

Musculoskeletal ultrasound imaging in the diagnosis of psoriatic arthritis: from the past to the future

Ultrasound (US) is a reliable imaging technique that has played a key role in the imaging process in rheumatology, in recent years, for the early detection and careful characterization of the inflammatory process in arthritides. Its use in psoriatic arthritis (PsA) has become common in both clinical and research fields, focusing on joints and tendons, entheses (which have been shown to be involved not only in patients with PsA but also in subjects presenting only skin psoriasis) and some new fields (skin and nails). US allows a more precise and earlier diagnosis and therapy monitoring. There are also some new hypotheses that US could be used to discriminate between different arthritis and also between PsA and the other spondyloarthritides.

Keywords: differential diagnosis • joint • nail • psoriatic arthritis • ultrasound • skin • tendon

Ultrasound (US) is a well known reliable imaging technique that has played a key role in the imaging process in rheumatology in the last 15 years, allowing early detection and careful characterization of the inflammatory process in arthritides. Its use in psoriatic arthritis (PsA) has become very common place in both clinical and research fields. One of the main points where US has been focused, apart from joints and tendons, is the entheses, which is considered the main characteristic involvement in spondyloarthritides (SpA) (which PsA is part of). Enthesis involvement have been shown not only in patients with PsA but also in subjects presenting only skin psoriasis, determining a sort of preclinical disease [1,2]. The benefit of US lies in the added value given to help in the diagnosis, in the evaluation of disease activity and in therapy monitoring (showing structural and inflammatory changes). It is still debatable whether US is able to help in the differential diagnostic process between PsA and other kinds of chronic arthritis (i.e., rheumatoid arthritis [RA]). Lately, US has also been used in 'uncommon' areas for the rheumatologist, such as skin and nails, providing important information in those fields and, therefore, in

the whole psoriatic disease activity. Another possible use of US in PsA patients is the assessment of cardiovascular diseases [3–15] but this aspect will not be part of the present review.

The past: US of the musculoskeletal system

Joints and tendons

PsA is an inflammatory arthropathy associated with psoriasis, part of the seronegative SpA, that can show a great variability in clinical features and severity. If it is true that a great part of the literature is reporting the involvement of joints and tendons in symptomatic PsA patients, several studies have also reported US pathological findings in PsA patients who do not complain of active pain and/or swelling at the time of the clinical examination and in psoriatic patients with no signs of musculoskeletal disease as well [1,2,16–22]. In 2000, Galluzzo *et al.*, when studying ankle involvement in 31 patients with PsA, discovered US pathological findings at both enthesal and tendon level in a high proportion of them, most of whom exhibited no ankle pain or swelling [21]. More relevant data are provided on enthesal involvement (see chapter on *Entheses*).

Andrea Delle Sedie*¹
& Lucrezia Riente¹

¹Rheumatology Unit,
University of Pisa, Italy

*Author for correspondence:
adellese@lycos.com

The musculoskeletal US findings in PsA are not different with respect to the one from other arthritis, in fact at a joint level we can have effusion and synovial proliferation (characterized by clusters of soft echoes with bushy and villous appearance) and/or homogeneous synovial thickening. Tendons may present exudative or proliferative tenosynovitis (with different echotexture of the sheath content allowing the distinction), swelling (for acute or even chronic tendonitis), tears of the tendon fibers and fibrosis or loss of the normal fibrillar echotexture (in tendinosis).

The literature shows us the US prevalence of knee, hip, shoulder, hand and foot involvement in PsA patients [17–20,23–24], demonstrating good sensitivity in the detection of synovitis with respect to clinical examination. An example of this higher sensitivity is reported by Delle Sedie *et al.* investigating knee joints US findings in a series of 83 PsA patients, showing at least one US inflammatory finding in almost all of them (84.3% of joints), while clinically involvement was present in only 74.7% of the evaluated joints [17]. With regard to the foot, in another paper, 183 feet were investigated in 101 PsA patients and US findings were positive for metatarsophalangeal joint inflammation in 77 (76.2%) patients, while only 34 (33.7%) patients were positive at the clinical examination [19]. When considering ‘difficult’ joints to be assessed, we have papers on the shoulder and the hip. In the assessment of 97 PsA consecutive patients, US showed a rather low prevalence of pathologic findings, with gleno-humeral joint effusion in only four shoulders (three of them with synovial hypertrophy but no PD signal) [20]. This changes when considering the hip; in fact the US bilateral examination of the hip in 65 PsA patients detected effusion, with or without synovial proliferation, in 21% of the subjects (eight hips were also negative for pain and/or tenderness) [18].

Recently, a qualitative and quantitative scoring system to evaluate large joint involvement and treatment monitoring in PsA or ankylosing spondylitis (AS) has been proposed [25].

The comparison between US and other imaging techniques (MRI, x-ray and scintigraphy) and/or US and clinical examination in PsA patients have been ruled out in two other papers [23,24]. Wiel *et al.* examined 2nd–5th metacarpophalangeal (MCP) and 1st–5th metatarsophalangeal joints, using US, contrast-enhanced MRI, x-ray and clinical assessment, in a small number of patients (15 PsA, five RA and five healthy controls) [23]. Similarly, Weiner *et al.* examined hands and feet of 13 PsA patients using US, MRI, bone scintigraphy and x-ray [24]. Both studies showed a higher sensitivity of US for inflammatory findings (especially synovitis) with respect to radiography and

clinical examination. More recently, in a paper comparing clinical examination and US findings in 49 patients affected by early-PsA, subclinical synovitis was really frequent, allowing a re-classification of the patients from oligoarthritis to polyarthritis [26]. This result confirmed a previous study by Scarpa *et al.* [27], where US was able to identify all of the sites showing inflammation in early PsA patients assessed using bone scintigraphy, which is significantly more sensitive than clinical examination.

Moving from joints to tendons, US examination has shown the involvement of tendon with synovial sheaths in PsA patients (i.e., posterior tibialis, flexor digitorum and peroneal), even in those who were asymptomatic [21]. We know that tendons without a sheath can also be involved, similar to what was shown in the shoulders of 97 PsA where the most common abnormal finding was represented by tendinosis (particularly of the supraspinatus, which was also the most frequently involved anatomical structure when considering tendon tear). Again, clinical examination failed to detect any abnormality in several patients in whom US examination showed pathological findings [20].

Many years ago, Fourniè *et al.* compared US findings in patients with RA and PsA. erosive synovitis and tenosynovitis were present in both diseases, while extra-synovial abnormalities (enthesitis, enthesopathy of deep flexor tendon insertion on the distal phalanx, juxtaarticular periosteal reaction and subcutaneous soft tissue thickening of the finger pad or entire finger) were found only in the PsA group [28]. This point leads directly to the importance of entheses involvement (see paragraph on Enteses) and to the definition of dactylitis. Conflicting data on the US finding of the definition and frequency of dactylitis are present in the literature [28–30]. Kane *et al.*, studying 25 dactylitic fingers and toes, reported subcutaneous soft-tissue enlargement in all affected digits with flexor tenosynovitis in 96% of cases and joint synovitis in about half of the digits [29]. On the contrary, Olivieri *et al.*, in 12 dactylitic fingers, demonstrated effusion inside the sheath of the flexor tendons (tenosynovitis) but no involvement of the peritendinous soft tissues or the synovial joints [30].

Enteses

Enteses involvement is very frequent in SpA [31], and enthesitis is considered the typical feature and the first step in the pathogenetic process of this diseases. Most papers refer to ‘SpA group,’ instead of PsA or AS groups, because of the fact that the features of enthesopathy are similar regardless of the diagnosis. This began in 1994, when Lehtinen *et al.* [32] first described US findings in SpA enthesitis; since then,

many papers have focused on this topic. However, we need to remember some of the limits of US imaging of the entheses, like the scarce number of vessels in the enthesis (that means low power Doppler frequency with respect to the synovitis process) and the risk of Doppler artifacts due to the proximity of the cortical bone. In any case, the most important point to keep in mind is the difference in the meanings of enthesopathy and enthesitis. The OMERACT (Outcome Measures in Rheumatology) US group identified the enthesopathy as ‘an abnormal hypoechoic region with loss of normal fibrillar architecture and/or thickened tendon or ligament at its bony attachment, seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions or irregularity.’ In this definition, signs of acute and chronic inflammation are combined with findings of structural damage [33].

The involvement of the enthesis in any pathologic process, whether metabolic, inflammatory, traumatic or degenerative, is referred to as ‘enthesopathy,’ while ‘enthesitis’ is restricted to the presence of inflammation of tendons, ligaments and capsules insertions into the bone and it appears to be a cardinal feature of SpA [34]. Unfortunately, many studies have applied US to the evaluation of entheses in SpA patients using different definitions for enthesitis, as well as different sets of entheses to be examined [35]. To solve this methodological problem, the OMERACT recently released the definitions of normal entheses and enthesitis [36].

The OMERACT US Task Force also started the same process in order to eliminate the discrepancies already existing on the definition of dactylitis [37].

What is actually well accepted is that the presence of a power Doppler signal, at the insertion of tendons, ligaments, fascia and capsules into the bone, is considered as a primary lesion that may underlie all SpA skeletal manifestations and is considered to be seen exclusively in SpA patients [38]. It is also accepted that enthesophytosis cannot be considered a specific sign of SpA-related enthesitis, as it is also reported with high prevalence in mechanical and osteoarthritis-related enthesopathy and in normal asymptomatic subjects (multiple and irregular enthesophytes and calcific deposits are possibly more specific for SpA-related enthesitis), and the use of enthesophytosis alone as sign of arthritis-related enthesitis is an incorrect assumption [39].

Enthesitis can occur everywhere but, especially in SpA, the more frequent and clinically relevant involved sites are localized in the lower limbs and, most of all, heel entheses (both the plantar fascia or the Achilles enthesis) [34,40].

Several quantitative scoring systems have been developed to quantify US abnormalities of the entheses,

and few of them are used quite frequently in clinical practice. GUESS (Glasgow Enthesitis Scoring System), D’Agostino, SEI (Spanish Enthesitis Index) and MASEI (Madrid Sonographic Enthesitis Index). The GUESS score was the first to be published, it is well accepted and assesses five enthesal sites in the lower limb (that evaluate Achilles, quadriceps, patellar entheses and plantar aponeurosis) only using gray-scale (GS) US [41]. The D’Agostino scoring system combines GS and Doppler and the severity of entheses involvement is given according to the severity of the Doppler signal and the presence of structural damage [40]. The Spanish Enthesitis Index (SEI), developed at the patient level (i.e., providing information about different enthesitis sites and allowing the evaluation of global patient inflammatory activity or entheses structural damage) uses GS abnormalities only. This scoring system, however, does not differentiate between involvement of enthesis, body of tendon and bursa [42], according to the ‘enthesis organ concept’ where the bursa is considered part of the synovio-entheseal complex [43]. The Madrid Sonographic Enthesitis Index (MASEI), combines abnormalities detected by GS US and PDUS (also including the involvement of the bursa) and evaluates not only the lower limbs, but also an enthesis site in the upper extremity (the attachment of the triceps tendon to the olecranon). Finally, it scores bone erosions, power Doppler signal and also enthesophytes [44]. All of those different scoring systems combine inflammatory signs (in GS alone or with PD) and structural signs (erosions, enthesophytes, etc.), allowing a possibly good combination for diagnostic purposes, but it may not be sensitive enough for follow-up purposes. However, they are not comparable, in fact the GUESS and D’Agostino scoring systems were developed to grade enthesis involvement (i.e., enthesitis level). The MASEI and SEI were developed as enthesitis indices at patient level. For this reason, these scoring systems cannot be compared (see Table 1). Currently, there is still a need to reach a consensus on the best system to use [38].

The relevance of the entheses in the disease process has led to the publication of many papers focused on it, even if most of time the papers are focused on SpA or AS patients and only a few are restricted to PsA patients alone. Frediani *et al.* [45] evaluated the knees of 40 PsA patients and 40 RA patients, reporting quadriceps enthesitis in 45% of patients with PsA, while Delle Sedie *et al.*, in a study on 83 PsA patients, showed a prevalence of knee enthesitis of 39.7% [17].

The US assessment of the entheses has been used to demonstrate the efficacy of the treatment with TNF α -inhibitors. In fact, in a large group of patients with SpA, Naredo *et al.* demonstrated a significant decrease in US findings related to entheses involvement that was not

Table 1. Main characteristics of the different enthesis scoring systems.

System	Gray scale	Power Doppler	Tendon	Bursa	Enthesis	Sites	Features assessed	Ref.
GUESS	Y	N	N	N	Y	Proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps	Bursitis, enthesis thickness, erosion, enthesophyte	[41]
SEI	Y	N	Y	Y	Y	Proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps	Hypoechoogenicity, increased tendon thickness, peritendinous oedema and bursitis (for active inflammation); insertional bone erosions, intratendinous calcifications, decreased thickness and tears (for chronic injury)	[42]
MASEI	Y	Y	N	Y	Y	Proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps and brachial triceps tendons	Enthesis thickness and structure, calcifications, erosions, bursae	[43]
D'AGOSTINO	Y	Y	N	N	Y	Proximal plantar fascia, distal Achilles tendon, proximal patellar ligament, distal quadriceps, greater trochanter, pubis, tibialis anterior tendon insertion, and medial and lateral epicondyles	Thickening or intratendinous focal changes of the tendon insertion, calcific deposits at the tendon insertion, or periosteal changes	[40]

N: No; Y: Yes.

correlated with changes in the clinical and laboratory variables throughout follow-up [46]. In another paper on the disease activity monitoring, after treatment (methotrexate *vs* adalimumab), focused on tendons and entheses, it was shown that several US parameters (i.e., Achilles tendon and plantar aponeurosis) were significantly improved in the adalimumab group with respect to the methotrexate one [47].

We also know that enthesopathic findings have already been demonstrated in patients with psoriasis without any clinical musculoskeletal involvement [2,16]. In fact, Gisondi *et al.* assessed 30 patients with psoriasis and 30 controls by US using the GUESS score, reporting that both the mean score, the thickness of the tendons and the number of enthesophytes, in all sites examined, were significantly higher in the psoriasis group. The GUESS score was directly correlated with age, BMI and waist circumference, but not to the duration and severity of psoriasis (according to the Psoriasis Area Severity Index – PASI) and body surface area involvement [2]. According to the authors, these findings could be related to a subclinical enthesal psoriatic inflammation. Similar results were also found by Gutierrez *et al.*, who studied 45 patients with psoriasis and 45 healthy controls [16]. In a paper by El Miedany *et al.*, higher basal values of the GUESS score, like the involvement of joints, in patients with psoriasis resulted to be predictive of the development of PsA [48]. More recently, Naredo *et al.* studied 162 patients with plaque psoriasis (without musculoskeletal diseases) and 60 controls, examining joints, tendons and entheses. US synovitis and enthesopathy were significantly more frequent in the psoriatic patients than in the controls [1]. The higher prevalence of enthesal abnormalities in PsA and psoriatic patients, with respect to the healthy subjects, was also demonstrated using the MASEI scoring system. In this paper, Eder *et al.* [49] found a cut-off point to categorize the patients as having PsA or psoriasis with a low sensitivity (30%) and a high specificity (95% vs healthy subjects and 89% vs psoriatic patients). Finally, Ash *et al.* performed a US evaluation of entheses of upper and lower limbs of patients with psoriasis (most of them presenting nail disease) and healthy controls. Entesopathy scores were higher in patients with nail disease than in patients without, and the authors concluded that psoriasis patients with nail disease have more frequently underlying systemic subclinical enthesopathy than those with normal nails [50].

All of these findings suggest the importance of a careful follow-up in patients with psoriasis and enthesal abnormalities to possibly give an early diagnosis of PsA. This should be remembered also because Farouk *et al.* found a nonstatistically significant difference between

psoriasis and PsA patients when comparing US entheseal abnormalities of both calcaneal insertions of Achilles tendons [51].

The future: new areas of interest, US as a tool for differential diagnosis & disease monitoring

US of the skin

The incredible advances in technology over the last few years have produced US machines equipped with very high frequency probes (18 MHz or more), which are mandatory to clearly distinguish epidermidis, dermis and subcutaneous fat, allowing the visualization of detailed findings of psoriatic plaque including the dermal blood flow. So, if it is true that US examination of psoriatic plaque in patients with psoriasis has shown a significant correlation between PDUS findings and both PASI and histological degree of vascularization before and after etanercept treatment [52], similar data have been published on PsA patients. In fact, De Agustin *et al.* demonstrated significant improvement for clinical variables (i.e., visual analog scale (VAS), tender and swollen joint counts (TJC and SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), synovitis and PD signal, PASI and plaque thickness) in 24 patients treated with infliximab [53].

US of the nails

Nail disease is common in psoriasis and can be a clinical predictor of PsA, as recently demonstrated by El Miedany *et al.*, [48], where US nail involvement was associated with structural joint damage. The nail is intimately linked to the enthesis of the extensor tendon [54,55] and DIP joint disease in PsA is associated with diffuse inflammation that envelops the nail root and the adjacent bone [55,56]. Aydin *et al.*, using US and clinical assessment (with modified nail psoriasis severity index) investigated the nail and adjacent tendons in 86 subjects with psoriatic nail disease. They concluded that the demonstration of extensor tendon enthesopathy in both psoriasis and PsA supports the importance of enthesopathy in nail disease pathogenesis whether clinical arthritis is present or not [57]. This hypothesis was also supported by Ash *et al.* as previously seen [50]. However, even if not considering the strict link to the tendon, US can provide useful data on the nail structure itself. We already know that the normal nail plate appears as a trilaminar structure, characterized by two hyperechoic sharp margins with an interposed thin anechoic line. In the early stages of psoriatic nail disease, a minimal loss of the sharpness of the hyperechoic definition of the ventral plate (which may appear focally curved and/or thickened) may be seen.

As the disease progresses, the US assessment shows the loss of the intermediate anechoic layer, which may be focal or complete, leading to the thickening and fusion of both plates. Also the nail bed (distance between the ventral plate and the bone margin of the distal phalanx) can be involved with a thickening (>2.5 mm). Finally, PD mode can show an increased blood flow within the nail bed, in the presence of a psoriatic nail disease, with respect to healthy subjects [58,59]. Similar data, attesting the increased distance between the nail ventral plate and the bone of the phalanx, have been shown by Sandobal *et al.* [60], where PsA and psoriatic patients had significantly higher values than RA patients. Using a cut-off point of 2 mm the Authors were able to define the subjects as part of one of the two groups. Besides, power Doppler was increased in PsA patients. Finally, a different US pattern of involvement of the nails was described between PsA and psoriatic patients. The added value of nail US for the rheumatologist could also be represented by the fact that nail disease is included in the CASPAR classification criteria for PsA [61]. In this light, the specificity of the findings in nail psoriatic disease, apparently not present in other possible causes of onychopathy [DELLE SEDIE A, DINI V, CARLI L ET AL. NAIL DISEASE: WHEN ULTRASOUND CAN HELP THE DERMATOLOGIST (2014) SUBMITTED.], could be helpful in the characterization of the patient.

US of the peripheral nerves

PsA is frequently showing synovitis or tenosynovitis (that could create a nerve entrapment) and, at the same time, carpal tunnel syndrome is more frequent in some other rheumatic diseases than in healthy controls, especially in systemic sclerosis patients [62,63]. This could lead the researcher to focus on the US assessment of the peripheral nerves. Unfortunately, up to now, no published data are available.

US as a tool for differential diagnosis

The most important thing to remember is that, until now, it had not been possible to distinguish whether a synovitis was due to RA or PsA (or any other arthritis) because the features are the same. This may not be true for some particular aspects such as hypoechoic swelling of the soft tissue surrounding the extensor digitorum tendon or the 5th metatarsal bone bursitis (mirroring an inflammation of the soft tissue). This pattern was firstly reported by De Filippis *et al.* [64] in psoriatic patients without musculoskeletal involvement but a few years later, Gutierrez *et al.* described it (with or without peritendinous PD signal) in PsA patients. The 'PTI pattern' (as they named it) was detected in the clinically involved MCP joints in a high percentage of PsA but in none of the RA patients. The authors

concluded that the PTI pattern, which is highly characteristic of PsA, could have a potential role in the differential diagnosis between RA and PsA at MCP joint level [65].

Another particular finding was described by Ciancio *et al.*, while evaluating the involvement of the bursa located next to the head of the 5th metatarsal bone in PsA or other SpA patients; they demonstrated the presence of this bursitis in the PsA group (11.3%) but not in the SpA or healthy controls. The authors concluded that this finding, if confirmed in future studies, could be useful for the differential diagnosis between PsA and other SpA [66].

Finally, as already stated, nail US examination could be helpful in the differentiation between PsA or psoriasis and RA patients [60].

US disease activity monitoring

Up to now, no guidelines to assess disease activity using US (neither alone nor combined with clinical assessment) are given. A preliminary composite PDUS score (merging the knowledge on different structures involved in PsA) for the assessment of blood flow changes induced by anti-TNF- α therapy in PsA patients at five target areas (joint, tendon, enthesi-sis, skin and nail) has recently been proposed [67], allowing an 'all-inclusive' evaluation of the disease activity in those patients.

Less comprehensive modalities could be given by using the enthesitis scoring systems already described in the enthesi-sis section of this review or, simply by scoring joint or tendon inflammatory findings (using the already existing general scoring systems) or structural changes (i.e., monitoring the occurrence, number or dimensions of the erosions).

Conclusion

US represents a useful tool to assess patients with psoriasis and PsA in order to better define the diagnosis (in psoriasis patients) or the extent of the disease (in PsA), providing useful data about the soft tissue – musculo-skeletal involvement (both meaning structural damages and inflammatory activity) that has been demonstrated to be responsive to treatment. Future studies are necessary to confirm a possible use of US in the differential diagnosis between PsA and other kind of arthritis, also within the same family of the SpA.

Future perspective

It appears quite likely that US will have more and more importance in the evaluation of PsA patients because of the necessity of early treatments (to avoid structural damage and so a decrease in the quality of life). A great deal of work still needs to be carried out to finally understand if US will really be useful in the differential diagnosis between PsA and other chronic arthritis. Finally, the efficacy of the treatments (frequently quite expensive) needs to be monitored (in the light of the optimization of the resources) and US has already proven to be a better tool with respect to clinical and laboratory data to be used for this aim.

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Executive summary

- Ultrasound (US) is able to demonstrate signs of inflammation in any peripheral joint or tendon or enthesi-sis with a higher sensitivity with respect to clinical examination.
- US is able to follow-up the disease activity during treatment (regardless of which one).
- There are a few scoring system proposed and all of them work well (even if not comparable).
- US is able to assess the disease activity also on skin and nail disease, reinforcing the concept of 'psoriatic disease' and the necessity of a global assessment.
- US could be useful to differentiate between psoriatic patients who will probably develop arthritis and between different kinds of chronic arthritis.

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