment
D'Agostino									
2016	Perrotta[21]	Cross sectional	PsA 21	50.2	NA	2	1.2	MyLab 70 XVG	Diagnostic
2011	D'Agostino[52]	Prospective	Suspected SpA 118	40.1	NA	0.6	2.2	Esaote Technos MPX	Diagnostic
2003	D'Agostino[4]	Cross sectional	SpA 164	38	NA	2.11	16	Esaote AU5 Epi	Diagnostic
2011	Spadaro[16]	Cross sectional	AS 36	51.3	NA	3.5	15.8	MyLab 70 XVG	Diagnostic
2014	Mouterde[25]	Prospective	SpA 14	41.2	NA	3.67	14.2	MyLab 70	Response to treatment
2012	Marchesoni[27]	Cross sectional	PsA 30	52	25	0.51	9.8	Logiq5 machine	Diagnostic
BUSES									
2015	Milutinovic[6]	Prospective	SpA 76	47.36	NA	1.27	10.67	Logiq 9	Diagnostic
2015	Janta[31]	Cross sectional	PsA102	52.4	NA	1.08	13.2	Logiq E9	Response to treatment
2012	Freeston[44]	Cross sectional	PsA 42	45.7	28.15	0.79	1	Philips HDI 5000	Diagnostic
2010	Naredo[23]	Prospective	SpA 327	44.5	NA	2.37	10	Logiq 5 PRO	Response to treatment
PsASon									
2014	Ficjan[7]	Prospective	PsA 83	51.8	27.2	2.8	7.5	MyLab Twice	Diagnostic
Other									
2016	Kristensen[29]	Cross sectional	PsA 20	49	NA	NA	18.1	Hitachi HA710	Diagnostic
2012	Feydy[45]	Cross sectional	SpA 51	50	NA	1.12	1.35	Toshiba Aplio	Diagnostic
2011	Naredo[22]	Cross sectional	Psoriasis 162	41.8	NA	0.77	13.4	Logiq 9	Diagnostic
2011	Ibrahim[32]	Cross sectional	PsA 71	51.3	NA	0.96	5.5	Bradford, Philips HDI 5000	Diagnostic
2011	Hu[35]	Cross sectional	AS 161	27.2	NA	5.7	4.6	Acuson Sequoia 512 Siemen	Diagnostic
2006	Kiris[30]	Cross sectional	AS 30	34.1	NA	NA	10	Toshiba, Aplio SSA 770A	Diagnostic
2003	Falsetti[46]	Cross sectional	OA, RA, PsA 548	60	NA	0.58	3	Toshiba Tosbee SAL 240	Diagnostic
2010	Delle Sedie[49]	Cross sectional	PsA 83	53.4	NA	2.2	9.1	Logiq 9	Diagnostic

Table 1. Continued

Year	Authors, Ref No.	Study Design	Population and Size	Age, yrs	BMI	Sex Ratio (M:F)	Disease Duration, yrs	US Machine Model	Purpose of Study
Other uncommon sites									
2015	El Miedany[47]	Prospective	Early PsA 126	35.9	35.1	1.3	2	NA	Diagnostic
2016	Ward[15]	Cross sectional	SpA 20	43.4	27.4	0.81	NA	MyLab 70	Diagnostic
2013	Ali Ou Alla[58]	Cross sectional	AS 38	36	NA	1.37	9.6	Toshiba Xario	Diagnostic
2012	Gutierrez[39]	Cross sectional	SpA 46	50.6	24.9	2.83	4.7	MyLab 70 XVG	Diagnostic
2016	Zabotti[14]	Cross sectional	PsA 26	50.4	NA	0.42	0.5	MyLabClassC	Diagnostic
2013	Aydin[55]	Cross sectional	SpA 21	41.1	NA	0.61	1.5	Philips 5000	Diagnostic

BMI: body mass index; PsA: psoriatic arthritis; US: ultrasound; SpA: spondyloarthritis; JIA: juvenile idiopathic arthritis; AS: ankylosing spondylitis; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; OA: osteoarthritis; NA: not available; MASEI: Madrid Sonographic Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; SEI: Sonographic Entheseal Index; BUSES: Belgrade Ultrasound Enthesitis Score; PsASon: Ultrasound composite scores for the assessment of inflammatory and structural pathologies in PsA.

the patient is prone and the foot is overlying the bed. MASEI appreciate the triceps tendon while the arm is flexed and the tendon is stretched. The score by D'Agostino did not specify a standardized positioning. No major differences in limb positioning were documented. The majority of the studies (88.2%) used instruments that included Doppler evaluation.

Assessment of measurement properties of included studies following the algorithm of the OMERACT filter. Feasibility was reported in 8 (15.6%) studies[4,6,7,17,26,28,33,48]. Five (9.8%) assessed patients with PsA[7,26,28,33,48], and the time range for assessing entheseal involvement with US was reported between 15 to 90 min.

The results of the evaluation of the various components of the OMERACT filter are presented in Table 3. Concerning the OMERACT filter, reliability was assessed in 28 (54%) studies [3,4,5,6,7,18,19,22-26,28,30,33,35,39-41,44,45,47-49,51,54,56,57]. Ten (35.7%) of them included patients with PsA[7,18,26,28,33,44,47,48,54,56]. Reliability metrics including κ and ICC were used and showed moderate to excellent correlation, although reliability assessed mostly reading of the US images and not the acquisition process.

The construct validity of the various sonographic instruments as related to clinical examination of enthesitis was reported in 26 (51%) studies[3,4,5,7,16-19,21-23,25-28,30,32,33,36,37,44,53-56]. In 9 (34.6%) of them, positive statistically significant correlation was found[17,18,28,30,36,37,53,55,56]. Only 11 (21.5%) studies compared sonographic enthesitis findings to clinical examination of enthesitis in patients with PsA[29] and only 3 (27%) had demonstrated a positive correlation[28,29,56]. The construct validity of the various scoring systems as related to biomarkers of inflammation (CRP and/or ESR) was assessed in 10 (19.6%) studies[3,5,7,19,20,22, 23,34,43,53], and in only 3 (30%) of them, statistically significant positive correlation was found[19,20,34]. Only 1 (2%) study assessed it in PsA and did not find a significant association[7]. The construct validity of the various scoring systems as related to other imaging modalities was evaluated in only 6 (11.7%) studies[36,37,38,52,53,55]. In 4 (66%) of those studies, positive significant correlation was found[36,38,52,53], and none of the studies evaluated this topic in patients with PsA. Discriminative validity, as defined by the ability of certain cutoff values to distinguish between disease states (e.g., remission vs active disease) or disease status (PsA vs control) was assessed in 6 (11.7%) studies[6,24,27,48,50,51]. Only 2 (4%) of them were done in patients with PsA[27,48]. The responsiveness of the various sonographic scores to treatment, defined as a statistically significant change in the score in response to an intervention, was evaluated in 7 studies (13.7%)[5,19,23,25,34,42,59]; however, none of them was conducted in patients with PsA. In 5 (71%) studies, responsiveness was found[5,19,23,25,34].

Quality assessment. The QUADAS-2 tool items are summarized in Table 4. In 21 studies, there was a low risk of bias and applicability concern[3,4,6,7,14,16-20, 22,28,31,33,34,41,48,50,51,52,56]. In 22 studies there was unclear risk of bias mostly due to lack of details related to the recruitment method and limited description of the flow and timing of patient recruitment[21,23,24,27,30,32,35-40,42,44,45,47,49,53,55,57,58,59]; in 3 studies there was unclear risk of applicability concern due to comparison of the US results to an uncommon reference standard[36,60,61]. High risk of bias due to unblinding of the sonographer to the clinical results was reported in 2 studies[15,26]. High risk of bias in patient selection was present in 1 study that included a highly selective study population[29]. In 6 studies, high risk in applicability concern was assumed because of a highly selective population or inclusion of a less relevant population for this review[5,15,25,43,46,54]. Because of the descriptive character of this review, studies identified as having high risk of bias were not excluded.

DISCUSSION

Enthesitis is a key clinical and pathophysiologic feature in PsA and is included in the OMERACT PsA core domain set, which warrants the evaluation of enthesitis in every clinical trial and observational study. The inherent limitations in clinical evaluation of enthesitis led to a growing interest in the use of musculoskeletal US to improve the precision of enthesitis evaluation. This SLR represents a critical exami-

Table 2A. Characteristics of the entheseal instruments included in the systematic literature review.

Year	Authors	Entheseal Sites	Echogenicity	Thickness	Enthesophytes
MASEI					
Weight of each lesion			0 or 1	0 or 1	0–3
2016	Lackner[28]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	No
2015	Hamdy[36]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	Yes
2014	Husic[33]	PF, A, PTDI, PTPI, Q, TT, CET	Yes	Yes	Yes
2014	Eder[48]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	Yes
2011	de Miguel[50]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	Yes
2009	Munoz-Fernandez[24]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	Yes
2009	de Miguel[51]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	No
2016	Shenoy[17]	PF, A, PTDI, PTPI, Q, TT, gluteus medius	Yes	Yes	No
2015	Acquacalda[59]	PF, A, PTDI, PTPI, Q, TT	Yes	Yes	Yes
GUESS					
Weight of each lesion			NA	0 or 1	0 or 1
2013	Hamdi[38]	PF, A, PTDI, PTPI, Q	No	Yes	Yes
2013	Aydin[56]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2011	Ruta[18]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2011	Gutierrez[40]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2008	Gisondi[41]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2007	Genc[42]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2006	Borman[53]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2005	Genc[43]	PF, A, PTDI, PTPI, Q, biceps and supraspinatus at the shoulder	Yes	Yes	Yes
2002	Balint[3]	PF, A, PTDI, PTPI, Q	No	Yes	Yes
2013	Bandinelli[54]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2016	Rovisco[20]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2016	Michelsen[26]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2012	Ash[57]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2015	Ruta[19]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
SEI					
Weight of each lesion			0 or 1	0 or 1	0 or 1
2011	Hamdi[37]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2007	Alcalde[5]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
2015	Hu[34]	PF, A, PTDI, PTPI, Q	Yes	Yes	Yes
D'Agostino					
Weight of each lesion			Present or absent	Present or absent	Present or absent
2016	Perrotta[21]	A, PTDI, Q, CET, medial collateral ligament	Yes	Yes	Yes
2011	D'Agostino[52]	PF, A, PTPI, Q, gluteus medius, CET, CFT	Yes	Yes	Yes
2003	D'Agostino[4]	PF, A, PTDI, PTPI, Q, greater trochanter, pubis, tibialis anterior, CET, CFT	Yes	Yes	Yes
2011	Spadaro[16]	PF, A, PTDI, PTPI, Q, CET, gluteus tendons	Yes	Yes	Yes
2014	Mouterde[25]	PF, A, Q, gluteus medius, tibialis anterior, CET, CFT	Yes	Yes	Yes
2012	Marchesoni[27]	PF, A, PTDI, PTPI, Q, CET, CFT, great trochanter	No	Yes	Yes
BUSES					
Weight of each lesion			0 or 1	0 or 1	0 or 1
2015	Milutinovic[6]	PF, A, PTDI, PTPI, Q, CET, gluteus PF, A, PTDI, PTPI, Q, CET	Yes	Yes	Yes
2015	Janta[31]	PF, A, PTDI, PTPI, CET	Yes	Yes	No
2012	Freeston[44]	PF, A, PTDI, CET	Yes	Yes	Yes
2010	Naredo[23]	PF, A, PTDI, PTPI, Q, CET, CFT	Yes	Yes	Yes
PsASon					
Weight of each lesion			Present or absent	Present or absent	Present or absent
2014	Ficjan[7]	PF, A, PTDI, PTPI, Q, CET	Yes	Yes	Yes
Other					
2016	Kristensen[29]	PF, A, PTPI, Q, supraspinatus, CFT, CET, adductors on medial femur epicondyle	Yes	Yes	Yes
2012	Feydy[45]	PF, A	Yes	Yes	Yes
2011	Naredo[22]	PF, A, PTDI, deep flexor tendons of the fingers	Yes	Yes	Yes
2011	Ibrahim[32]	A, CET, adductors on medial femur	Yes	Yes	Yes
2011	Hu[35]	PF, A, PTDI, medial collateral ligament, lateral collateral ligament	Yes	Yes	No
2006	Kiris[30]	A, CET, adductors on medial femur, 1st and 7th costochondral joints, ASIS, iliac crest, PSIS, fifth lumbar spinous	Yes	Yes	Yes
2003	Falsetti[46]	PF, A	Yes	Yes	Yes
2010	Delle Sedie[49]	PTDI, PTPI, Q	Yes	Yes	No

Table 2A. Continued.

Year	Authors	Entheseal Sites	Echogenicity	Thickness	Enthesophytes
Other uncommon sites					
2015	El Miedany[47]	1st and 7th costosternal joints, ASIS, iliac crest, PSIS, 5th lumbar spinous process, rotator cuff	Yes	Yes	Yes
2016	Ward[15]	Posterior tibialis, peroneus brevis	Yes	Yes	Yes
2013	Ali Ou Alla[58]	Rotator cuff tendons	Yes	Yes	Yes
2012	Gutierrez[39]	Gluteus minimus, anterior and posterior insertion of gluteus medius	No	Yes	Yes
2016	Zabotti[14]	PIP joints central slip enthesis	Yes	Yes	No
2013	Aydin[55]	Medial and lateral collateral ligaments, semimembranosus tendon	Yes	Yes	Yes

Table 2B. Further characteristics of the entheseal instruments included in the systematic literature review.

Year	Authors	Entheseal Sites	Calcifies Deposits	Tear	Erosions	Cortical Irregularities	Bursitis	PD
MASEI								
Weight of each lesion			NA	NA	0 or 3	NA	0 or 1	0 or 3
2016	Lackner[28]	PF, A, PTDI, PTPI, Q, TT	No	No	Yes	No	Yes	Yes
2015	Hamdy[36]	PF, A, PTDI, PTPI, Q, TT	Yes	No	Yes	No	Yes	Yes
2014	Husic[33]	PF, A, PTDI, PTPI, Q, TT, CET	Yes	No	Yes	Yes	Yes	Yes
2014	Eder[48]	PF, A, PTDI, PTPI, Q, TT	Yes	No	Yes	No	Yes	Yes
2011	de Miguel[50]	PF, A, PTDI, PTPI, Q, TT	No	No	Yes	No	Yes	Yes
2009	Munoz-Fernandez[24]	PF, A, PTDI, PTPI, Q, TT	Yes	No	Yes	No	Yes	Yes
2009	de Miguel[51]	PF, A, PTDI, PTPI, Q, TT	Yes	No	Yes	No	Yes	Yes
2016	Shenoy[17]	PF, A, PTDI, PTPI, Q, TT, gluteus medius	Yes	Yes	Yes	No	Yes	Yes
2015	Acquacalda[59]	PF, A, PTDI, PTPI, Q, TT	Yes	No	Yes	Yes	No	Yes
GUESS								
Weight of each lesion			NA	NA	0 or 1	NA	0 or 1	NA
2013	Hamdi[38]	PF, A, PTDI, PTPI, Q	Yes	No	Yes	No	No	No
2013	Aydin[56]	PF, A, PTDI, PTPI, Q	Yes	No	Yes	No	Yes	Yes
2011	Ruta[18]	PF, A, PTDI, PTPI, Q	Yes	No	Yes	No	Yes	Yes
2011	Gutierrez[40]	PF, A, PTDI, PTPI, Q	No	No	Yes	No	Yes	Yes
2008	Gisondi[41]	PF, A, PTDI, PTPI, Q	No	No	Yes	No	Yes	No
2007	Genc[42]	PF, A, PTDI, PTPI, Q	No	No	Yes	No	Yes	Yes
2006	Borman[53]	PF, A, PTDI, PTPI, Q	No	No	Yes	No	Yes	Yes
2005	Genc[43]	PF, A, PTDI, PTPI, Q, biceps and supraspinatus at the shoulder	No	No	Yes	No	Yes	No
2002	Balint[3]	PF, A, PTDI, PTPI, Q	No	No	Yes	No	Yes	No
2013	Bandinelli[54]	PF, A, PTDI, PTPI, Q	No	No	Yes	No	Yes	Yes
2016	Rovisco[20]	PF, A, PTDI, PTPI, Q	No	No	Yes	Yes	No	Yes
2016	Michelsen[26]	PF, A, PTDI, PTPI, Q	Yes	No	Yes	No	No	Yes
2012	Ash[57]	PF, A, PTDI, PTPI, Q	No	No	Yes	Yes	Yes	Yes
2015	Ruta[19]	PF, A, PTDI, PTPI, Q	Yes	No	Yes	No	Yes	Yes
SEI								
Weight of each lesion			NA	0 or 1	0 or 1	NA	0 or 1	NA
2011	Hamdi[37]	PF, A, PTDI, PTPI, Q	No	Yes	Yes	No	Yes	Yes
2007	Alcalde[5]	PF, A, PTDI, PTPI, Q	No	Yes	Yes	No	Yes	No
2015	Hu[34]	PF, A, PTDI, PTPI, Q	No	Yes	Yes	No	Yes	Yes
D'Agostino								
Weight of each lesion			NA	NA	Present or absent	NA	Present or absent	Present or absent
2016	Perrotta[21]	A, PTDI, Q, CET, medial collateral ligament	Yes	No	Yes	No	Yes	Yes
2011	D'Agostino[52]	PF, A, PTPI, Q, gluteus medius, CET, CFT	Yes	No	Yes	No	Yes	Yes
2003	D'Agostino[4]	PF, A, PTDI, PTPI, Q, greater trochanter, pubis, tibialis anterior, CET, CFT	Yes	No	Yes	No	Yes	Yes
2011	Spadaro[16]	PF, A, PTDI, PTPI, Q, CET, gluteus tendons	Yes	No	Yes	Yes	Yes	Yes
2014	Mouterde[25]	PF, A, Q, gluteus medius, tibialis anterior, CET, CFT	Yes	No	Yes	No	No	Yes
2012	Marchesoni[27]	PF, A, PTDI, PTPI, Q, CET, CFT, great trochanter	Yes	No	Yes	Yes	No	Yes

Table 2B. Continued.

Year	Authors	Entheseal Sites	Calcifies Deposits	Tear	Erosions	Cortical Irregularities	Bursitis	PD
BUSES								
Weight of each lesion			NA	NA	0 or 4	NA	NA	0 or 4
2015	Milutinovic[6]	PF, A, PTDI, PTPI, Q, CET, gluteus PF, A, PTDI, PTPI, Q, CET	Yes	No	Yes	Yes	No	Yes
2015	Janta[31]	PF, A, PTDI, PTPI, CET	No	No	No	No	No	Yes
2012	Freeston[44]	PF, A, PTDI, CET	Yes	No	Yes	No	Yes	Yes
2010	Naredo[23]	PF, A, PTDI, PTPI, Q, CET, CFT	Yes	No	Yes	Yes	Yes	Yes
PsASon								
Weight of each lesion			NA	NA	Present or absent	NA	Present or absent	Present or absent
2014	Ficjan[7]	PF, A, PTDI, PTPI, Q, CET	No	No	Yes	No	Yes	Yes
Other								
2016	Kristensen[29]	PF, A, PTPI, Q, supraspinatus, CFT, CET, adductors on medial femur epicondyle	Yes	No	Yes	Yes	No	Yes
2012	Feydy[45]	PF, A	Yes	No	Yes	No	Yes	Yes
2011	Naredo[22]	PF, A, PTDI, deep flexor tendons of the fingers	No	No	Yes	Yes	No	Yes
2011	Ibrahim[32]	A, CET, adductors on medial femur	No	No	Yes	No	Yes	Yes
2011	Hu[35]	PF, A, PTDI, medial collateral ligament, lateral collateral ligament	Yes	No	Yes	Yes	No	Yes
2006	Kiris[30]	A, CET, adductors on medial femur, 1st and 7th costochondral joints, ASIS, iliac crest, PSIS, fifth lumbar spinous	Yes	No	Yes	Yes	Yes	Yes
2003	Falsetti[46]	PF, A	No	No	Yes	Yes	Yes	No
2010	Delle Sedie[49]	PTDI, PTPI, Q	No	No	No	No	No	Yes
Other uncommon sites								
2015	El Miedany[47]	1st and 7th costosternal joints, ASIS, iliac crest, PSIS, 5th lumbar spinous process, rotator cuff	No	No	Yes	No	No	Yes
2016	Ward[15]	Posterior tibialis, peroneus brevis	No	No	Yes	Yes	No	Yes
2013	Ali Ou Alla[58]	Rotator cuff tendons	Yes	Yes	Yes	No	Yes	Yes
2012	Gutierrez[39]	Gluteus minimus, anterior and posterior insertion of gluteus medius	Yes	No	Yes	No	Yes	Yes
2016	Zabotti[14]	PIP joints central slip enthesis	No	No	No	No	No	Yes
2013	Aydin[56]	Medial and lateral collateral ligaments, semimembranosus tendon	Yes	No	Yes	No	Yes	Yes

A: Achilles tendon; ASIS: anterior superior iliac spines; PSIS: posterior superior iliac spine; CET: common extensor tendon insertion on lateral epicondyle; CFT: common flexor tendon insertion on medial epicondyle; PF: plantar fascia; PTDI: patellar tendon distal insertion; PTPI: patellar tendon proximal insertion; Q: quadriceps; TT: triceps tendon; NA: not assessed; MASEI: Madrid Sonographic Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; SEI: Sonographic Entheseal Index; BUSES: Belgrade Ultrasound Enthesitis Score; PsASon: Ultrasound composite scores for the assessment of inflammatory and structural pathologies in psoriatic arthritis.

nation of the published data regarding the state of validation of the most commonly used sonographic enthesitis instruments in PsA and SpA. The study identified significant limitations related to the lack of standardization of existing instruments and major gaps in knowledge about their validity as outcome measures for assessment of enthesitis patients with PsA.

Several sonographic instruments have been developed to provide a global estimation of the extent of enthesitis at the patient level. The present SLR critically evaluated the properties and the validity of available sonographic enthesitis scoring systems. We highlight several important limitations and gaps in knowledge related to the validity of these outcome measures in patients with PsA. One of the important issues is that only about a third of the studies included in this SLR focused on patients with PsA, so we decided to extend the study population to also include patients with SpA. All of the instruments except 1 were originally developed and validated in patients with axSpA and their use was subsequently applied to PsA. This is an important limitation, because the distribution of enthesitis in patients with PsA may be different from that in patients with axSpA. Additional important limitations are the lack of standardization regarding the number and location of entheseal sites included in each score, the variation in the elementary lesions, and their weight in the total score. These issues complicate the direct comparison of the performance of available instruments. Additionally, the development process of existing instruments was primarily based on experts' opinion rather than data-driven and the initial validation process was based on a small sample of patients (< 50 patients in the 2 most commonly used instruments).

Table 3. Appraisal of measurement properties of enthesitis indices according to the OMERACT filter.

Year	Author	Reliability	Construct Validity Biomarkers	Clinical	Imaging	Responsiveness	Discriminative Validity	Feasibility
MASEI								
2016	Lackner[28]	Yes	NA	Yes	NA	NA	NA	Yes
2015	Hamdy[36]	NA	NA	Yes	Yes	NA	NA	NA
2014	Husic[33]	Yes	NA	No	NA	NA	NA	Yes
2014	Eder[48]	Yes	NA	NA	NA	NA	Yes	Yes
2011	de Miguel[50]	NA	NA	NA	NA	NA	Yes	NA
2009	Munoz-Fernandez[24]	Yes	NA	NA	NA	NA	Yes	NA
2009	de Miguel[51]	Yes	NA	NA	NA	NA	Yes	NA
2016	Shenoy[17]	NA	NA	Yes	NA	NA	NA	Yes
2015	Acquacalda[59]	NA	NA	NA	NA	No	NA	NA
Total no. studies (found positive)		5	0 (0)	4 (3)	1 (1)	1 (0)	4	4
Total no. studies in PsA (found positive)		3	0 (0)	2 (1)	0 (0)	1 (0)	1	3
GUESS								
2013	Hamdi[38]	NA	NA	NA	Yes	NA	NA	NA
2013	Aydin[56]	Yes	NA	Yes	NA	NA	NA	NA
2011	Ruta[18]	Yes	NA	Yes	NA	NA	NA	NA
2011	Gutierrez[40]	Yes	NA	NA	NA	NA	NA	NA
2008	Gisondi[41]	Yes	NA	NA	NA	NA	NA	NA
2007	Genc[42]	NA	NA	NA	NA	No	NA	NA
2006	Borman[53]	NA	No	No	Yes	NA	NA	NA
2005	Genc[43]	NA	No	NA	NA	NA	NA	NA
2002	Balint[3]	Yes	No	No	NA	NA	NA	NA
2013	Bandinelli[54]	Yes	NA	No	NA	NA	NA	NA
2016	Rovisco[20]	NA	Yes	NA	NA	NA	NA	NA
2016	Michelsen[26]	Yes	NA	No	NA	NA	NA	Yes
2012	Ash[57]	Yes	NA	NA	NA	NA	NA	NA
2015	Ruta[19]	Yes	Yes	No	NA	Yes	NA	NA
Total no. studies (found positive)		9	5 (2)	6(2)	2 (2)	2	0	1
Total no. studies in PsA (found positive)		3	0	3 (1)	0	0	0	1
SEI								
2011	Hamdi[37]	NA	NA	Yes	No	NA	NA	NA
2007	Alcalde[5]	Yes	No	No	NA	Yes	NA	NA
2015	Hu[34]	NA	Yes	NA	NA.	Yes	NA	NA
Total no. studies (found positive)		1	2 (1)	2 (1)	1 (0)	2 (2)	0	0
Total no. studies in PsA (found positive)		0	0	0	0	0	0	0
D'Agostino								
2016	Perrotta[21]	NA	NA	No	NA	NA	NA	NA
2011	D'Agostino[52]	NA	NA	NA	Yes	NA	NA	NA
2003	D'Agostino[4]	Yes	NA	No	NA	NA	NA	Yes
2011	Spadaro[16]	NA	NA	No	NA	NA	NA	NA
2014	Mouterde[25]	Yes	NA	No	NA	Yes	NA	NA
2012	Marchesoni[27]	NA	NA	No	NA	NA	Yes	NA
Total no. studies (found positive)		2	0	5 (0)	1 (0)	1 (1)	1 (1)	1
Total no. studies in PsA (found positive)		0	0	2 (0)	0	0	1 (1)	0
BUSES								
2015	Milutinovic[6]	Yes	NA	NA	NA	NA	Yes	Yes
2015	Janta[31]	NA	NA	NA	NA	NA	NA	NA
2012	Freeston[44]	Yes	NA	No	NA	NA	NA	NA
2010	Naredo[23]	Yes	No	No	NA	Yes	NA	NA
Total no. studies (found positive)		3	1 (0)	2 (0)	0	1 (1)	1	1
Total no. studies in PsA (found positive)		1	0	1 (0)	0	0	0	0
PsASon								
2014	Ficjan[7]	Yes	No	No	NA	NA	NA	Yes
Other								
2016	Kristensen[29]	NA	NA	Yes	NA	NA	NA	NA
2012	Feydy[45]	Yes	NA	NA	NA	NA	NA	NA
2011	Naredo[22]	Yes	No	No	NA	NA	NA	NA
2011	Ibrahim[32]	NA	NA	No	NA	NA	NA	NA

Table 3. Continued

Year	Author	Reliability	Construct Validity			Responsiveness	Discriminative Validity	Feasibility
			Biomarkers	Clinical	Imaging			
2011	Hu[35]	Yes	NA	NA	NA	NA	NA	NA
2006	Kiris[30]	Yes	NA	Yes	NA	NA	NA	NA
2003	Falsetti[46]	NA	NA	NA	NA	NA	NA	NA
2010	Delle Sedie[49]	Yes	NA	NA	NA	NA	NA	NA
Total no. studies (found positive)		5	1 (0)	4 (2)	0	0	0	0
Total no. studies in PsA (found positive)		1	0	2 (1)	0	0	0	0
Other uncommon sites								
2015	El Miedany[47]	Yes	NA	NA	NA	NA	NA	NA
2016	Ward[15]	NA	NA	NA	NA	NA	NA	NA
2013	Ali Ou Alla[58]	NA	NA	NA	NA	NA	NA	NA
2012	Gutierrez[39]	Yes	NA	NA	NA	NA	NA	NA
2016	Zabotti[14]	NA	NA	NA	NA	NA	NA	Yes
2013	Aydin[56]	NA	NA	Yes	No	NA	NA	NA
Total no. studies (found positive)		2	0	1 (1)	1 (0)	0	0	1
Total no. studies in PsA (found positive)		1	0	0	0	0	0	1
Summary – All studies								
Total no. studies (found positive)		28	10 (3)	26 (9)	6 (2)	7 (5)	6	8
Total no. studies in PsA (found positive)		10	1 (0)	11 (3)	0	0	2 (1)	5

NA: not assessed; PsA: psoriatic arthritis; Yes: assessed with positive findings; No: assessed with negative findings; MASEI: The Madrid Sonographic Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; SEI: Sonographic Entheseal Index; BUSES: Belgrade Ultrasound Enthesitis Score; PsASon: Ultrasound composite scores for the assessment of inflammatory and structural pathologies in PsA.

One of the important issues noted in the SLR is the wide variation in the entheseal sites included in each instrument. In fact, apart from the studies that used the 6 established sonographic scores, we included in this SLR 14 studies that used ad hoc enthesitis scoring systems. These studies used various combinations of entheseal sites that were different from those included in previously validated methods. The selection process of entheseal sites included in each instrument was primarily based on expert opinion. To date, no study has investigated the optimal combination of entheseal sites to represent the construct of "enthesitis" in PsA.

The majority of the entheseal sites included in the sonographic scores are located in the lower extremities, an area that is heavily affected by biomechanical stress and thus could be confounded by aging, physical activity, and obesity. Two scores (GUESS and SEI) include only sites in the lower extremities (quadriceps, patella, Achilles, and plantar fascia) while others (MASEI and BUSES) include only a single upper extremity site (triceps and common extensors respectively). The score developed by D'Agostino is the only one that uses 2 upper extremity sites (common extensors and common flexors). Entheseal sites around the shoulders and unconventional entheseal sites, such as those around the fingers or functional enthesis sites (e.g., tibialis posterior around the medial malleolus), are not included in any score.

There is no consensus on which elementary lesions define acute/active enthesitis and which represent chronic/irreversible entheseal damage. However, previous studies have largely considered the presence of power Doppler signal at the enthesis as an indicator of active enthesitis, while irreversible lesions such as enthesophytes, erosions, and calcification represent damage from previously active enthesitis or enthesopathy due to noninflammatory reasons. Most of the instruments do not differentiate between acute and chronic lesions but instead summarize the scores of all lesions together to a general score. This limits the ability of the instruments to distinguish between active versus inactive disease states and to assess treatment response.

None of the instruments graded the degree of Doppler vascularization. With the availability of US machines with highly sensitive Doppler, semiquantitative grading of the degree of Doppler vascularization may be more appropriate. Because the scanning position (e.g., relaxed or stretched tendon) may affect the ability to detect Doppler signal, such standardization is important to reduce variability in results. The optimal positioning of the enthesis for Doppler evaluation is when the tendon is in a relaxed position.

The issue of the borders of the enthesis was defined by the OMERACT US group as up to 2 mm from the enthesis[2]. However, many of the studies, particularly the validation work for the commonly used enthesitis scores, were published prior to the publication of this definition. Regarding the thickening of the enthesis, although the OMERACT definition does not consider specific cutoff points for each entheseal site, 3 of the commonly used scoring systems (GUESS, MASEI, and PsASon[3,7,51]) used the same cutoff points to defined thickened entheses. The remaining scoring systems did not define what was considered thickened entheses. The lack of clear and acceptable sonographic definition of the borders and dimen-

Table 4. Quality assessment of identified studies according to QUADAS 2.

Year	Author	Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
MASEI								
2016	Lackner[28]	☺	☺	☺	☺	☺	☺	☺
2015	Hamdy[36]	☺	?	?	☺	?	☺	?
2014	Husic[33]	☺	☺	☺	☺	☺	☺	☺
2014	Eder[48]	☺	☺	☺	☺	☺	☺	☺
2011	de Miguel[50]	☺	☺	☺	☺	☺	☺	☺
2009	Munoz-Fernandez[24]	?	☺	☺	☺	☺	☺	☺
2009	de Miguel[51]	☺	☺	☺	☺	☺	☺	☺
2016	Shenoy[17]	☺	☺	☺	☺	☺	☺	☺
2015	Acquacalda[59]	?	☺	☺	☺	☺	☺	☺
GUESS								
2013	Hamdi[38]	☺	?	?	?	☺	?	☺
2013	Aydin[56]	☺	☺	☺	☺	☺	☺	☺
2011	Ruta[18]	☺	☺	☺	☺	☺	☺	☺
2011	Gutierrez[40]	?	☺	☺	☺	☺	☺	☺
2008	Gisondi[41]	☺	☺	☺	☺	☺	☺	☺
2007	Genc[42]	☺	☺	☺	?	☺	☺	☺
2006	Borman[53]	?	☺	☺	?	☺	☺	☺
2005	Genc[43]	☺	☺	☺	?	☺	☹	☺
2002	Balint[3]	☺	☺	☺	☺	☺	☺	☺
2013	Bandinelli[54]	☺	☺	☺	?	☹	☺	☺
2016	Rovisco[20]	?	☺	☺	☺	☺	☺	☺
2016	Michelsen[26]	☺	☹	☺	☺	☺	☺	☺
2012	Ash[57]	?	☺	☺	☺	☺	☺	☺
2015	Ruta[19]	☺	☺	☺	☺	☺	☺	☺
SEI								
2011	Hamdi[37]	☺	☺	☺	?	☺	☺	☺
2007	Alcalde[5]	?	☺	☺	☺	☺	☹	☺
2015	Hu[34]	☺	☺	☺	☺	☺	☺	☺
D'Agostino								
2016	Perrotta[21]	☺	☺	☺	?	☺	☺	☺
2011	D'Agostino[52]	☺	☺	☺	☺	☺	☺	☺
2003	D'Agostino[4]	☺	☺	☺	☺	☺	☺	☺
2011	Spadaro[16]	☺	☺	☺	☺	☺	☺	☺
2014	Mouterde[25]	?	☺	☺	☺	☺	☹	☺
2012	Marchesoni[27]	☺	☺	☺	?	☺	☺	☺
BUSES								
2015	Milutinovic[6]	☺	☺	☺	☺	☺	☺	☺
2015	Janta[31]	☺	☺	☺	☺	☺	☺	☺
2012	Freeston[44]	?	☺	☺	☺	☺	☺	☺
2010	Naredo[23]	?	☺	☺	☺	☺	☺	☺
PsASon								
2014	Ficjan[7]	☺	☺	☺	☺	☺	☺	☺
Other								
2016	Kristensen[29]	☹	☺	☺	☺	☺	☺	☺
2012	Feydy[45]	?	☺	☺	☺	☺	☺	☺
2011	Naredo[22]	☺	☺	☺	☺	☺	☺	☺
2011	Ibrahim[32]	?	☺	☺	☺	☺	☺	☺
2011	Hu[35]	?	☺	☺	?	☺	☺	☺
2006	Kiris[30]	?	☺	☺	☺	☺	☺	☺
2003	Falsetti[46]	☺	?	☺	?	☺	☹	☺
2010	Delle Sedie[49]	☺	☺	☺	?	☺	☺	☺
Other uncommon sites								
2015	El Miedany[47]	?	☺	☺	☺	☺	☺	☺
2016	Ward[15]	?	☹	?	☺	☺	☺	☹
2013	Ali Ou Alla[58]	?	?	☺	☺	☺	☺	☺
2012	Gutierrez[39]	?	☺	☺	☺	☺	☺	☺
2016	Zabotti[14]	☺	☺	☺	☺	☺	☺	☺
2013	Aydin[56]	☺	☺	☺	?	☺	☺	☺

☺: Low risk of bias; ?: Unclear risk of bias; ☹: High risk of bias; MASEI: Madrid Sonographic Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System; SEI: Sonographic Entheseal Index; BUSES: Belgrade Ultrasound Enthesitis Score; PsASon: Ultrasound composite scores for the assessment of inflammatory and structural pathologies in psoriatic arthritis.

sions of the normal enthesis adds to the variability between scoring systems.

Considering the validity of the existing instruments in PsA according to the OMERACT filter, significant gaps in knowledge are highlighted. First, only a minority of studies assesses solely patients with PsA and not the general SpA population. Construct validity (correlation between sonographic enthesitis and theoretical concepts of enthesitis) was evaluated primarily in relation to clinical assessment of enthesitis. As expected, there was a relatively poor correlation between sonographic and clinical enthesitis representing the higher sensitivity of US as well as the mixed active and inactive sonographic lesions included in the scoring systems. Limited information exists about the construct validity of existing instruments against laboratory markers of inflammation and other imaging modalities, especially in patients with PsA.

The responsiveness of existing sonographic scores to treatment is an area with sparse data especially in PsA, where there were no studies assessing it. Out of 7 studies (in patients with ankylosing sponylitis or SpA), 5 showed good correlation between treatment and global improvement of the sonographic score. It is possible that similar responsiveness exists in PsA as well; however, as was mentioned, no study to date evaluated this aspect. Concerning the discrimination ability of the sonographic scores, there is also scant data regarding the ability of a score to discriminate between sick and healthy populations, with only 2 studies assessing this issue in PsA. In 1 study, US was found to be a useful tool in differentiation between PsA and fibromyalgia[27], and the second study found US a valuable tool in discriminating between PsA, psoriasis, and healthy controls[48]. A common situation that often arises in the clinical aspect is whether the patient with small joints involvement of the hands has rheumatoid arthritis, PsA, or osteoarthritis; unfortunately, the current evidence does not support any sonographic entheseal score to assist in this dilemma.

It is worth noting that it is not expected that each study will assess all measurements of the OMERACT filter. For instance, in a study assessing responsiveness to treatment, construct validity would probably not be evaluated. However, one would expect from a comprehensive instrument's score being used for assessing certain variables, such as responsiveness to treatment, to have a proper validation process supporting its use.

Sonographic entheseal instruments that assess the extent of enthesitis at the global patient level have progressed in recent years. Some of these instruments have been validated in patients with SpA; however, the validity of these tools in PsA is largely unknown. There is a need for a well-validated instrument for assessment of sonographic enthesitis in PsA that includes the unique features of PsA and will assist in diagnosis, disease burden quantification, clinical decisions, and prognosis.

REFERENCES

1. D'Agostino MA. Ultrasound imaging in spondyloarthropathies. Best Pract Res Clin Rheumatol 2010;24:693-700.
2. Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, et al. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. Arthritis Care Res 2014;66:741-8.
3. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis 2002;61:905-10.
4. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power doppler: a cross-sectional study. Arthritis Rheum 2003;48:523-33.
5. Alcalde M, Acebes JC, Cruz M, Gonzalez-Hombrado L, Herrero-Beaumont G, Sanchez-Pernaute O. A sonographic enthesitic index of lower limbs is a valuable tool in the assessment of ankylosing spondylitis. Ann Rheum Dis 2007;66:1015-9.
6. Milutinovic S, Radunovic G, Veljkovic K, Zlatanovic M, Zlatkovic Svenda M, Perovic Radak M, et al. Development of ultrasound enthesitis score to identify patients with enthesitis having spondyloarthritis: prospective, double-blinded, controlled study. Clin Exp Rheumatol 2015;33:812-7.
7. Ficjan A, Husic R, Gretler J, Lackner A, Graninger WB, Gutierrez M, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in psoriatic arthritis (PsASon-score). Arthritis Res Ther 2014;16:476.
8. Aydin SZ, Can M, Alibaz-Oner F, Keser G, Kurum E, Inal V, et al. A relationship between spinal new bone formation in ankylosing spondylitis and the sonographically determined Achilles tendon enthesophytes. Rheumatol Int 2016;36:397-404.
9. Mandl P, Navarro-Compan V, Terslev L, Aegerter P, van der Heijde D, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015;74:1327-39.
10. The OMERACT Handbook. [Internet. Accessed June 5, 2018.] Available from: www.dropbox.com/s/q3ti8fympqqrfk0/OMERACT%20Handbook%20Jan%2019%202018.pdf?dl=0
11. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.
12. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. J Clin Epidemiol 2009;62:1006-12.
14. Zabotti A, Salvin S, Quartuccio L, De Vita S. Differentiation between early rheumatoid and early psoriatic arthritis by the ultrasonographic study of the synovio-entheseal complex of the small joints of the hands. Clin Exp Rheumatol 2016;34:459-65.
15. Ward IM, Kissin E, Kaeley G, Scott JN, Newkirk M, Hildebrand BA, et al. Ultrasound features of the posterior tibialis tendon and peroneus brevis tendon entheses: A comparison study between healthy adults and inflammatory arthritis. Arthritis Care Res 2016;20:20.
16. Spadaro A, Iagnocco A, Perrotta FM, Modesti M, Scarno A, Valesini G. Clinical and ultrasonography assessment of peripheral enthesitis in ankylosing spondylitis. Rheumatology 2011;50:2080-6.
17. Shenoy S, Aggarwal A. Sonologic enthesitis in children with enthesitis-related arthritis. Clin Exp Rheumatol 2016;34:143-7.
18. Ruta S, Gutierrez M, Pena C, Garcia M, Arturi A, Filippucci E, et al. Prevalence of subclinical enthesopathy in patients with spondyloarthropathy: an ultrasound study. J Clin Rheumatol 2011;17:18-22.

19. Ruta S, Acosta Felquer ML, Rosa J, Navarta DA, Garcia Monaco R, Soriano ER. Responsiveness to therapy change of a global ultrasound assessment in spondyloarthritis patients. Clin Rheumatol 2015;34:125-32.
20. Rovisco J, Duarte C, Batticcioto A, Sarzi-Puttini P, Dragresshi A, Portela F, et al. Hidden musculoskeletal involvement in inflammatory bowel disease: a multicenter ultrasound study. BMC Musculoskelet Disord 2016;17:84.
21. Perrotta FM, Astorri D, Zappia M, Reginelli A, Brunese L, Lubrano E. An ultrasonographic study of enthesis in early psoriatic arthritis patients naive to traditional and biologic DMARDs treatment. Rheumatol Int 2016;36:1579-83.
22. Naredo E, Moller I, de Miguel E, Batlle-Gualda E, Acebes C, Brito E, et al. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study. Rheumatology 2011;50:1838-48.
23. Naredo E, Batlle-Gualda E, Garcia-Vivar ML, Garcia-Aparicio AM, Fernandez-Sueiro JL, Fernandez-Prada M, et al. Power Doppler ultrasonography assessment of entheses in spondyloarthropathies: response to therapy of entheseal abnormalities. J Rheumatol 2010;37:2110-7.
24. Munoz-Fernandez S, de Miguel E, Cobo-Ibanez T, Madero R, Ferreira A, Hidalgo MV, et al. Enthesis inflammation in recurrent acute anterior uveitis without spondylarthritis. Arthritis Rheum 2009;60:1985-90.
25. Mouterde G, Aegerter P, Correas JM, Breban M, D'Agostino MA. Value of contrast-enhanced ultrasonography for the detection and quantification of enthesitis vascularization in patients with spondyloarthritis. Arthritis Care Res 2014;66:131-8.
26. Michelsen B, Diamantopoulos AP, Hammer HB, Soldal DM, Kavanaugh A, Haugeberg G. Ultrasonographic evaluation in psoriatic arthritis is of major importance in evaluating disease activity. Ann Rheum Dis 2016;75:2108-13.
27. Marchesoni A, De Lucia O, Rotunno L, De Marco G, Manara M. Entheseal power Doppler ultrasonography: a comparison of psoriatic arthritis and fibromyalgia. J Rheumatol Suppl. 2012 Jul;89:29-31.
28. Lackner A, Duftner C, Ficjan A, Gretler J, Hermann J, Husic R, et al. The association of clinical parameters and ultrasound verified inflammation with patients' and physicians' global assessments in psoriatic arthritis. Semin Arthritis Rheum 2016;46:183-9.
29. Kristensen S, Christensen JH, Schmidt EB, Olesen JL, Johansen MB, Arvesen KB, et al. Assessment of enthesitis in patients with psoriatic arthritis using clinical examination and ultrasound. Muscles Ligaments Tendons J 2016;6:241-7.
30. Kiris A, Kaya A, Ozgocmen S, Kocakoc E. Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography. Skeletal Radiol 2006;35:522-8.
31. Janta I, Martinez-Estupinan L, Valor L, Montoro M, Baniandres Rodriguez O, Hernandez Aragues I, et al. Comparison between full and tapered dosages of biologic therapies in psoriatic arthritis patients: clinical and ultrasound assessment. Clin Rheumatol 2015;34:935-42.
32. Ibrahim G, Groves C, Chandramohan M, Beltran A, Valle R, Reyes B, et al. Clinical and ultrasound examination of the Leeds Enthesitis Index in psoriatic arthritis and rheumatoid arthritis. ISRN Rheumatol 2011;2011:731917.
33. Husic R, Gretler J, Felber A, Graninger WB, Duftner C, Hermann J, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis 2014;73:1529-36.
34. Hu Z, Xu M, Wang Q, Qi J, Lv Q, Gu J. Colour doppler ultrasonography can be used to detect the changes of sacroiliitis and peripheral enthesitis in patients with ankylosing spondylitis during adalimumab treatment. Clin Exp Rheumatol 2015;33:844-50.
35. Hu Y, Zhu J, Xue Q, Wang N, Hu B. Scanning of the sacroiliac joint and entheses by color Doppler ultrasonography in patients with ankylosing spondylitis. J Rheumatol 2011;38:1651-5.
36. Hamdy M, Omar G, Elshereef RR, Ellaban AS, Amin M. Early detection of spondyloarthropathy in patients with psoriasis by using the ultrasonography and magnetic resonance image. Eur J Rheumatol 2015;2:10-15.
37. Hamdi W, Chelli-Bouaziz M, Ahmed MS, Ghannouchi MM, Kaffel D, Ladeb MF, et al. Correlations among clinical, radiographic, and sonographic scores for enthesitis in ankylosing spondylitis. Joint Bone Spine 2011;78:270-4.
38. Hamdi W, Bouaziz Chelli M, Ghannouchi MM, Hawel M, Ladeb MF, Kchir MM. Performance of ultrasounds compared with radiographs to detect chronic enthesitis signs in patients with ankylosing spondylitis. Rheumatol Int 2013;33:497-9.
39. Gutierrez M, Luccioli F, Salaffi F, Bartoloni E, Bertolazzi C, Bini V, et al. Ultrasound revealing subclinical enthesopathy at the greater trochanter level in patients with spondyloarthritis. Clin Rheumatol 2012;31:463-8.
40. Gutierrez M, Filippucci E, De Angelis R, Salaffi F, Filosa G, Ruta S, et al. Subclinical entheseal involvement in patients with psoriasis: an ultrasound study. Semin Arthritis Rheum 2011;40:407-12.
41. Gisondi P, Tinazzi I, El-Dalati G, Gallo M, Biasi D, Barbara LM, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: A hospital-based case-control study. Ann Rheum Dis 2008;67:26-30.
42. Genc H, Duyur Cakit B, Nacir B, Saracoglu M, Kacar M, Erdem HR. The effects of sulfasalazine treatment on enthesal abnormalities of inflammatory rheumatic diseases. Clin Rheumatol 2007; 26:1104-10.
43. Genc H, Cakit BD, Tuncbilek I, Erdem HR. Ultrasonographic evaluation of tendons and enthesal sites in rheumatoid arthritis: Comparison with ankylosing spondylitis and healthy subjects. Clin Rheumatol 2005;24:272-7.
44. Freeston JE, Coates LC, Helliwell PS, Hensor EM, Wakefield RJ, Emery P, et al. Is there subclinical enthesitis in early psoriatic arthritis? A clinical comparison with power doppler ultrasound. Arthritis Care Res 2012;64:1617-21.
45. Feydy A, Lavie-Brion MC, Gossec L, Lavie F, Guerini H, Nguyen C, et al. Comparative study of MRI and power Doppler ultrasonography of the heel in patients with spondyloarthritis with and without heel pain and in controls. Ann Rheum Dis 2012; 71:498-503.
46. Falsetti P, Frediani B, Fioravanti A, Acciai C, Baldi F, Filippou G, et al. Sonographic study of calcaneal entheses in erosive osteoarthritis, nodal osteoarthritis, rheumatoid arthritis and psoriatic arthritis. Scand J Rheumatol 2003;32:229-34.
47. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Nasr A. Tailored approach to early psoriatic arthritis patients: clinical and ultrasonographic predictors for structural joint damage. Clin Rheumatol 2015;34:307-13.
48. Eder L, Jayakar J, Thavaneswaran A, Haddad A, Chandran V, Salonen D, et al. Is the Madrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls? J Rheumatol 2014;41:466-72.
49. Delle Sedie A, Riente L, Filippucci E, Scire CA, Iagnocco A, Gutierrez M, et al. Ultrasound imaging for the rheumatologist XXVI. Sonographic assessment of the knee in patients with psoriatic arthritis. Clin Exp Rheumatol 2010;28:147-52.
50. de Miguel E, Munoz-Fernandez S, Castillo C, Cobo-Ibanez T, Martin-Mola E. Diagnostic accuracy of enthesis ultrasound in the diagnosis of early spondyloarthritis. Ann Rheum Dis 2011;70:434-9.
51. de Miguel E, Cobo T, Munoz-Fernandez S, Naredo E, Uson J, Acebes JC, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. Ann Rheum Dis 2009;68:169-74.
52. D'Agostino MA, Aegerter P, Bechara K, Salliot C, Judet O,

Chimenti MS, et al. How to diagnose spondyloarthritis early? Accuracy of peripheral enthesitis detection by power Doppler ultrasonography. Ann Rheum Dis 2011;70:1433-40.
53. Borman P, Koparal S, Babaoglu S, Bodur H. Ultrasound detection of entheseal insertions in the foot of patients with spondyloarthropathy. Clin Rheumatol 2006;25:373-7.
54. Bandinelli F, Prignano F, Bonciani D, Bartoli F, Collaku L, Candelieri A, et al. Ultrasound detects occult entheseal involvement in early psoriatic arthritis independently of clinical features and psoriasis severity. Clin Exp Rheumatol 2013;31:219-24.
55. Aydin SZ, Tan AL, Hodsgon R, Grainger A, Emery P, Wakefield RJ, et al. Comparison of ultrasonography and magnetic resonance imaging for the assessment of clinically defined knee enthesitis in spondyloarthritis. Clin Exp Rheumatol 2013;31:933-6.
56. Aydin SZ, Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, et al. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. Ann Rheum Dis 2013;72:992-5.
57. Ash ZR, Tinazzi I, Gallego CC, Kwok C, Wilson C, Goodfield M, et al. Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. Ann Rheum Dis 2012;71:553-6.
58. Ali Ou Alla S, Bahiri R, Amine H, El Alaoui H, Rkain H, Aktaou S, et al. Ultrasound features of shoulder involvement in patients with ankylosing spondylitis: a case-control study. BMC Musculoskelet Disord 2013;14:272.
59. Acquacalda E, Albert C, Montaudie H, Fontas E, Danre A, Roux CH, et al. Ultrasound study of entheses in psoriasis patients with or without musculoskeletal symptoms: a prospective study. Joint Bone Spine 2015;82:267-71.
60. Wang CH, Feng Y, Ren Z, Yang X, Jia JF, Rong MY, et al. Performance of ultrasound to monitor Achilles enthesitis in patients with ankylosing spondylitis during TNF-a antagonist therapy. Clin Rheumatol 2015;34:1073-8.
61. Merot O, Guillot P, Maugars Y, Le Goff B. Three-dimensional versus two-dimensional ultrasonographic assessment of peripheral enthesitis in spondylarthritis. Clin Rheumatol 2014;33:131-5.