Musculoskeletal ultrasonography for psoriatic arthritis and psoriasis patients: a systematic literature review

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TITLE

MUSCULOSKELETAL ULTRASONOGRAPHY FOR PSORIATIC ARTHRITIS AND PSORIASIS PATIENTS. A SYSTEMATIC LITERATURE REVIEW.

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Key messages:

•This is the first systematic literature review on the use of ultrasonography in psoriasis and psoriatic arthritis;

•The systematic literature review points up the importance and potential of ultrasonography in the management of psoriatic arthritis and psoriasis but it also underlines the need of a large amount of research to optimise the use of ultrasonography in the diagnosis and monitoring of psoriatic disease in clinical practice;

•Based on the evidence arising from the literature review, a research agenda has been proposed.

Abstract

Objective: To systematically review the role of musculoskeletal ultrasound (MSUS) in patients suffering from psoriatic arthritis (PsA) or psoriasis (Pso) in terms of prevalence, diagnosis, prognosis, monitoring and treatment.

Methods: A systematic literature review was conducted through medical databases (MEDLINE via PubMed, Embase) and the grey literature up to September 2015 to inform a new study of the Musculoskeletal Ultrasound Study Group of the Italian Society for Rheumatology. All articles reporting data on MSUS in PsA or PsO were included and extracted according to the underlying clinical question.

Results: 86 publications were included. The prevalence of US abnormalities showed a wide range for each examined feature (e.g. 37% to 95% for entheses thickness of the lower limbs). The performance of US for diagnosis of disease or elementary lesions was variable across studies but no study evaluated the overall performance of US in addition to clinical findings to diagnose PsA. Considering US in defining PsA and Pso prognosis, several works focused on US of entheses of lower limbs in Pso while for the monitoring of PsA activity, 5 different scoring systems were identified. Lastly, the results of the role of US to guide intra-articular interventions were controversial for the clinical outcomes while in favour of US for accuracy.

Conclusion: despite the recognised importance of US in the management of PsA and Pso , this review clearly demonstrated the need of a pivotal research to optimise the use of US in the diagnosis and monitoring of psoriatic disease.

Introduction

Psoriatic arthritis (PsA) is a systemic inflammatory disease with articular and extra-articular features. In the last years, imaging is playing an increasing important role in the differential diagnosis and in monitoring treatment response in PsA. Recently, the European League Against Rheumatism (EULAR) recommendations for the use of imaging in the diagnosis and management of spondyloarthritis (SpA) advise the use of magnetic resonance imaging (MRI) and ultrasound (US) for the diagnosis, monitoring activity and evaluating structural changes in peripheral SpA (1). US demonstrated good accuracy, reliability and sensitivity to change in the assessment of various structures which may be involved in PsA, i.e. tendons, enthesis, synovium and bone (1–3). In addition, the information given by US assessment can be integrated to those obtained by clinical examination thus improving differential diagnosis (e.g. early seronegative polyarthritis), stratification of patients and therapeutic strategies in a treat-to-target (T2T) context (4,5). Currently, the utility of US in clinical practice is not yet supported by adequate evidence (6), therefore, reflecting the need to determine the role of US in diagnosis and prognostic stratification and to support prioritisation of US studies in PsA, the Musculoskeletal Ultrasound Study Group of the Italian Society of Rheumatology decided to perform a systematic literature review (SLR) on the use of US in the management of PsA.

METHODS

The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) were followed to design and report this review(7). The most relevant areas of application of US in PsA and psoriasis (Pso) (prevalence and diagnosis of the disease, diagnosis of elementary lesions typical of PsA, prognosis, follow-up and treatment guide) were identified and pre-specified inclusion criteria for each item were developed (Table S1).

Data Sources and Search

PubMed and Embase were searched, without time limits, up to September 27th, 2015. The search strategy was developed based on search terms aiming at identifying studies including patients with PsA or Pso in which musculoskeletal US was performed. The search strategy is presented in Table S2. Abstract of the American College of Rheumatology (ACR) and EULAR congresses (2014 and 2015) were hand searched. Studies had to be published in English, no publication restriction or selection based on quality were applied.

Study Selection

Studies included patients with suspected or confirmed PsA, including mixed population of arthritis, only when a part of patients diagnosed with PsA. Studies on patients with skin psoriasis without known arthropathy were also eligible for inclusion. US was considered as index test/intervention, details on the comparators, outcomes and eligible study designs are shown in Table 1. The reviewers (FB, AB, AZ) worked in pairs for each area of interest, independently screening titles and abstracts. The full-text of potentially eligible articles was obtained; inclusion assessment was performed by one reviewer and checked by a second.

Data extraction and quality assessment

Study characteristics and data were extracted using separate standardised forms for each area of interest. For diagnostic accuracy items, when possible data were extracted as 2x2 tables and sensitivity, specificity, positive and negative likelihood ratios (LR) with 95% confidence intervals (CI) were calculated. Pre-specified meta-analyses were not planned, due to the expected heterogeneity across studies. The hypothesis of heterogeneity was tested in the subgroup of studies assessing the performance of US in detecting elementary lesions. The risk of bias and methodological quality of the included studies were assessed with different tools, depending on study design. For diagnostic studies, the QUADAS-2 tool was used (8), for RCTs the risk of bias tool proposed by the Cochrane collaboration (9) while for observational studies the Newcastle-Ottawa scale (NOS) (10).

RESULTS
Selected studies

Of the 365 studies produced by PubMed and Embase search, 71 studies met the criteria for the inclusion. Furthermore 15 additional studies were included, 2 from hand search and 13 from the 2014-2015 abstracts of ACR and EULAR. Figure 1 shows the flowchart of the study selection process. Table 2 highlights on high quality studies on prevalence, diagnosis and prognosis.

Prevalence of US abnormalities in PsA and Pso

The search retrieved 56 studies examining the prevalence of US abnormalities in PsA (50/56 studies) and isolated Pso (6/50 studies) (11), (12), (13), (14), (15), (16), (17), (18), (19), (20), (21), (22), (23), (24), (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), (43), (44), (45), (46), (47), (48), (49), (50), (51), (52), (53), (54), (55), (56), (57), (58), (59), (60), (61), (62), (63), (64), (65), (66). The results are summarized in Table 1, while complete results are shown in table S3. Regarding the examined US abnormalities, synovitis, erosions and enthesopathy were often studied, less frequently soft tissue inflammation, described as oedema and/or PD peri-tendinous. The prevalence of the examined lesions had a wide range in the studies: 10 to 100% for synovitis (22), (34), (48), (52), (55); 37% to 94.5% for entheses thickness of the lower limbs (14), (17), (15), (24), (27), (30), (35), (36); and 10.8 to 52% for erosions (16), (34), (53), (55). The sites examined were very variable, except for studies of US entheses in which the lower limbs were the most frequently studied. For entheses evaluation Glasgow Ultrasound Enthesitis Scoring System (GUESS) as the most commonly employed score (15), (17), (27), (41), (50), (59), followed by MASEI score (12), (26). Furthermore two studies evaluated the synovial contrast enhancement   with a prevalence in PsA of approximately 30 percent (33), (55). The risk of bias for all selected studies, assessed using the NOS, is reported in table S3.

Making a diagnosis of PsA

Performance of US in the diagnosis of PsA and Pso

The search retrieved 23 studies, including a qualitative systematic review (67), examining the performance of US to diagnose PsA (37), (40), (42), (45), (46), (47), (56), (58), (59), (12), (26), (27), (17), (20), (28), (19), (31),(30), (29), (21), (34) ,(68). The results of the studies are summarized in Table S4,, figures 2, S1 and S2 . The diagnostic performance of US was variable across studies, in particular no study evaluated the overall performance of US in addition to clinical findings to diagnose PsA, while most studies were focusing on single lesions. However, no study demonstrated an adequate performance for US variables, considered separately. The performance of US to detect PsA was broadly variable among studies, with sensitivities ranging from 0.22 to 1.00 for enthesopathy, from 0.16 to 0.76 for synovial hypertrophy and from 0.14 to 0.58 form joint bone erosions. Also sensitivities were extremely variables, ranging from 0.20 to 1.0 for enthesopathy, from 0 to 1.0 for synovial hypertrophy and from 0.40 to 1.0 for bone erosions. Most of the studies (22 out of 23) followed a cross-sectional case-control design, and the evaluation of

the diagnostic performance of US was in many cases not the primary objective of the study. As expected, the studies were heterogeneous in terms of examined sites and reference standard, although clinical diagnosis or classification criteria were the only standard adopted. The risk of bias, assessed by the modified version of the QUADAS, was in general considered high for the items concerning patients recruitment, unclear for the items dealing with the index test and mostly low for the items covering the reference standard and the timing (Figure S3).

Performance of US in the diagnosis of PsA and Pso elementary lesions

The search retrieved 30 studies examining the performance of US to diagnose PsA elementary lesions (11), (15), (16), (20), (23), (24), (25), (30), (32), (69), (33), (34), (37), (38), (39), (44), (45), (70), (47), (48), (51), (52), (71), (53), (55), (57), (58), (63), (64),(72). The results of the studies are summarized i in Table S5. The PsA elementary lesions evaluated were heterogeneous for type of lesions (e.g. synovial or extra-synovial features), anatomic structures and reference standard. The reference standard was clinical examination in 14 studies, MRI in 5, Conventional Radiography (CR) and arthroscopy in 3, Computer Tomography (CT) and Histological Evaluation (HE) in 1. Considering MRI as reference standard, the sensibility and specificity underwent wide variations depending on examined anatomic structures and types of lesions, for example considering synovitis, sensibility ranged from 0.49 to 0.94 while specificity from 0.20 to 0.91 (Figure S4). In the unique study using histopathology as reference, the amount of power Doppler did not significantly associate with a global histopathological inflammatory score (44); while for the single study comparing US with CT, a large proportion of bone lesions detected by US could be verified by CT (32). The risk of bias, assessed by the modified version of the QUADAS, was in general considered high for the items concerning patients' recruitment, unclear for the items dealing with the reference standard and mostly low for the index test and flow and timing (Figure S5). This subgroup of studies was used to test the presence of heterogeneity across studies (Supplementary Figure S6, available online only), showing a significant degree of heterogeneity (for joint abnormalities: Chi square= 785.46, p<0.0001 for the presence of heterogeneity; for entheseal abnormalities: Chi square=1027.29, p<0.0001 for the presence of heterogeneity).

Prognosis and follow up

Role of US in defining PsA and Pso prognosis

The search retrieved 15 studies examining the role of US in defining PsA and Pso prognosis (11), (14), (73), (41), (74), (75), (56), (59), (23), (76), (77), (78),(79),(80), (49) with only two having a prospective design (75), (80). The results of the studies are summarized in Table S6. Several works, selected for this item, focused on target enthesis US in Pso patients revealing a high rate of subclinical inflammatory signs. Subclinical enthesitis, confirmed by a significant higher GUESS score, was found more frequently in Pso compared to healthy controls (14), (73), (41), while only one study focused on the prevalence of subclinical synovitis in Pso (49). There was only one prospective study, published by *Tinazzi et al,* in which GUESS scores of patients with Pso who developed PsA compared to those who did not develop PsA did not statistically differ. Furthermore, in the logistic regression analysis, baseline thickness of the quadriceps tendon was

found to be an independent predictor of the development of PsA (75). Moreover, the presence of PD signal in enthesis, evaluated as entheseal-organ in *Aydin et al 2013* and within 2 mm of bone insertion in *Gutierrez et al 2011*, was found to be highly specific for psoriatic disease (14), (41) . The risk of bias for all selected studies, assessed using the NOS, is reported in Table S6.

Role of US in the follow-up of PsA and Pso

The search retrieved 15 studies exploring the role of US in PsA follow up (81), (82), (18), (83), (69), (84), (85), (86), (87), (88), (89), (90), (91), (92), (63). The results are summarized in Table 3. In several studies, US assessment was used to analyze the response to a standardize therapeutic approach with inhomogeneous US endpoints. The comparison between articles is made difficult by the variability in definitions of elementary lesions and scoring systems, machine settings and image acquisition. Among selected articles, five different scoring systems have been tested. The US Group of Spanish Society of Rheumatology demonstrated that the PDUS examination of 14 peripheral entheses was able to monitor the 6 months therapeutic response in 197 SpA patients (87). The German US7 scores, significantly reflected the therapeutic response of PsA patients evaluating synovitis, tenosynovitis and erosions of small joints whereas the SOLAR score, used to evaluate synovitis and tenosynovitis (GS and PD) of the large joints was able to monitor the treatment response in a cohort of PsA (82), (89). The "Five Targets Power Doppler for Psoriatic Disease" (5TPD) score was the first score including all domains characterizing PsA (joint, tendon with synovial sheath, enthesis, skin and nail) and those, one for each target area, showing the highest expression of PD were selected for monitoring an anti-TNF therapy for 8 weeks in 16 PsA patients (91). The 5TPD score showed a significant improvement during therapy but it did not correlate with HAQ-modified for SpA. Lastly, Ficjan et al. developed two US score (PsA-Son22 and PsA-Son13) in a prospective study on 83 consecutive PsA patients, these scores explored joints, peri-articular structures and entheses. Both composite scores had sufficient sensitivity to change and the bilateral score (PsA-Son22) was more sensitive than the unilateral score to detect PsA lesions whereas the unilateral (PsA-Son13) was faster (90). The risk of bias, assessed using the "NOS, the "PRISMA Checklist" and the Cochrane diagnostic test Accuracy, was reported in Table 3.

US to guide intra-articular interventions

The search retrieved 4 studies, including two randomised controlled trials, examining the role of US to guide intra-articular interventions (93), (94), (95), (96). Among the twoRCT, comparing blinded and US-guided injections, the results were controversial for the clinical outcomes while the accuracy was better for US-guided procedures (95),(96). In *Sibbit et al.*, US directed intra-articular injections were superior to palpation-guided methods in all therapeutic measures: absolute VAS pain scores for injection pain were 81% less, responder rates were increased by 38%, and non-responder rates were reduced by 34% (96). Conversely, in the study published by *Cunnington et al.* there was no statistically significant difference between US-guided and blind injections for any of the major outcome variables (e.g. VAS pain, function and stiffness) measured at 2 weeks or 6 weeks (95). Only one study focused on tenosynovitis while no study focused on

enthesitis or bursitis (94). The risk of bias, assessed by the Cochrane Collaboration's tool for intervention studies, is reported in figure S7.

DISCUSSION

The usefulness of US in diagnosis, prognosis, and follow-up of inflammatory arthritis in clinical practice is still a matter of debate, despite the evidence of a higher sensitivity over clinical examination. Recently, an EULAR task force developed evidence-based recommendations on the use of imaging in the clinical management of RA and SpA (1) (97), acknowledging the need of further extensive research to optimise the use of imaging in routine clinical practice. On this basis, and in order to identify and prioritise its research agenda in the field of PsA, the Musculoskeletal Ultrasound Study Group of the Italian Society of Rheumatology, decided to plan a SLR with the aim to highlight the current state of knowledge. Currently, in early inflammatory arthritis, rheumatologists need supporting tools to strengthen the diagnosis (98). Among imaging modalities, US is the most attractive one, as less time consuming, safe and readily and easily used. For this reason, an increasing number of studies about US to diagnose PsA has been recently published. However, its use in clinical practice is still a matter of debate. In the SLR the diagnostic performance of US was widely variable and no study evaluated the overall performance of US in addition to clinical findings to diagnose PsA. Moreover, most of the selected diagnostic studies followed a cross-sectional case-control design, introducing a bias in patients selection and leading to an overestimation of the diagnostic performance of the index test. The ability of US to detect elementary lesions, which may support the diagnosis of PsA, is widely described in literature. Considering the potential pathogenetic role of enthesis in PsA, US of entheses was not surprisingly the most frequently used for diagnosis (42), (45), (46), (59), (81), (26), (27), (17), (31), (30), (11), (15), (23), (38), (39), (25), (24), (52). Furthermore, US was used to image synovitis, tenosynovitis, bursitis and erosions and less frequently soft tissue and hand nails. Clinical examination was often the reference standard for both the diagnosis of PsA and psoriatic elementary lesions. Only one study examined the performance of PD to identify synovitis using histopathology as gold standard, showing that a negative PD in the synovium did not exclude the possibility of synovitis (44). In axial, SpA imaging (conventional radiography and MRI of sacro-iliac joints) is a key component of classification criteria, mostly due to the absence of specific clinical symptoms (1), while in the classification of peripheral inflammatory arthritis, its use is not mandatory. However, in early disease imaging might play an important role supporting diagnosis and directing the treatment. Regarding the differential diagnosis, studies seem to support the idea that PsA could be differentiated from RA for a major extra-synovial involvement. Soft tissue inflammation, described as oedema and/or PD peri-tendinous, could be a very distinctive sign of PsA, being absent in RA controls (45), (34), (40). *Fourniè et al*. highlighted a major synovial involvement in RA than PsA (i.e. 100% vs 76%) and furthermore, the prevalence of erosions was lower in PsA than in RA (34), (58), (60), (63), even though this result was recently questioned by another study (45). Moreover, the prevalence of features differed greatly between selected studies, mainly due to the heterogeneity of inclusion criteria, elementary lesion definitions and equipment. In addition, possible sources of bias mainly related to patient selection might have been present. With clinical remission being the ideal treatment target, the application of US to predict development of arthritis in Pso patients or to identify PsA patients with poorer outcome, is of interest. Considering the importance of enthesitis as the key lesion in PsA, some studies focused on entheses of lower limbs in psoriatic

disease (with or without arthritis) revealing an high rate of enthesopathy signs (73), (14), (41), particularly for PD activity. The results of SLR supported the idea that entheseal PD, rather than GS changes, is a highly specific feature for PsA. However, the prognostic role of these lesions in the development of arthritis in Pso patients is not clear yet. There was only one prospective work by *Tinazzi et al.* demonstrating that in Pso patients, baseline thickness of quadriceps tendons was an independent predictor of PsA development, and suggesting the need of further investigation in larger cohorts in order to understand the real predictive value of the entheses US (75). Currently, in RA synovitis, tenosynovitis and bone marrow oedema appear to be predictors of radiographic progression and synonymous of disease activity (99), (100), (101), (94). To date, in PsA, US predictors of poorer outcome have not been identified, moreover many studies had an unappropriated design to evaluate prognostic measures. Since in RA T2T studies based solely on US did not prove a superiority of imaging over clinical management (102), the potential role of US in monitoring disease activity has to be tested in addition to clinical follow-up. The integration of US with clinical examination to stratify patients and to decide treatments in a T2T strategy also represents an interesting possibility. The SLR identified few US scores to monitor disease activity in PsA patients. German US7 scores, developed in RA, was the first applied and was able to significantly reflect the therapeutic response of PsA patients evaluating synovitis, tenosynovitis and erosions (82). Focusing on large joints, the SOLAR score, was used to evaluate activity in a cohort of PsA and Ankylosing Spondylitis patients and the authors concluded that it was a valuable tool (89). Furthermore, the Group of Spanish Society of Rheumatology demonstrated that the PDUS examination of 14 peripheral entheses was able to monitor the response of SpA patients during anti-TNF therapy, and interestingly the authors highlighted that the score may contribute to the development of a cumulative scoring system of combined elementary lesions (87). Considering the clinical heterogeneity of PsA with different domains and peculiar sites involved, a dedicated ultrasound composite score is arguably necessary. First, Gutierrez et al. developed a PsA dedicated preliminary five target score for the assessment of PsA patients during anti-TNF therapy (91). Later, also *Ficjan et al.* proposed two PsA specific US score (PsASon-13 and PsASon-22) to monitor disease activity in PsA (90)**.** All these last three scores are original and interesting, but they are not applied in other series, thus remaining preliminary scores despite good sensitivity for the detection of inflammation and feasibility. Despite the extensive use in clinical practice, superiority for clinical outcome of US-guided injections over blinded injections remains doubtful in PsA and further studies are needed to better define the efficacy of one over the other. US-guided injections resulted to be overall more accurate. Accordingly *Cunnington et al.* recommended US-guided procedures in joints that were frequently injected inaccurately (e.g. shoulder, ankle, hip) and in order to reduce tissue necrosis or the possible damage to surround tissues (98). Therefore actually, safety data seem to be an added value of US-guided injections. Although the SLR pointed up the importance and potential of US in the management of PsA and Pso, it also underlined the need of a large amount of research to optimise the use of US in the diagnosis and monitoring of psoriatic disease in clinical practice. In particular, several gaps in the literature were underlined, as well as the presence of possible biases, such as patient selection and reference standard for diagnostic studies or to randomisation in interventional studies. In addition, since the presence of publication bias was not investigated, it cannot be excluded. Based on the evidence arising from

the literature review, a research agenda has also been proposed (Table 4). Considering the gaps of the literature underlined by the SLR, the Ultrasound Study Group of the Italian Society for Rheumatology gave priority to a novel study aiming to identify clinical and US predictors of Minimal Disease Activity in PsA patients with active peripheral arthritis starting a new course of therapy (Ultrasound in Psoriatic Arthritis Treatment – UPSTREAM study). Identifying prognostic factors of achieved remission or low disease activity will help a better selection of patients with poorer outcome and possibly the improvement of therapeutic strategies, responding to the need of personalized medicine, optimizing the outcome of patients with PsA as well as the treatments management.

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TABLES

Table 1: prevalence of US abnormalities (range, %) across primary studies

PsA patients	Prevalence on site examined (%)	Prevalence on patient (%)
Gray Scale Synovitis	14.0 – 57.0	10.0-100.0
Power Doppler Synovitis	2.0 – 8.7	28.6 – 73.0
Joint erosions	6.1 – 57.7	10.8 – 52.0
Increased thickness of lower	10.0 – 43.1	37.0 - 94.5
Limbs entheses:		
PD at enthesis	0.0 - 7.4	15.6 - 40.2
Entheseal erosions	5.0 – 14.9	0.0 – 10.8
Soft tissue inflammation	38.9 – 65.8	14.3 – 32.0

Table 2. Summary table on prevalence, diagnosis and prognosis reporting high quality studies (i.e. relevant results for the reviewers and including at least 20 PsA patients or 30 Pso patients). that included at least 20 PsA patients or 30 Pso patients . Full results are reported in the supplementary online material.

Study	N	Population	Control	Examined structures	Equipment	Area of interest
Aydin et al. 2012	42 PsA	Cutaneous psoriasis with nail disease	20 HC	Nail	GE Logiq E9, 10-18 Mhz	Disease prevalence; Diagnosis of PsA and elementary lesions
Aydin et al. 2013	58 PsA	Cutaneous psoriasis including PsA	42 Pso; 23 HC	Lower limb entheses	GE Logiq E9 and Logiq5 machine	Disease prevalence; Diagnosis of PsA and elementary lesions; Prognosis
Bandinelli et al. 2015	112 PsA	PsA with symptoms onset < 1 year	-	MCP-PIP-DIP joints; flexor and extensor digitorum tendons; radio and intercarpal joints	Esaote MyLab70 XVG, 6-18 Mhz	Disease prevalence; Diagnosis of elementary lesions
Eder et al. 2014	50 PsA	PsA	66 Pso; 60 HC	Enthesis included in the MASEI score	Esaote MyLab 70XVG, 6‑18 MHz	Disease prevalence; Diagnosis of PsA and elementary lesions
Fourniè et al. 2006	20 PsA	PsA and RA	21 RA	Hand joints (MCP, PIP and DIP); Extensor and flexor tendon; Soft tissue	Siemens Sonoline Elegra, 13.5 Mhz	Disease prevalence; Diagnosis of PsA and elementary lesions
Freeston et al. 2012	42 PsA	Early PsA (<24 months)	10 HC	Lateral epicondyles of the elbow, inferior patellar tendon insertion, Achilles tendon, plantar fascia	Philips HDI 5000, 5-12 and 7-15 MHz	Disease prevalence; Diagnosis of PsA and elementary lesions
Freeston et al. 2014	49 PsA	Early PsA (<24 months)	8 HC	Bilateral posterior glenohumeral joints, olecranon fossa,	Philips HDI 5000 machine, 5-12 MHz and 7-15	Disease prevalence; Diagnosis of elementary lesions

				wrists, MCP and PIP joints, knees, tibiotalar and MTP joints	MHz	
Gisondi et al. 2008	30 Pso	Pso without any clinical evidence of arthritis or enthesitis	30 HC	Target enthesis (GUESS score)	ATL HDI 3000, 10–15 MHz probe	Prognosis
Gutierrez et al. 2011	20 PsA	PsA and RA	18 RA	MCP joints	Esaote MyLab70 XVG 6-18 Mhz	Disease prevalence; Diagnosis of PsA and elementary lesions
Gutierrez et al. 2011	45 Pso	Pso without any clinical evidence of arthritis or enthesitis	45 HC	Target enthesis of GUESS score	Esaote MyLab70 XVG 6-18 Mhz	Disease prevalence; Prognosis
Husic et al. 2014	70 PsA	PsA	-	68 joints and 14 entheses	Esaote MyLabTwice, 6-18 Mhz	Prognosis
Marchesoni et al. 2012	30 PsA	PsA and Fibromyalgia (FM)	30 FM	14 target enthesis	GE Logiq5, 8-15 Mhz	Disease prevalence; Diagnosis of PsA
Naredo et al. 2011	162 Pso	Plaque psoriasis	60 controls with other skin disease	wrist, MCP- PIP and DIP joints of the hands, knee, tibiotalar joint; extensor tendon of the wrist; finger flexor tendon; target enthesis	GE Logiq 9, 8-14 Mhz	Disease prevalence; Prognosis
Tinazzi et al. 2011	30 Pso	Pso	-	Target enthesis (GUESS score)	ATL HDI 3000, 10–15 MHz probe; GE Logiq5, 10-15 Mhz	Prognosis
Zayat et al. 2015	60 PsA	PsA, RA, gout and OA	70 RA, 60 gout, 60 OA, 60 HC	distal articular radius and ulna, II-III and V MCP joints, II-III PIP joints and I and V MTP joints, 2nd, 3rd	GE LogiqE9, 6-15 Mhz	Disease prevalence; Diagnosis of elementary lesions

Table 3: Studies evaluating US in monitoring PsA. US: ultrasonography.

Study	N	Study design	Inclusion criteria	Examined structures	Equipment	Results	Risk of bias
Acquacalda **2015**	22 Pso 12 PsA	Prospective cohort	CASPAR before introduction of the first systemic treatment or biologic	5 entheses Hypoechogenicity, thickness, erosion, calcification, PD, morphological/structural lesion	Esaote MyLab70 XVG	US morphological abnormalities (baseline vs **6 months**) PsO 30% vs 17.7% P=0.021 PsA (PD) 33% vs 24% p=0.164	Sel ** Comp ** Exp **
Backhaus **2009**	120 patients (PsA 9%)	Prospective cohort	PSA starting new therapy	Wrist, 2nd- 3rd MCP and PIP, 2nd-5th MTP GS and PD	Different US machines	**3 months:** synovitis GSUS/DAS28 r=0.44, p<0.05 PDUS/DAS28 r=0.44, p<0.05 tenosynovitis GSUS/DAS28 r=0.11, p>0.05 PDUS/DAS28 r=0.11, p>0.05 Erosions/DAS28 r=0.11, p>0.05 **6 months:** synovitis GSUS/DAS28 r=0.38, p<0.05 PDUS/DAS28 r=0.31, p<0.05 tenosynovitis GSUS/DAS28 r=0.26, p<0.05 PDUS/DAS28 r=0.24, p<0.05 Erosions/DAS28 r=0.16, p>0.05	Sel *** Comp Exp *
Bonifati **2014**	25 PsA	Retrospective cohort	CASPAR criteria, ETA o ADA (>12 months)	Target joints US contrast-enhanced	-	Positive CEUS (baseline vs **12 months**) 22/25 vs 3/25 p<0.0001	Sel *** Comp Exp **
Cozzi 2015	36 PsA	RCT	CASPAR, TNFi >6 months	All joints of both hands	Esaote My Lab	**CEUS in PsA receiving mud-bath (baseline-45 days):**	High Risk

				US contrast enhanced	70	**seconds, mean (sd)**	
						Time of appearance 22.21 (8.79) vs 25.71 (12.81) $p<0.05$	
						Washout rate 9.32 (0.49) vs 9.12 (0.78) $p>0.05$	
						Peak value 0.14 (0.06) vs 0.13 (0.04) $p>0.05$	
						Contrast flow 0.07 (0.03) vs 0.06 (0.03) $P<0.05$	
Ficjan 2014	83 PsA	Prospective cohort	CASPAR, peripheral articular manifestations	PsASon 22, bilateral score included 22 joints and 4 entheses.	Esaote My Lab Twice	PsASon 22 and 13 (6 months)	Sel ***
						Global ultrasound inflammation subscore:	Comp
						SRM: −0.53 to −0.04 (entire cohort)	Exp ***
				PsASon13, unilateral score included 13 joints and 2 entheses		−1.04 to −0.09 (pts from active disease to MDA)	
						ICC: 0.84 (PsASon22), 0.54 (PsASon 0.96)	
Fiocco 1996	23 patients (11 PsA)	Prospective cohort	Moll and Wright, Knee joint pain, patients treated with NSAIDs and second-line drugs >6 months	Knee Joint effusion/Synovial Tickness	7.5 MHz electronic linear transducer/10 MHz mechanical sectorial transducer	Significant correlation between clinical and US indexes at all timepoints (baseline, 2 months, 6 months, 12 months)	Sel ** Comp * Exp **
Fiocco 2005	27 patients (8 PsA)	Prospective cohort	Moll and Wright Criteria, eligible for TNFi	Involved knee Synovitis PD	Elegra, Siemens	**F/SI-PD** mean (sd) Baseline 1.31 (0.30) ; 3 months 0.63 (0.21) $p<0.001$; 12 months 0.44 (0.20) $p<0.05$ **P/CI-PD** mean (sd) Baseline 1.59 (0.21), 3 months 1.62 (0.018) $p>0.05$; 12 months 0.89 (0.18) <0.05	Sel *** Comp Exp **
Fraser 2005	72 PsA	RCT	18-70 years, PsA criteria 1994 >24 weeks,	2nd-5th MCP and PIP of the	ATL HDI 3000	US synovitis reduction after 12 months	Unclear

			active PsA and Pso, no response to MTX	dominant hand		-2.5 (95% CI -4.07, -1.01)	
Keen 2011	-	Systematic review	published studies in English, humans, comparing imaging of structural tissue	Involved knee Synovial thickness, effusion size, PD	-	US internal responsiveness was found with regard to synovial thickness, effusion size, and popliteal cyst size. External responsiveness was demonstrated against several referenced health status measures. No quantitative synthesis, references were screened.	PRISMA Checklist: 20/28
Gutierrez 2012	16 PsA	Prospective cohort	CASPAR, starting therapy with ADA, ETA, IFX	MCPs, MTPs, wrists, finger flexor tendons, tibialis posterior tendons, peroneous tendons, entheses (Achilles tendon, distal and proximal insertion of patellar tendon), psoriatic plaques, nails.	Esaote My Lab 70 XVG	Median (IQR) 5 target PD: **Baseline** 9 (4-12), **8 weeks** 3 (1-5), p=0.0001 I**nter-reader realiability baseline k**: joint 0.74, tendon 0.79 enthesis 0.97, nail 0.65, skin 0.88 **Intra-reader reliability baseline k:** joint 0.98, tendon 0.98, enthesis 0.97, nail = 0.82, skin 0.94	Sel *** Comp Exp **
Naredo 2010	327 SpA	Prospective cohort	ESSG or Amor criteria, starting TNF i	14 peripheral entheses. Morphologic abnormalities, Calcific deposits, Cortical abnormalities, adjacent bursitis, PD	Logiq 5 PRO; (General Electric)	Baseline vs 6 months (mean , sd) **Morphologic abnormality score** 2.19 (2.66) vs 1.34 (2.02) p<0.0005 **Calcific deposit score** 1.11 (1.63) vs 1.23 (1.79) p =0.142 **Cortical abnormality score** 3.92 (3.73) vs 4.17 (3.86) p=0.036 **Adjacent bursitis score** 0.94 (1.21) vs 0.76 (1.19) p=0.036 **Intraenthesis PD** 1.36 (2.11) vs 0.68 (1.64) p<0.0005 **Perienthesis PD** 1.75 (2.92) vs 0.98 (2.23) p<0.0005	Sel *** Comp Exp ***
Teoli 2012	40 PsA	Retrospective cohort	CASPAR; therapy with ADA	Most clinically involved joints. Synovial effusion, synovial	Logiq 5 Pro (General	**Baseline vs 24 months score** (mean , IQR) Synovial effusion 2.3 (1–3) vs 0.1 (0-1)	Sel *** Comp

				proliferation, PD	Electric)	Synovial proliferation 1,125 (0–2) vs 0,025 (0-1)	Exp **
						PD 2.5 (1–3) vs 1 (0–2)	
						Bone erosions 0,2 (0–2) vs 0,25 (0–2)	
Schafer	126 SpA	Prospective cohort	CASPAR	Shoulder, elbow, hip, knee	-	**Baseline vs 6 months score** (mean, sd)	Sel ***
2013				Solar score (GS/PD)		Shoulder GS 2.8 (1.9) vs 1.1 (1.2) p<0.05	Comp
						PD 1.7 (1.6) vs 0.4 (0.8) p<0.05	Exp ***
						Elbow GS 4,3 (2.6) vs 0.9 (1.5) p<0.05	
						PD 2.3 (2.0) vs 0.6 (1.1) p<0.05	
						Hip GS 2.0 (0.8) vs 1.0 (1.1) p<0.05	
						PD 0.7 (0.9) vs 0.3 (0.5) p>0.05	
						Knee GS 5.3 (2.9) vs 2.8 (2.8) p<0.001	
						PD 2.9 (3.1) vs 1.4 (2.4) p<0.05	
Coates 2015	89 PsA	Retrospective cohort	Early PsA	Hands US Erosions	Unclear	Erosions (%) baseline vs 48 weeks 3.5% vs 5.6%	Unclear

PsA: psoriatic arthritis; Pso: psoriasis; HC; N: number; GS: grey-scale, PD: power Doppler; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints; MTP: metatarsophalangeal joints; CASPAR: Classification criteria for psoriatic arthritis, PASI: psoriasis area severity index; TNFi: tumor necrosis factor inhibitors; ADA: adalimumab; ETA: etanercept; IFX: inflizimab; MTX: methotrexate; CSA: cyclosporine A; NSAIDs: non steroideal anti-inflammatory drugs; F/SI-PD: fluid/synovium interface; P/CI-PD pannus/cartilage or pannus/ capsule interface.

Table 4: Research Agenda of US in PsA and Pso patients

1. To investigate the integration of US in clinical practice in order to improve the certainty of diagnosis

2. To investigate which US elementary lesions could be highly specific for PsA

3. To investigate the prognostic role of US in identifying Pso patient at risk to develop PsA

4. To further analyse US score in order to monitor disease activity

5. To identify US predictors of treatment response in order to stratify treatment regimen (i.e. better selection of

    patients with poorer outcome)

6. To further analyse the supposed superiority of US guided injection compared to palpation guided injection

FIGURES
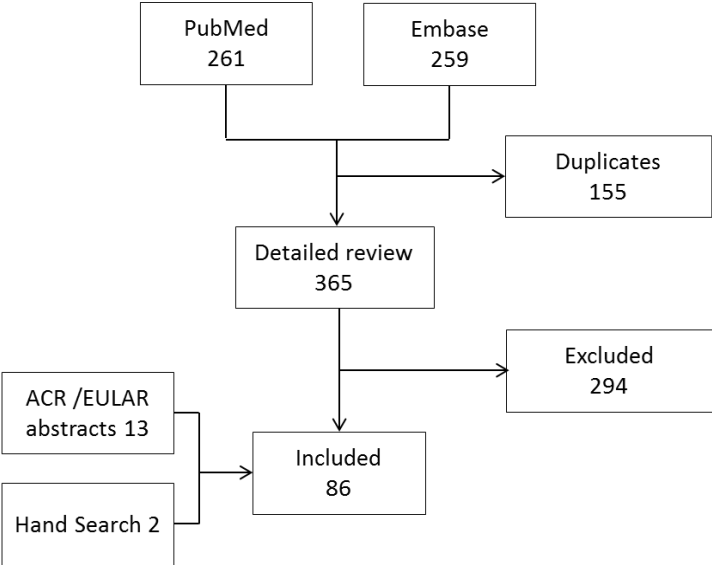
Figure 1: flow-chart showing the selection process.
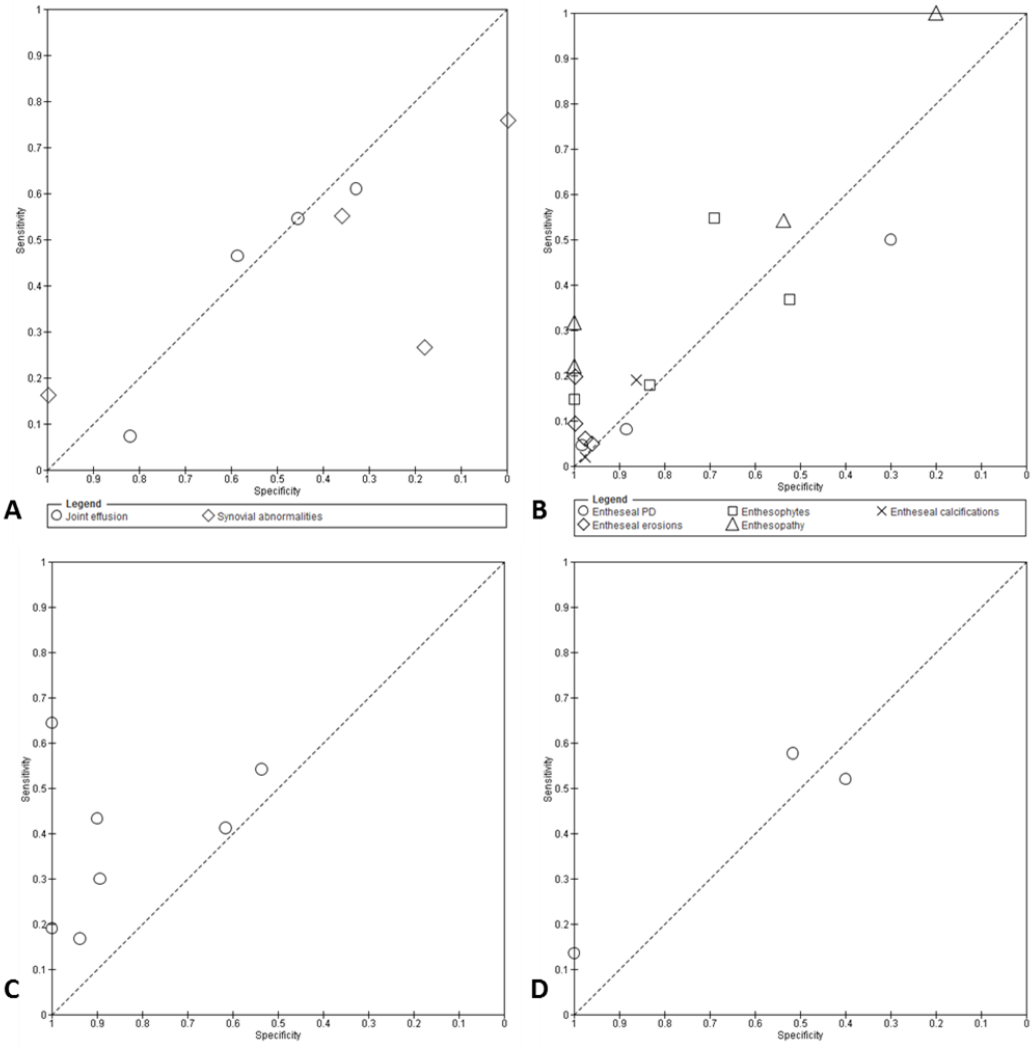
Figure 2: Performance of US variables to diagnose PsA: sensitivities and specificities of primary studies. A: synovial abnormalities/joint effusion; B: entheseal abnormalities; C: tendon abnormalities; D: bone erosions. No US abnormality, considered alone, had an optimal diagnostic performance to diagnose PsA.