Review

Ultrasonographic evaluation of entheses in patients with spondyloarthritis: a systematic literature review

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Received on July 29, 2014; accepted in revised form on December 1, 2014.

Clin Exp Rheumatol 2014; 32: 969-978.

Key words: ultrasonography, enthesopathy, spondyloarthritis

Competing interests: none declared.

ABSTRACT

Objective. *Enthesitis represents a characteristic features of spondyloarthritis (SpA) and, in the context of the early management of the disease, its reliable assessment has emerged as a central issue. Musculoskeletal ultrasonography (US) has proven to be of value in the assessment of peripheral entheses. Our aim was to systematically review the literature from 2010 to 2013 in order to summarise the evidence on the evaluation of entheses by US in patients with diagnosed or suspected SpA.*

Methods. *PubMed and Embase were searched developing a search strategy based on terms related to SpA and US. The target population were patients with SpA or suspected SpA, the intervention was entheseal US, the outcomes were the prevalence of US abnormalities, the reliability, the diagnostic accuracy, the sensitivity to change. The possible comparators were clinical evaluation and other imaging techniques. Cohort studies (cross-sectional or longitudinal), case-control studies, diagnostic accuracy studies, systematic literature reviews and meta-analyses were eligible for inclusion.*

Results. *Out of 3368 retrieved references, 34 papers were finally included. 22 of which reported information on the prevalence of US findings, yielding highly variable results. US was sufficiently reliable, as reported in 6 papers. A minority of studies reported data on sensitivity to change, which was good, and on the application of US for differential diagnosis and diagnosis of SpA, thus demonstrating the value of US also in this context.*

Conclusion. *US confirms its validity and reliability in the assessment of entheseal involvement in patients with SpA. Further application in the help of diagnosis will be provided by future research.*

Introduction

Inflammation at the entheses is a typical pathological feature of spondyloarthritides (SpA) and its presence characterises all disease subtypes, including ankylosing spondylitis (AS) and psoriatic arthritis (PsA) (1). Peripheral entheses are mainly composed of fibrocartilage, especially at the lower limbs. These structures have the role of distributing on large surfaces high levels of mechanical stress, and they can be surrounded by bursae and fat pads, which are meant to reduce attrition (2). At the level of enthesis, therefore, several structures play the same functional role and can potentially be involved as a whole in the pathologic process as an *entheseal organ* (3). In patients with SpA, entheseal involvement can occur early in the disease course and may constitute its prevalent manifestation, often involving multiple sites (4). The assessment of entheses for diagnostic and follow-up purposes has commonly been based on clinical examination, since conventional radiography could mainly identify bony changes such as erosions and new bone formation, occurring later in the disease (5).

New imaging techniques, ultrasonography (US) and magnetic resonance imaging (MRI) in particular, have been applied for the assessment of peripheral joint involvement in SpA. A number of studies have investigated the potential application of US in joints of patients with SpA (6-8). Nevertheless, specific features driving differential diagnosis were not consistently found, with inflammatory and structural alterations being similar to those reported in other inflammatory arthritides. Entheseal involvement instead represents a specific feature of SpA and its assessment by US has proven to be more sensitive than clinical examination (9). The

use of US in this field has some advantages over MRI, which has shown some limitations in the assessment of peripheral entheses (10); it does not allow the evaluation of multiple sites and carries some relevant costs. US, on the other hand, allows the interactive and dynamic evaluation of multiple sites without the use of ionising radiation. It has shown reliability in the assessment of peripheral entheses, with good correlation with clinical and laboratory measures of disease activity indicating validity (11). US of the entheses can detect both structural abnormalities, such as changes in the US texture of the tendon, increased thickness, calcifications a the insertion or in the context of the tendon, bone erosions, and signs of hypervascularisation suggesting active inflammation, detected by Doppler and power Doppler (PD) in particular (12). Entheseal US has also proven to be responsive to change after the initiation of treatment (13). For these reasons, US has been proposed in the diagnosis and the follow-up of entheseal involvement in patients with SpA.

A consensus on the US definition of enthesitis has been reached only recently. The core elementary lesions of US-detected enthesitis include hypoechogenicity, increased thickness of the tendon at the insertion, calcifications, enthesophytes, erosions, and Doppler signal. The intra-reader reliability on these findings has shown however to be highly variable, with kappa ranging from 0.24 for the detection of enthesophytes to 0.64 for the evaluation of the presence of entheseal PD. Similarly, also inter-reader realibility varied depending on the lesion (14).

In 2011, a systematic literature review addressed the issue of enthesitis defined by US, evaluating literature up to 2010 with the aim of describing several US definitions of enthesitis and examining their metrologic properties (15). The review included 48 articles, published up to 2010, of which only 22 applied PD. Information on validity was available for 21 studies, 14 papers reported reliability and responsiveness was evaluated in 9 studies. Scoring systems were applied in only 3 studies. Since 2010, the application of US in the field of SpA has increased. Moreover, scoring systems focusing on entheses such as the Madrid sonographic enthesitis index (MASEI) and the Glasgow Ultrasound Enthesitis Scoring System (GUESS) have been more frequently applied in research settings (16, 17). It seemed, therefore, timely to review the literature on this topic in the last 4 years, also in the light of the new definition of US enthesitis. For this purpose, we systematically reviewed the literature and reported qualitatively the available evidence emerging in the last four years.

Table I. Search strategy.

PubMed	**#1** Spondylitis, Ankylosing [Mesh] **#2** "bechterew disease" **#3** "Marie Struempell" **#4** (ankylos* spondyl*) **#5** Spondyloarthritis [Mesh] **#6** (spondyl*) **#7** Arthritis, Reactive [Mesh] **#8** "reactive arthritis" **#9** (reiter* syndrome) **#10** (reiter*disease) **#11** OR 1-10 **#12** Arthritis, Psoriatic [Mesh] **#13** (arthri* psoria*) **#14** (arthro* psoria*) **#15** OR 12-14 **#16** (enthes*) **#17** Inflammatory Bowel Diseases [Mesh] **#18** Arthritis [Mesh] **#19** #17 AND #18 **#20** ("Crohn" OR (enteropath*) NEXT (arthri* OR arthrop*)) **#21** #19 OR #20 **#22** #11 OR # 16 OR #21 **#23** "Ultrasonography"[Mesh] **#24** "Ultrasonography, Doppler"[Mesh] **#25** (ultraso*) **#26** "Doppler" **#28** OR 23-27 **#29** #22 AND #28
EMBASE	**#1** ankylosing AND ('spondylitis'/de OR spondylitis) AND [humans]/lim AND [embase]/lim **#2** 'spondyloarthropathy'/exp OR spondyloarthropathy AND [humans]/lim AND [embase]/lim **#3** bechterew AND ('disease'/exp OR disease) AND [humans]/lim AND [embase]/lim **#4** reactive AND ('arthritis'/exp OR arthritis) AND [humans]/lim AND [embase]/lim **#5** reiter AND ('syndrome'/exp OR syndrome) AND [humans]/lim AND [embase]/lim **#6** psoriatic AND ('arthritis'/exp OR arthritis) AND [humans]/lim AND [embase]/lim **#7** 'enthesitis'/exp OR enthesitis AND [humans]/lim AND [embase]/lim **#8** inflammatory AND ('bowel'/exp OR bowel) AND ('disease'/exp OR disease) AND ('arthritis'/exp OR arthritis) AND [humans]/lim AND [embase]/lim **#9** #1 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 **#10** 'ultrasonography'/exp OR ultrasonography AND [humans]/lim AND [embase]/lim **#11** doppler AND [humans]/lim AND [embase]/lim **#12** #11 OR #12 **#13** #9 AND #12

Methods

A search strategy based on terms related to SpA and US was developed (Table I). We searched MEDLINE (PubMed) and Embase up to March 9th 2014. The references of the relevant studies were also hand searched to look for additional references. The search was limited to humans and adults, was made by one author and checked by a second author. Data were extracted using a standardised form.

The target population were patients with diagnosed or suspected SpA. This included AS, PsA, undifferentiated SpA, reactive arthritis, arthritis related to inflammatory bowel diseases (IBD). The intervention was US of entheses, with several possible comparators: clinical evaluation or other imaging techniques (MRI or radiography). The outcomes of interest were the prevalence of US abnormalities, the diag-

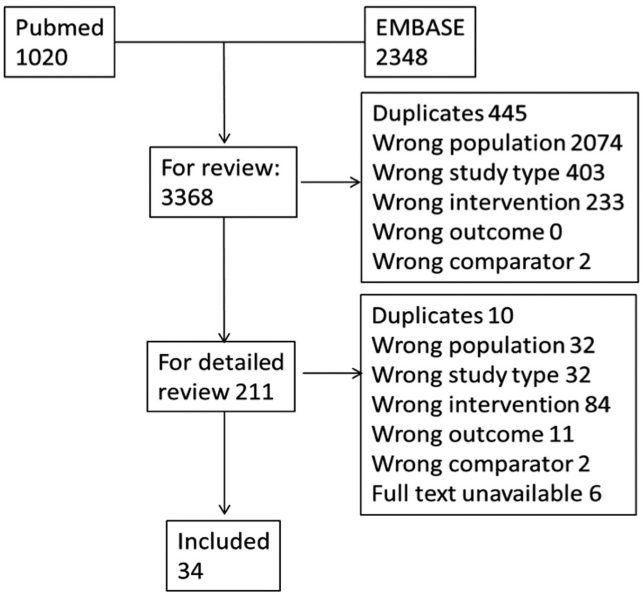

Fig. 1. Flow-chart showing the selection process

nostic accuracy of US, the reliability of the technique, the responsiveness to change. Cohort studies (cross-sectional or longitudinal), case-control studies, diagnostic accuracy studies, systematic literature reviews and meta-analysis were eligible for inclusion.

Results

The search initially retrieved 3368 papers. Of these, 34 studies were finally included. The selection process is shown in Figure 1. When differentiating studies according to the population examined, 4 of the included studies focused on AS (17-21), 7 studies involved patients with psoriatic arthritis (PsA) (22-28), 13 were based on mixed populations or populations of undifferentiated SpA (29-41), with a single study focusing on the SAPHO syndrome (42). A total of 12 studies involved patients without a definite diagnosis of SpA, but included subgroups with suspected diagnosis or at risk of developing SpA; in particular, 10 studies enrolled patients with psoriasis in the absence of diagnosed arthropathy (24, 25, 28, 43-49), 1 patient with IBD (50) and only one study on consecutive patients with suspected new-onset SpA (51). When examining the technique of application of US, 24 studies applied PD, and one study investigated sonoelastography. Two studies evaluated the use of three-dimensional (3D) US for the study of entheses and only one study examined the application of contrast-enhanced US. Scoring methods were applied in 12 studies, in particular MASEI in 4 studies, and GUESS in 5 studies. Most of the studies had a cross-sectional design, while 4 provided follow-up data. The main characteristics of the included studies and their results are reported in Tables II–V.

Prevalence of entheseal US abnormalitites

The prevalence of US abnormalities was reported in 21 studies. In patients with AS, the most common lesion, as reported by a single study (18), was entesophytes, present in 31.7% of involved sites. The same study reports a lower prevalence of entheseal PD (6%). Scoring systems were not applied in this population.

In patients with PsA, PD is reported in up to 40.2% of cases, the same study reports at least a single entheseal abnormality detected by GS in all patients (26), consistent with a previous study reporting US signs of enthesopathy in 98.3% of PsA patients (28). The mean MASEI in this group of patients ranged from 13 to 18.5 (24, 28).

Studies examining mixed populations reported highly variable prevalence of US-detectable enthesopathy, depending on the region of interest and on the features of the population. Overall, the prevalence of enthesopathy ranged from 100% at the elbows in symptomatic patients (39) to 40.5% in the trochanteric entheses of patients with PsA (33), while studies examining multiple sites reported prevalences ranged from 60.8 to 76% (34,37). Entesophytes were reported in 95% of patients (33). Bone erosions at the tendon insertion were seen in 7.4% to 26.3% of patients (29, 30). The prevalence of entheseal PD ranged from 1% in the trochanteric region to 56% seen in symptomatic Achilles tendon. In two studies the MASEI was applied, with a mean value MASEI of 23.36 (11.40) (31).

Validity, reliability, sensitivity to change

A total of 6 studies correlated the results of entheseal US with relevant clinical and laboratory variables. In patients with AS, the presence of entheseal PD was significantly related with clinimetric measures of disease activity (19). Similarly, in patients with PsA, US findings were correlated with clinical assessment (22), although in one study the GUESS and the presence of PD did not correlate with MASEI, PASI or clinical indexes (27). In patients with SpA, the presence of erosions was significantly related to acute phase reactants and clinical measures of disease activity at the level of Achilles tendon enthesis (30), while at the knee the agreement between US and clinical assessment was poor (37).

The reproducibility of entheseal US was examined in 6 studies, testing the intra and inter-reader reliability (22, 23, 30, 35, 43, 50). The overall intra- and inter-reader reliabilities were good for both GS and PD alterations, and were also shown to be good for the assessment of bone erosions. The reproducibility was not tested in AS patients, but only in the remaining populations. Also, the reproducibility of 3D US proved to be good (30).

Sensitivity to change was tested in 2 studies. GS signs of enthesitis have shown to decrease along with clinical parameters of disease activity in PsA (23), while a single study confirmed the ability of CEUS to present different changes in patients stopping and then re-starting non-steroidal anti-inflammatory drugs (NSAIDs) (36).

Table II. Included studies – ankylosing spondylitis.

Sudy	Population	Region of interest	US equipment	Outcome	Results
Spadaro A 2011 (18)	36 AS	Extensor of the forearm, gluteus, quadricipital tendon, patellar tendon (proximal and distal), Achilles tendon, plantar fascia	ESAOTE MyLab 70 6-18 MHz GS and PD	Prevalence of entheseal abnormalities	enthesophytes 31.7% calcifications 33.7% thickening 29.8% hypo-echogenicity 26.6% Erosions 9.7% PD 6%
Hamdi W 2011 (19)	60 AS	Quadricipital tendon, patellar tendon (proximal and distal), Achilles tendon, plantar fascia	Philips HD 11 GS and PD	Correlation of US with clinical findings	PD score significantly correlated with VAS pain, BASDAI, BASFI, and ASQoL
Hamdi W 2013 (20)	60 AS	Quadricipital tendon, patellar tendon (proximal and distal), Achilles tendon and plantar fascia erosion, thickness, and new bone formation	Philips HD11 15 MHz GS	Diagnostic accuracy of US compared to radiography for the diagnosis on entesopathy	**Erosions:** Se 100% Sp 20% PPV 93.22 NPV 100 **Thickening:** Se 95.5% Sp 13.3% PPV 76.7 NPV 100 **New bone formation:** Se 96.7% Sp 6.9% PPV 52.63 NPV 66.6
Turan A 2013 (21)	41 AS 32 HC	Achilles tendon enthesis	Sonoelesatography Hi vision preirus Hitachi	Association between elastography and conventional US	The distal third of the Achilles tendons was the most frequently affected region in AS, while the central part in HC Softening detected by sonoelastography in the distal third was associated with enthesopathy and tendinous enlargement on conventional US (p=0.07)

AS: ankylosing spondylitis; HC: healthy controls; GS: grey scale; PD: power Doppler; TNFi: TNF-α inhibitors; US: ultrasonography; CRP: C-reactive protein; ESR: erythrosedimentation rate; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value.

Utility of US for diagnosis

Only a few studies specifically addressed the issue of the additional value of entheseal US for diagnostic purposes. In the context of AS, a single study examined the diagnostic accuracy of US for the diagnosis of enthesopathy, using conventional radiography as reference standard. US achieved high values of sensitivity (between 0.95 and 1), while specificity was lower, as a likely consequence of the low sensitivity of radiographs in detecting soft tissue abnormalities (20).

In general, many studies describe a higher frequency of US-detectable entheseal abnormalities in patients with PsA compared to healthy controls; in the setting of patients with psoriasis those with PsA more frequently had US abnormalities compared to those without arthropathy. In particular, using a cut-off of 20 for the MASEI, considering clinical diagnosis as reference standard, PsA could be diagnosed with a sensitivity of 0.3 and a specificity of 0.89 (24), with a positive LR of 2.63 to differentiate PsA from psoriasis without joint involvement. Moreover, a study investigated the use of US of the entheses to help the differential diagnosis between PsA and fibromyalgia. In this setting, entheseal abnormalities were seen more frequently in PsA, and bone erosions were seen exclusively in this group of patients.

However, only one study applied entheseal US in a setting fully reproducing clinical practice. Consecutive patients with clinical suspicion of SpA were enrolled and the diagnostic accuracy of US to detect SpA was tested against clinical diagnosis after a follow-up of two years (51). The presence of at least one site showing PD had a sensitivity of 0.76, a specificity of 0.81, a positive likelihood ratio (LR) of 4.1 and a negative LR of 0.3 for the diagnosis of SpA.

A number of studies have investigated the utility of US to detect subclinical enthesitis in populations at risk of developing SpA. In particular, 10 studies (24, 25, 28, 43-49) included patients with psoriasis, without a definite diagnosis of PsA. The result that seems to consistently emerge through the studies is that of a higher prevalence of subclinical enthesitis in patients with psoriasis compared to healthy controls, although patients with PsA still show US entheseal alterations more frequently and to a greater extent. Moreover, nail involvement was associated with subclinical entheseal involvement (43). A single study examined the prognostic potential of US in identifying psoriatic patients at risk of development of PsA: in this context baseline quadricipital tendon thickness predicted a subsequent development of PsA. In addition, this subgroup had a higher median baseline GUESS score (46). In the only study focusing on patients with IBD, a prevalence of entheseal abnormalities in 92.6% of patients is reported, and PD was seen in 5% of entheses, while entheseal PD was not seen in controls (50).

Discussion

With more effective treatments and treatment strategies becoming available for the management of SpA, specific issues such as timely diagnosis, evaluation of subclinical diseases, monitoring of treatment effect have emerged as central issues in the care of SpA (52). While for axial involvement MRI has emerged as the reference technique, despite some possible limitations (53), and has also been included in the classification criteria (54), for peripheral involvement and entheseal involvement in particular US has emerged as a feasible, easily accessible and reliable technique (55). For the assessment of

Table III. Included studies – psoriatic arthritis.

Study	Population	Region of interest	US equipment	Outcome	Results
Freeston J.E. 2012 (22)	42 early PsA 10 HC	Common extensors of the forearm Patellar tendon (distal insertion) Achilles tendon Plantar fascia	Philips HDI 5000 12-5 MHz 15-7 MHz GS score (0-3): composite score of tendon/aponeurosis thickening and hypoechogenicity PD (0-3)	Agreement between clinical examination and US (GS >1 and PD >0) on the presence of active enthesitis Intra-reader reliability	Agreement on the presence of activity: 34% Agreement on the absence of activity: 90.7% Subclinical enthesitis 4% Intra-reader reliability: GS 0.73 (0.6-0.86); PD 0.91 (0.85-0.98)
Gutierrez M. 2012 (23)	16 PsA starting TNFi Involvement of at least 2 articulations and 1 skin/nail target. One region was selected for the follow-up 8 weeks of follow-up	3 articular targets: joints, tendons, entheses 2 dermatological targets: skin and nail	ESAOTE MyLab 70 6-18 MHz PD	Development of a preliminary PD score to monitor PsA Sensitivity to change Intra and inter-reader reliability	Median change from9 (4-12) at baseline to 3 (1-5) at the end of the follow-up (p=0.0001) All measures were sensitive to change Inter-reader reliability: joints 0.787, tendon 0.844, enthesis 0.895, skin 0.945, nail 0.665 Intra-reader reliability: joint 0.977, tendon 0.986, enthesis 0.966, skin 0.904, nail 0.812
Eder L. 2014 (24)	55 PsA 66 psoriasis without PsA 60 healthy controls	Plantar fascia Achilles tendon Patellar tendon (distal and proximal) Quadricipital tendon Brachial triceps tendon Evaluation of: erosions, calcifications, tendon structure, tendon lesion, bursa, PD MASEI	ESAOTE MyLab 6–18 MHz GS and PD	Comparing entheseal abnormalities between PsA, psoriasis and HC Performance of MASEI in classifying patients as PsA	Overall median MASEI: PsA 13, psoriasis 6, HC 3.5 (p<0.0001) MASEI inflammatory: PsA 6, psoriasis 2, HC 1 (p<0.0001) MASEI damage: PsA.5, psoriasis 4, HC 3 (p<0.0010) At least 1 inflammatory abnormality in 90% PsA patients, 72% psoriasis, 48.3% HC (p<0.0001) MASEI≥ 20: **Se** 30% psoriasis *vs*. PsA, 30% HC *vs*. PsA **Sp** 95% HC *vs*. PsA, 89% psoriasis *vs*. PsA **LR+:** 2.63 psoriasis *vs*. PsA, 5.8 HC *vs*. PsA
Farouk H.M. 2010 (25)	30 PsA 30 psoriasis	Achilles tendon	ESAOTE MyLab 70 9–11 MHz GS and PD	Entheseal US in the preclinical diagnosis of PsA	Entheseal abnormalities not significantly different between groups 33.3% psoriasis, 46.7% PsA (p>0.05)
Marchesoni A. 2012 (26)	30 PsA 30 FM	14 entheses	GS and PD	Prevalence of PD at entheses in PsA and FM	At least 1 abnormality in 100% of PSA and 80% of FM (p=0.01) Inflammatory abnormalities in 70% of PsA and 23% of FM (p=0.001) Erosions seen only in PsA 3 ore more alterations had the best discriminative cut-off between the diseases
Bandinelli F. 2013 (27)	92 early PsA	GUESS lower limbs Quadricipital, patellar, achilles tendons and plantar fascia	ESAOTE MyLab 70 15 MHz PD and GS	Prevalence of US abnormalities and correlation with clinical features	All patients had a GUESS>1 40.2% of patients had PD clinical involvement in 29.3% GUESS and PD did not correlate with MASEI, PASI and clinical variables
Eder L. 2012 (28)	79 psoriasis 59 PsA 60 HC	patella tendon (proximal and distal insertion), Achilles tendon, plantar fascia, triceps tendon MASEI GUESS	ESAOTE MyLab 70 6-18 MHz	GUESS, MASEI and prevalence of US abnormalities in the three groups	Enthesopathy in 98.3% of PsA patients, 97.5% of patients with psoriasis and 86.7% of HC Mean (sd) GUESS: PsA 8.9 (4.6), psoriasis 5.6 (3.5), HC 4.4 (3.9), p<0.001, Mean (sd) MASEI: PsA 18.5 (3) psoriasis 9.9 (7.4), HC 7.7 (9.2), p<0.001

PsA: psoriatic arthritis; HC: healthy controls; GS: grey scale; PD: power Doppler; TNFi: TNFα inhibitors; US: ultrasonography; CRP: C-reactive protein; ESR: erythrosedimentation rate; Se: sensitivity; Sp: specificity; LR: likelihood ratio, FM: fibromyalgia; MASEI: Madrid Sonographic Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System.

entheses in particular, the availability of higher frequency probes has allowed the diffusion of US at this level with a more reliable assessment.

In this review, the latest applications of US in the assessment of entheseal involvement in adult patients with SpA were examined. The review did not focus on the issue of paediatric rheumatology, about which the information is more limited (56), and for which a specific search should be performed. In this specific field, the absence of a single definition of entheseal US involvement has represented a limitation. In fact, the US features described in the included papers varied consistently, leading to a relevant heterogeneity across studies, with studies evaluating in different combinations increased thickness, reduced echogenicity, new bone formation, erosions and PD. The variability seen in the results concerning the prevalence of US abnormalities might therefore be due to different definitions adopted, beside differences in the recruited populations.

Table IV. Application of entheseal US in patients with potential subclinical disease.

Study	Population	Region of interest	US equipment	Outcome	Results
Ash Z. 2012 (43)	46 psoriasis without PsA (31 with nail involvement) 21 HC	Achilles tendon, plantar fascia, quadricipital tendon, patellar tendon (proximal and distal)	GE Logiq 9 and Logiq 5 9-14 MHz GS and PD	Prevalence of subclinical enthesitis in psoriatic patients with nail involvement Inter-reader reliability	NAPSI significantly related to inflammation (rho=0.45, p=0.005) and chronicity scores (rho=0.35, p=0.05) Inter-reader reliability: ICC 0.91-0.93 (0.79, 0.97) for GS, 0.74-0.95 (0.45,0.98) for PD, 0.89-0.93 (0.76, 0.98) for chronicity scores, overall score 0.92-0.95 (0.81, 0.98
Bandinelli F. 2011 (50)	81 IBD 40 HC	GUESS	GE Logiq 5 10 MHz GS and PD	Prevalence of US abnormalities Intra- and inter-reader reliabilities	92.6% of pts at least one alteration: 81.5% increased thickness 67.9% entesophytes 27.1% bursitis 16.1% erosions PD 16% In controls: 5% had entesophytes, no patient had PD Mean (sd) GUESS: 5.1 (3.5) in patients Intra-reader reliability ICC 0.99 (0.98,1) Inter-reader reliability: ICC 0.97 (0.9, 0.99)
D'Agostino M.A. 2011 (51)	118 with suspected SpA	Plantar fascia Achilles tendon Ptellar tendon (proximal) Quadricipital tendon Gluteus medius Common extensor and flexor of the forearm	ESAOTE Technos MPX	Diagnostic accuracy of PD in the diagnosis of SpA Reference standard: rheumatologic diagnosis at 2 years	75% ofsubjects hads at least one abnormality Abnormal enthesis: 32% in SpA *vs*. 26% in non-SpA (p<0.01) At least 1 abnormal enthesis: 86% in SpA *vs*. 75% in non-SpA (p=0.003) Achilles tendon: 43% in SpA *vs*. 33% in non-SpA (p=0.01) Lateral epicondyle: 37% in SpA *vs*. 28% in non-SpA (p=0.03) At least 1PD psotive enthesis: 76% in SpA *vs*. 47% in non-SpA (p<0.0001) At least 1 PD enthesis: Se 76.5 (76.3,76.5), Sp 81.2 (81.1, 81.4) LR+ 4.1 (3.5, 4.7), LR- 0.3 (0.2, 0.8) OR 14.8 (5.3, 37.2) (p=0.003)
De Simone 2011 (44)	52 psoriatic patients with pain at fingers of joints 50 asymptomatic patients with psoriasis	All joints and tendons of fingers and toes	Toshiba Aplio XV 5–12 MHz GS and PD	Prevalence of US abnormalities	GS abnormalities: 36/52 patients PD abnormalities: 29/52 patients No GS abnormalities in controls, one patient showed PD
Naredo E. 2011(45)	162 patients with psoriasis without PsA 60 HC	36 joints 18 entheses 22 tendons	GE Logiq 9 8-14 MHz GS and PD	Prevalence of entheseal abnormalities	Entheseal PD 7.4% psoriasis patients *vs*. 0% in HC (p=0.05) OR of psoriasis over enthesopathy 2.6
Tinazzi I. 2011 (46)	30 patients with psoriasis without PsA followed for 3.5 years	GUESS	GE Logiq 5 ALT HDI 3000 10-15 MHz GS and PD	Predictive value of GUESS over the development of PsA	Baseline GUESS of patients who developed PsA was significantly higher (mean 9.54±2.02 *vs*. 6.61±3.60, p=0.0127) Baseline thickness of the quadricipital tendon was an independent predictor of the development of PsA
Aydin S. 2013 (47)	42 psoriasis 58 PsA 23 HC	Lower limb entheses (inflammatory and chronic features)	GS and PD	Prevalence of entheseal PD in psoriasis compared to PsA and HC	Significantly higher scores in psoriasis than HC (inflammation p<0.0001, chronicity p=0.02, total US scores p<0.0001). PsA patients had higher enthesopathy scores than patients with psoriasis (inflammation p=0.04, chronicity p=0.02) and HC (inflammation p<0.0001, chronicity p=0.003) In non-symptomatic entheses: PsA higher PD scores than psoriasis patients (p=0.003). PD was more frequently in PsA (21/58, 36.2%) than psoriasis (4/42, 9.5%; p=0.002)
Aydin S. 2012 (48)	86 psoriasis 20 HC	Nail and distal extensor of the finger enthesis	-	Linkage between nail involvement and extensor enthesopathy	Thickened tendon in nail involvement vs normal nail: Psoriasis: 38 *vs*. 16%, p=0.03 PsA 47 *vs*. 19%, p=0.008
Gutierrez M. 2011 (49)	45 psoriasis 45 HC	GUESS	GS and PD	Prevalence of subclinical entheseal involvement	Psoriasis: 32.9% GS abnormalities, 0.9% PD HC: 8.4% GS abnormalities, 0% PD

AS: ankylosing spondylitis; PsA: psoriatic arthritis; HC: healthy controls; GS: grey scale; PD: power Doppler; TNFi: TNF-α inhibitors; US: ultrasonography; CRP: C-reactive protein; ESR: erythrosedimentation rate; ICC: interclass correlation; GUESS: Glasgow Ultrasound Enthesitis Scoring System; IBD: inflammatory bowel disease, NAPSI: Nail Psoriasis Severity Index.

Despite some differences in defining enthesitis, a larger proportion of studies included PD assessment, compared to the 2011 systematic review, likely due to a greater diffusion of this technique (15). Moreover, the use of scoring methods has become more common in research settings for the evaluation of enthesitis, with several reports that support in particular the validity of GUESS and MASEI in the field of diagnosis and monitoring of SpA.

Examining study design, most of the studies were cross-sectional and their main aim was describing the prevalence

Table V. Included studies – SpA and mixed populations.

Study	Population	Region of interest	US equipment	Outcome	Results
Aydin S. 2010 (29)	19 SpA 21 HC	Achilles tendon	ESAOTE MyLab70 6-18 MHz GS	Prevalence of US abnormalities Thickness at the enthesis	95% enthesophytes and 26.3% erosions in SpA Thickness of the anechoic layer not different between SpA and HC
De Miguel 2011 (30)	68 early SpA	Achilles tendon insertion bone erosions Followed every 6 months for a year	GE Logiq 9 9-14 MHz 8-11 MHz 2D and 3D GS	To evaluate the persistence, increase or resolution of erosions Reliability of US and 3D US and the concurrent validity of Achilles enthesis erosions Intra and inter-reader reliability	US erosions: US 7.4% of entheses 3D 9.6% of entheses Erosions significantly associated with CRP, SJC, TJC, tendon PD Inter-reader reliability: kappa 0.84 (2D) and 0.85 (3D) Intra-reader reliability 0.84 (US) and 0.85 (3D)
De Miguel E. 2011 (2) (31)	113 early SpA 24 controls with inflammatory arthritis 57HC	Plantar fascia Achilles tendon patellar tendon (distal and proximal) Quadricepital tendon Brachial triceps tendon calcifications, erosions, tendon structure, tendon thickness, bursa, PD MASEI	GE Logiq 9 9-14 MHz GS and PD	(MASEI) Reference standard: clinical classification criteria	Mean (sd) MASEI 22.20 (7.22) in AS 24.25 (10.71) in SpA 19 (6) ReA 26.75 (27.93) IBD 19.56 (11.70) PsA 12.26 (6.85) Controls Mean (SD) MASEI 23.36 (11.40) in cases, 12.26 (6.85) in the non-inflammatory controls (p<0.001), 16.04 (9.94) in the inflammatory controls (p<0.01)
Feydy A. 2012 (32)	51 SpA 24 controls with mechanical back pain	Achilles tendon Plantar fascia echostructure abnormalities, retrocalcaneal bursitis, PD	Toshiba Aplio 7-15 MHz GS and PD	Performance of MRI and US of the heel to distinguish SpA from controls and SpA with and without enthesopathy.	No differences between patients and controls Abnormalities more frequent in painful heels : 58% *vs*. 17% (p<0.001) Achilles tendon thickening of >5.29 in symptomatic patients: 31% *vs*. 10% (p=0.033) Mean thickness: 3.9 mm in symptomatic patients *vs*. 3.1 mm in asymptomatic patients (p=0.007) PD not different between SpA and controls symptomatic and asymptomatic
Gutierrez M. 2012 (33)	46 SpA 46 HC	Trochanteric region thickening, calcifications, bone erosions, enthesophytes, bursitis, PD	ESAOTE MyLab 70 4-13 MHz GS and PD	Prevalence of US abnormalities	Enthesopathy: 40.5% in SpA *vs*. 29% in HC (p<0.0001) Calcifications: 33.9% in SpA *vs*. 28.7% in HC Enthesophytes: 25% in SpA *vs*. 20% in HC Thickness: 18.7% in SpA *vs*. 43.7% in HC Erosions: 11.6% in SpA *vs*. 7.5% in HC Bursitis 10.7% in SpA PD 1% in SpA
Hodgson R. 2011 (34)	25 Spa with painful Achilles tendon 10 HC	Achilles tendon	GE logiq 9 14 MHz GS and PD	Prevalence of US abnormalities detected through MRI, ultrashort echo time MRI and US	GS abnormalities: 76% PD: 56% Flogositic signs seen more often by ultrashort echo time MRI than US and MRI
Merot O. 2013 (35)	16 SpA	MASEI (conventional US *vs*. 3D)	-	Reliability of 3D US *vs*. US for the scoring enthesitis in SpA Intra and inter-reader reliability	Intra-reader reliability: ICC US: 0.776 (0.471-0.916) and 0.96 (0.892-0.986) ICC 3D US: 0.796 (0.498-0.921) and 0.703 (0.325-0.886 Inter-reader reliability ICC US: 0.641 (0.221-0.859) ICC 3D US: 0.776 (0.471-0.916) Correlation US-3D US: ICC 0.705 (0.329-0.887)
Mouterde G. 2014 (36)	14 SpA mildly active followed after stopping NSAIDS and after reassuming NSAIDs	Selected enthesis with doubtful PD on conventional US (more frequently common extensor tendon)	ESAOTE MyLAb 70 10-18 MHz 3-9 MHz	Responsiveness to change of CEUS PD	Decease of CEUS score from baseline to T1 (0.86 to 1.23; p=0.03) Increase after stopping NSAIDs (1.03 p>0.05)
Queiro 2012 (42)	15 SAPHO 30 HC	Common extensor and flexor tendons, quadricipital tendon, patellar tendon (proximal and distal), Achilles tendon and plantar fascia	GE Logiq5 7-12 MHz GS and PD	Prevalence of US abnormalities	7/15 (47%) at least an abnormality 15% in SAPHO *vs*. 4.8% in HC of entheses involved (p<0.01)
Ruta S. 2011 (37)	60 Spa without clinical enthesitis 60 RA 30 HC	Quadriceps tendon and patellar tendon (proximal and distal)	ESAOTE MyLab 60 6-18 MHz	Prevalence of subclinical enthesitis	331/544 (60.8%) of asymptomatic entheses showed at least one US abnormality

Table V continues on next page

Study	Population	Region of interest	US equipment	Outcome	Results
Wiell C. 2013 (38)	12 SpA 15 HC	Achilles tendon thickness, calcifications, erosions, enthesophytes, PD	GE Logiq 9 9-14 MHz GS and PD	Prevelence of abnormalities in painful Achilles tendon in SpA *vs*. HC	Entesophytes more frequent in SpA Intratendineous changes more frequent in SpA
Zytoon A . 2014 (39)	38 SpA with elbow enthesopathy 10 HC	elbow	HDI 3000 ATL 5-12 MHz	Prevalence of US abnormalities	100% loss of pattern 84.2% peritendineous oedema 100% tendon thickening 84% intratendineous defects 52.6% calcifications 13% erosions
Aydin S. 2013 (40)	SpA	Knee enthesopathy (8 entheseal sites)	-	Prevalence of US abnormalities Correlation with clinical examination	Enthesitis in 86% of patients Clinical enthesitis was associated with more hypoechogenicity (16 *vs*. 4%, p=0.007) and thickening (16 *vs*. 6%, p=0.03). Agreement between clinical assessment and US was very low: kappa (0.06-0.18) No correlations between the MRI and US scores (rho = 0.059)
Falcao S. 2013 (41)	66 early SpA 46 controls (HC and RA)	Achilles tendon bursa	Conventional US and 3D	Prevalence of US bursitis	67.4% bursitis in SpA, 58.7%in HC, 21.7 RA (p<0.01)

AS: ankylosing spondylitis; PsA: psoriatic arthritis; HC: healthy controls; GS: grey scale; PD: power Doppler; US: ultrasonography; CRP: C-reactive protein; ESR: erythrosedimentation rate; MASEI: Madrid Sonographic Enthesitis Index; GUESS: Glasgow Ultrasound Enthesitis Scoring System.

of US abnormalities in different SpA populations, providing in most cases data from control populations of healthy subjects or patients with other inflammatory pathology. These studies confirmed in general a higher prevalence of abnormalities in patients compared to controls, and the more frequent detection of abnormalities by US compared to clinical examination. However, recent studies (22) involving patients with PsA, reported a low prevalence of subclinical enthesitis (4%). US and clinical examination showed a poor agreement in detecting the presence of entheseal involvement, while the agreement in excluding enthesitis was good. The potential of US in excluding rather than detecting enthesitis has been explored also in the context of fibromyalgia, to distinguish non-specific tenderness from evident entheseal involvement, confirming a higher prevalence of US alterations in patients with PsA (26).

The validity of US in the assessment of entheses was confirmed in these studies, with US findings being significantly related to acute phase reactants and clinical measures of disease activity.

Several studies focused on the application of US in subgroups of patients at risk of developing SpA, in particular the majority of studies were based on patients with psoriasis. In this context, US alterations were detected more frequently in psoriatic subjects than in healthy controls, although the prevalence of US abnormalities was in general still higher in patients with diagnosed PsA. In this cathegory, US findings have also shown a prognostic value in the prediction of the subsequent development of clinically detectable arthropathy, with quadricipital tendon thickness being an independent predictor for a clinical diagnosis of arthritis (46). The GUESS and MASEI scores were applied in this field as well.

Data deriving from cross-sectional studies confirm what had emerged in the previous literature on the application of US in SpA. However, the prevalence of cross-sectional design leads to limited available information on the value of US in treatment monitoring, responsiveness to change and diagnostic potential. In particular, only a minority of the included studies examined the value of entheseal US for diagnostic purposes. This has probably been influenced by the absence of a reliable reference standard to define enthesitis, with difficulties in performing histological assessments and with several limitations in the evaluation performed both clinically and by imaging techniques, with conventional radiography and MRI lacking satisfactory performance for these structures (57). A single study investigated the diagnostic utility of US in a real clinical practice setting (51), examining consecutive patients presenting with clinical suspicion of SpA and using the clinical diagnosis after two years as reference standard and demonstrating good values of sensitivity, specificity and positive and negative likelihood ratios.

A limited number of studies report information on responsiveness to change, however, entheseal US has confirmed significant changes after the modification of effective treatment.

A minority of studies focused on US techniques which so far have not been introduced in common clinical practice, such as 3D US, contrast-enhanced US and elastosonography. The emerging data suggest a possible role of 3D US in the assessment of entheses, the application of CEUS in case of doubtful US involvement, and elastosonography to identify the most involved tendon region.

The overview of the literature confirms that a significant amount of information has accumulated in the field of the application of US in SpA, although the absence of uniform definitions for US enthesopathy have led to a general dishomogeneity of the results. The creation of a provisional definition of en-

thesitis will have an impact on upcoming research leading to more generalisable data. So far, US has shown to be a reliable tool, able to distinguish cases from controls in entheses in patients with SpA, with promising utility in the field of differential diagnosis and monitoring response to treatment. A larger number of prospective studies evaluating its potential in realistic clinical settings will help translate its application into widespread clinical practice.

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