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

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(Article begins on next page)
TITLE

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

RUNNING TITLE: ULTRASONOGRAPHY IN PSORIATIC ARTHRITIS

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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).
RESULT

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 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 56."
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 a high rate of enthesopathy signs (73), (14), (41), particularly for PD activity. The results of SLR supported the idea that enthesal 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.
REFERENCES


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

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

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Control</th>
<th>Examined structures</th>
<th>Equipment</th>
<th>Area of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aydin et al. 2012</td>
<td>42</td>
<td>PsA</td>
<td>20 HC</td>
<td>Nail</td>
<td>GE Logiq E9, 10-18 Mhz</td>
<td>Disease prevalence; Diagnosis of PsA and elementary lesions</td>
</tr>
<tr>
<td>Aydin et al. 2013</td>
<td>58</td>
<td>PsA</td>
<td>42 Pso; 23 HC</td>
<td>Lower limb entheses</td>
<td>GE Logiq E9 and Logiq5 machine</td>
<td>Disease prevalence; Diagnosis of PsA and elementary lesions</td>
</tr>
<tr>
<td>Bandinelli et al. 2015</td>
<td>112</td>
<td>PsA with symptoms onset &lt; 1 year</td>
<td>-</td>
<td>MCP-PIP-DIP joints; flexor and extensor digitorum tendons; radio and intercarpal joints</td>
<td>Esaote MyLab70 XVG, 6-18 Mhz</td>
<td>Disease prevalence; Diagnosis of elementary lesions</td>
</tr>
<tr>
<td>Eder et al. 2014</td>
<td>50</td>
<td>PsA</td>
<td>66 Pso; 60 HC</td>
<td>Enthesis included in the MASEI score</td>
<td>Esaote MyLab 70XVG, 6-18 Mhz</td>
<td>Disease prevalence; Diagnosis of PsA and elementary lesions</td>
</tr>
<tr>
<td>Fournié et al. 2006</td>
<td>20</td>
<td>PsA and RA</td>
<td>21 RA</td>
<td>Hand joints (MCP, PIP and DIP); Extensor and flexor tendon; Soft tissue</td>
<td>Siemens Sonoline Elegra, 13.5 Mhz</td>
<td>Disease prevalence; Diagnosis of PsA and elementary lesions</td>
</tr>
<tr>
<td>Freeston et al. 2012</td>
<td>42</td>
<td>Early PsA (&lt;24 months)</td>
<td>10 HC</td>
<td>Lateral epicondyles of the elbow, inferior patellar tendon insertion, Achilles tendon, plantar fascia</td>
<td>Philips HDI 5000, 5-12 and 7-15 MHz</td>
<td>Disease prevalence; Diagnosis of PsA and elementary lesions</td>
</tr>
<tr>
<td>Freeston et al. 2014</td>
<td>49</td>
<td>Early PsA (&lt;24 months)</td>
<td>8 HC</td>
<td>Bilateral posterior glenohumeral joints, olecranon fossa</td>
<td>Philips HDI 5000 machine, 5-12 MHz and 7-15 MHz</td>
<td>Disease prevalence; Diagnosis of elementary lesions</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Conditions</td>
<td>Contrast Media</td>
<td>Frequency</td>
<td>Other Details</td>
<td></td>
</tr>
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<td>-----------------------------</td>
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</tr>
<tr>
<td>Gisondi et al. 2008</td>
<td>30 PsA</td>
<td>PsO without any clinical evidence of arthritis or enthesitis</td>
<td>30 HC</td>
<td>Target enthesis (GUESS score)</td>
<td>ATL HDI 3000, 10–15 MHz probe</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Gutierrez et al. 2011</td>
<td>20 PsA</td>
<td>PsO and RA</td>
<td>18 RA</td>
<td>MCP joints</td>
<td>Esaote MyLab70 XVG 6-18 MHz</td>
<td>Disease prevalence; Diagnosis of PsO and elementary lesions</td>
</tr>
<tr>
<td>Gutierrez et al. 2011</td>
<td>45 PsO</td>
<td>PsO without any clinical evidence of arthritis or enthesitis</td>
<td>45 HC</td>
<td>Target enthesis of GUESS score</td>
<td>Esaote MyLab70 XVG 6-18 MHz</td>
<td>Disease prevalence; Prognosis</td>
</tr>
<tr>
<td>Husic et al. 2014</td>
<td>70 PsA</td>
<td>PsO</td>
<td>-</td>
<td>68 joints and 14 entheses</td>
<td>Esaote MyLabTwice, 6-18 MHz</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Marchesoni et al. 2012</td>
<td>30 PsA</td>
<td>PsO and Fibromyalgia (FM)</td>
<td>30 FM</td>
<td>14 target enthesis</td>
<td>GE Logiq5, 8-15 MHz</td>
<td>Disease prevalence; Diagnosis of PsO</td>
</tr>
<tr>
<td>Naredo et al. 2011</td>
<td>162 PsO</td>
<td>Plaque psoriasis</td>
<td>60 controls with other skin disease</td>
<td>GE Logiq 9, 8-14 MHz</td>
<td>Disease prevalence; Prognosis</td>
<td></td>
</tr>
<tr>
<td>Tinazzi et al. 2011</td>
<td>30 PsO</td>
<td>PsO</td>
<td>-</td>
<td>Target enthesis (GUESS score)</td>
<td>ATL HDI 3000, 10–15 MHz probe; GE Logiq5, 10-15 MHz</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Zayat et al. 2015</td>
<td>60 PsA</td>
<td>PsO, RA, gout and OA</td>
<td>70 RA, 60 gout, 60 OA, 60 HC</td>
<td>GE LogiqE9, 6-15 MHz</td>
<td>Disease prevalence; Diagnosis of elementary lesions</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Studies evaluating US in monitoring PsA. US: ultrasonography.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Examined structures</th>
<th>Equipment</th>
<th>Results</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquacalda 2015</td>
<td>22 Pso</td>
<td>Prospective cohort</td>
<td>CASPAR before introduction of the first systemic treatment or biologic</td>
<td>5 entheses</td>
<td>Esaote</td>
<td>US morphological abnormalities (baseline vs 6 months)</td>
<td>Sel **</td>
</tr>
<tr>
<td>Backhaus 2009</td>
<td>120 patients</td>
<td>Prospective cohort</td>
<td>PSA starting new therapy</td>
<td>Wrist, 2nd-3rd MCP and PIP, 2nd-5th MTP, GS and PD</td>
<td>Different US machines</td>
<td>3 months: synovitis GSUS/DAS28 r=0.44, p&lt;0.05, PDUS/DAS28 r=0.44, p&lt;0.05, tenosynovitis GSUS/DAS28 r=0.11, p&gt;0.05, PDUS/DAS28 r=0.11, p&gt;0.05 Erosions/DAS28 r=0.11, p&gt;0.05</td>
<td>Sel ***</td>
</tr>
<tr>
<td>Bonifati 2014</td>
<td>25 PsA</td>
<td>Retrospective cohort</td>
<td>CASPAR criteria, ETA o ADA (&gt;12 months)</td>
<td>Target joints</td>
<td>-</td>
<td>Positive CEUS (baseline vs 12 months)</td>
<td>Sel ***</td>
</tr>
<tr>
<td>Cozzi 2015</td>
<td>36 PsA</td>
<td>RCT</td>
<td>CASPAR, TNFi &gt;6 months</td>
<td>All joints of both hands</td>
<td>Esaote My Lab</td>
<td>CEUS in PsA receiving mud-bath (baseline-45 days): High Risk</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Design</td>
<td>Inclusion Criteria</td>
<td>Methods</td>
<td>Findings</td>
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</tbody>
</table>
| Ficjan 2014   | 83 PsA       | Prospective cohort | CASPAR, peripheral articular manifestations | US contrast enhanced | Time of appearance 22.21 (8.79) vs 25.71 (12.81) p<0.05
|               |              |        | PsASon 22, bilateral score included | Esaote My Lab | Washout rate 9.32 (0.49) vs 9.12 (0.78) p>0.05
|               |              |        | 22 joints and 4 entheses. | Twice | Peak value 0.14 (0.06) vs 0.13 (0.04) p>0.05
|               |              |        | PsASon13, unilateral score included | ICC: 0.84 (PsASon22), 0.54 (PsASon 0.96) | Contrast flow 0.07 (0.03) vs 0.06(0.03) P<0.05
| Fiocco 1996   | 23 PsA       | Prospective cohort | Moll and Wright, Knee joint pain, patients treated with NSAIDs and second-line drugs >6 months | Knee joint effusion/Synovial Tickness | Significant correlation between clinical and US indexes at all timepoints (baseline, 2 months, 6 months, 12 months)
|               |              |        | PsASon 22 and 13 (6 months) | 7.5 MHz | Sel **
|               |              |        | Global ultrasound inflammation subscore: | electronic linear transducer/10 MHz | Comp *
|               |              |        | SRM: −0.53 to −0.04 (entire cohort) | mechanical sectorial transducer | Exp **
|               |              |        | −1.04 to −0.09 (pts from active disease to MDA) | | |
| Fiocco 2005   | 27 PsA       | Prospective cohort | Moll and Wright Criteria, eligible for TNFi | Involved knee PD | Baseline 1.31 (0.30) ; 3 months 0.63 (0.21) p<0.001; 12 months 0.44 (0.20) p<0.05
|               |              |        | FSI-PD mean (sd) | Elegra, Siemens | P/Ci-PD mean (sd) |
| Fraser 2005   | 72 PsA       | RCT    | 18-70 years, PsA criteria 1994 >24 weeks, 2nd-5th MCP and PIP of the | US synovitis reduction after 12 months | Unclear
<p>|               |              |        | ATL HDI 3000 | | |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Design</th>
<th>Imaging Settings</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keen 2011</td>
<td>16 patients</td>
<td>Systematic review</td>
<td>MedScan, Esaote MyLab 70 XVG</td>
<td>US internal responsiveness was found with regard to synovial thickness, effusion size, and popliteal cyst size. Externally, responsiveness was demonstrated against several referenced health status measures. No quantitative synthesis, references were screened.</td>
</tr>
<tr>
<td>Gutierrez 2012</td>
<td>16 patients</td>
<td>Prospective cohort</td>
<td>Esaote My Lab 70 XVG</td>
<td>Median (IQR) 5 target PD: Baseline 9 (4-12), 8 weeks 3 (1-5), Po=0.0001</td>
</tr>
<tr>
<td>Naredo 2010</td>
<td>327 patients</td>
<td>Prospective cohort</td>
<td>Logiq 5 PRO; General Electric</td>
<td>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</td>
</tr>
<tr>
<td>Teoli 2012</td>
<td>40 patients</td>
<td>Retrospective cohort</td>
<td>Logiq 5 Pro; General Electric</td>
<td>Baseline vs 24 months score (mean, IQR) Synovial effusion 2.3 (1–3) vs 0.1 (0-1)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Sample</td>
<td>Study Design</td>
<td>Characteristics</td>
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<tr>
<td>Schäfer</td>
<td>2013</td>
<td>126 SpA</td>
<td>Prospective cohort</td>
<td>CASPAR</td>
</tr>
<tr>
<td>Coates</td>
<td>2015</td>
<td>89 PsA</td>
<td>Retrospective cohort</td>
<td>Early PsA</td>
</tr>
</tbody>
</table>

**Notes:**
- **PsA:** psoriatic arthritis; **Pso:** psoriasis; **HC:** 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:** infliximab; **MTX:** methotrexate; **CSA:** cyclosporine A; **NSAIDs:** non steroidal anti-inflammatory drugs; **F/S-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

![Flow-chart showing the selection process.](image)

**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.
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UPSTREAM study group

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest

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