Psoriatic arthritis: what ultrasound can provide us

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ABSTRACT

Ultrasound (US) is a valuable imaging technique for detection and characterisation of the inflammatory process in arthritides. US has widely been applied to psoriatic arthritis (PsA) in both clinical and research fields, especially focusing on enthesitis. US has proven to be useful to establish a diagnosis of PsA, to recognise subclinical involvement, (such as enthesis abnormalities in patients with PsA, and in patients with only clinically apparent skin psoriasis despite the absence of clinical symptoms of arthritis), to estimate disease activity, and to allow therapy monitoring showing structural and inflammatory changes (not only in joints and tendons, but also in domains not assessed in usual rheumatology care, such as the skin and nails).

Introduction

Ultrasound (US) is an imaging technique that has been used increasingly in rheumatology over the last 15 years for the detection and characterisation of the inflammatory process in arthritides. Psoriatic arthritis (PsA) is one of the disorders for which US has been widely applied in both clinical care and research, particularly with a focus on enthesitis, a well-known hallmark of spondyloarthritides (SpA). The advent of modern imaging modalities, US and magnetic resonance imaging (MRI), facilitate the recognition of enthesis abnormalities not only in patients with PsA, but also in patients with skin psoriasis who had no clinical symptoms of arthritis (1, 2). US has proven valuable in establishing a diagnosis, evaluating disease activity, monitoring of therapy, and documentary structural and inflammatory changes. It remains debatable whether US can help in the differential diagnosis of PsA from other kinds of chronic arthritis (*i.e.* rheumatoid arthritis [RA]). Recently, rheumatologists have also used US in areas outside the usual rheumatology domains, such as skin and nails, (and even in the assessment of cardiovascular disease, although this latter application will not be discussed in this review) (3-15).

US findings: joints and tendons

PsA is an inflammatory arthropathy associated with psoriasis belonging to the group of SpA, which show great variability in clinical features and severity. The musculoskeletal US features of PsA do not differ from those observed in other arthritides. Effusion and synovial proliferation and/or homogeneous synovial thickening are seen in affected joints, while the spectrum of pathologic changes within tendons includes tenosynovitis (exudative or proliferative), swelling, tears, dislocation and fibrosis. US results have been demonstrated to be closely correlated (using contrast enhanced US) with histopathological quantitative and morphologic estimation of synovial microvascular proliferation (16). A predominant asymmetric involvement of the wrists was described in an early PsA cohort (17). US has greater sensitivity to detect synovitis compared to clinical examination, and data concerning US prevalence of knee, hip, shoulder, hand and foot involvement in PsA patients has been reported (18–23). Delle Sedie *et al*. reported at least one US inflammatory finding in 84.3% of knee joints) in 83 PsA patients, although clinical involvement was present in only 74.7% of the evaluated joints (18). A study of feet in 101 PsA patients indicated metatarsophalangeal joint inflammation in 77 (76.2%) patients, by US examination compared to only 34 (33.7%) with abnormalities by clinical examination (20).

US can be of considerable value to assess shoulder and hip joints, which is difficult clinically, due to the complexity and deep position, respectively, to be assessed. In 14 of 65 PsA patients examined bilaterally for hip involvement, effusion (with or without syno-

vial proliferation) was detected in 8 of the 14 hips in which no pain and/or tenderness were elicited (19). In a study on the shoulders of 97 PsA consecutive patients, US showed a low prevalence of pathologic findings, as glenohumeral joint effusions were found in only four shoulders (21).

Recently, a qualitative and quantitative scoring system to evaluate large joint involvement and treatment monitoring in PsA or ankylosing spondylitis (AS) has been proposed (22). The higher sensitivity of US for inflammatory findings (especially synovitis) compared to plain x-ray and clinical examination has been confirmed also in studies which compared US and other imaging techniques (MRI, x-ray and scintigraphy) and/or clinical examination in PsA patients (23, 24).

US findings: entheses

Involvement of entheses is frequent in SpA (25), as enthesitis is the initial finding in the pathogenetic process and typical feature of the group of disorders generally regarded to as 'SpA group,' rather than PsA or AS. US examination of entheses is somewhat limited by the small number of vessels in enthesis, so power Doppler (PD) signal is low, and the possible Doppler artifacts (flash artifact) may be seen due to the proximity of the cortical bone.

The difference between "enthesopathy" and "enthesitis" must be recognised. The term "enthesopathy" refers to the involvement of enthesis in any pathologic process, whether metabolic, inflammatory, traumatic or degenerative, while "enthesitis" is restricted to the inflammation of tendons, ligaments and capsule insertions in the bone. Enthesitis is the cardinal feature of SpA (26). However, in 2005, the OMERACT (Outcome Measures in Rheumatology) US Task Force described 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", merging together findings seen in acute and chronic inflammation as well as in structural damage (27). Different definitions of enthesitis, as well as different sets of examined entheses, have been applied to US evaluation of entheses in SpA patients (28), yielding conflicting results. Recently the OMERACT US Task Force has worked on the new definitions of normal entheses and enthesitis (29).

Reports concerning features of dactyilitis detected by US (30) yield conflicting results (31-33). Kane *et al*. described subcutaneous soft-tissue enlargement in all of the 25 examined dactylitic fingers and toes, which was associated with flexor tenosynovitis and joint synovitis in 96% of cases and in about half of both fingers and toes, respectively (32). By contrast, Olivieri *et al*. reported tenosynovitis, but no involvement of the peritendinous soft tissues or the synovial joints (33). Most of the sonographers agree with the definition given by Kane.

The presence of a power Doppler signal at the insertion of tendons, ligaments, fascia and capsules in the bone, is, nowadays, considered the primary lesion that may underlie all SpA skeletal manifestations, and is considered almost unique in SpA patients (34). Enthesophytosis are not specific for SpA-related enthesitis because of their high prevalence in mechanical and osteoarthritis-related enthesopathy and in normal asymptomatic subjects, and it appears incorrect to regard this finding as sign of arthritis-related enthesitis (35). Enthesitis in SpA is frequently localised at the Achilles heel enthesis and the plantar fascia (26, 36) and those sites seem to be more "specific" for SpA with respect to other enthesis.

Several quantitative scoring systems have been developed to quantify US abnormalities of the entheses, although few of them are used quite frequently in clinical practice. The GUESS (Glasgow Enthesitis Scoring System) score was the first to be published, and is well accepted; GUESS assesses five bilateral entheseal sites in the lower limb (plantar aponeurosis, Achilles, quadriceps and patellar entheses) using only grey-scale (GS) US (37). The D'Agostino scoring system combines GS and PD findings and the severity of entheseal involvement is scored according to the combined severity of the Doppler signal and the presence of structural damage (36). The Spanish Enthesitis Index (SEI) is developed at the patient level (allowing the evaluation of global patient inflammatory activity or entheses structural damage) and uses GS abnormalities only: it does not differentiate between the involvement of enthesis, body of tendon and bursa (38), according to the 'enthesis organ concept,' in which the bursa is considered part of the synovio-entheseal complex (39). The Madrid Sonographic Enthesitis Index (MASEI), combines GS and PD US findings (including the bursa), evaluating the lower limbs, and one enthesis in the upper limb (the attachment of the triceps tendon to the olecranon); it scores bone erosions, PD signal and enthesophytes (40). All of those different scoring systems combine inflammatory signs (in GS alone or with PD) and structural signs (erosions, enthesophytes, etc.): this may be good for diagnostic purposes, but may not be sufficiently sensitive for longitudinal assessment. The GUESS and D'Agostino scoring systems were developed to grade enthesis involvement (*i.e*. enthesis level) while the MASEI and SEI were developed to assess the enthesis involvement at a patient level. To date, a consensus on the best system to use has not been reached (34) and it possibly will not be reached in the future, given the different aim for which it can be used (*i.e*. diagnosis, global or focal monitoring of the disease activity).

Frediani *et al*. (41) evaluated the knees of 40 PsA patients and 40 RA patients, reporting quadricipital enthesitis in 45% of patients with PsA. Delle Sedie *et al*. found a prevalence of knee enthesitis in 39.7% of 83 PsA patients (18). US assessment of entheses also has been used to demonstrate the efficacy of the treatment with TNFα-inhibitors (42, 43). Naredo *et al*. documented a significant decrease in US findings related to entheses involvement in a large group of patients with SpA (42). A study of several US parameters indicated significantly greater efficacy of adalimumab compared to methotrexate group (43).

US findings: skin and nails

High-end US machines and very high frequency probes (≥18 MHz) have the capacity to distinguish clearly between the epidermidis, dermis and subcutaneous fat, allowing the visualisation of detailed findings of psoriatic plaques, including the dermal blood flow. US examination of psoriatic plaques indicates a significant correlation between PD US findings and both PASI and histological degree of vascularisation before and after etanercept treatment in patients with psoriasis (44). Significant improvement for PASI and plaque thickness have been also reported in PsA patients treated with infliximab (45).

Nail disease is common in psoriasis and can be a clinical predictor of PsA (46, 47). A link between the nail and the enthesis of the extensor tendon and distal interphalangeal (DIP) joint is well-established (48, 49); PsA is associated with a diffuse inflammation that involves the nail root and the adjacent bone (49, 50). Aydin *et al*., demonstrated extensor tendon enthesopathy in both psoriasis and PsA in a study of nail and adjacent tendons in 86 subjects with psoriatic nail disease using both US and clinical assessment with a modified nail psoriasis severity index (51). These findings support the importance of enthesis involvement in the pathogenesis of nail disease, regardless of the presence of clinical arthritis (51), as already proposed by Ash *et al*. (47). US also is useful to study the nail structure itself. The normal nail plate presents a US trilaminar appearance, characterised 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) can be depicted. As the disease progresses, US assessment shows the loss of the intermediate anechoic layer, which may be focal or complete, leading to thickening and fusion of both plates.

In addition, 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, compared to healthy subjects (52, 53). Similar data, attesting the increased distance between the nail ventral plate and the bone of the phalanx, have been shown by Sandobal *et al*. (54). Finally, since nail disease is included in the CASPAR classification criteria for PsA (55), it is fundamental to recognise the specificity of the US findings in nail psoriatic disease, in order not to misclassify psoriasis-related onychopathy with other conditions, as recently demonstrated [Delle Sedie A, Dini V, Carli L *et al*. Nail disease: when ultrasound can help the dermatologist (2014) Submitted].

Subclinical involvement

Most studies report joint and tendon involvement in symptomatic PsA patients, but several studies describe US pathological findings in PsA patients who do not report pain and/or swelling at the time of the clinical examination (18–21, 56, 57). A few reports indicated that synovitis is frequent in early PsA patients, despite the absence of clinical symptoms of arthritis (17, 58) allowing a re-classification of patients from oligoarthritis to polyarthritis based on the US examination. Scarpa *et al*. (59) concluded that US was able to identifiy all inflamed sites in early PsA patients which were assessed using bone scintigraphy, a more sensitive imaging tool than clinical examination. US examination also recognised involvement of tendon with synovial sheaths (*i.e*. posterior tibialis, flexor digitorum and peroneal) in PsA patients who were asymptomatic for clinical findings (56). Similarly, tendons without a sheath can be involved, as demonstrated in a study on the shoulders of 97 PsA; clinical examination failed to detect abnormalities in several patients in whom US examination showed pathological findings (21).

Enthesopathic findings have already been demonstrated in patients with psoriasis without any clinical musculoskeletal involvement (1, 2, 60). Gisondi *et al*., using the GUESS US score, reported that both the mean score, tendons thickness, and number of enthesophytes were significantly higher in the psoriasis group with respect to the healthy subjects. The GUESS score was positively correlated with age, BMI and waist circumference, but not to the duration and severity of psoriasis and body surface area involvement [2]. The authors suggested that these findings could identify patients with subclinical entheseal psoriatic inflammation. Gutierrez *et al*., who studied 45 patients with psoriasis and 45 healthy controls (60), found similar results. More recently, Naredo *et al*. documented that synovitis and enthesopathy were significantly more frequent in patients with plaque psoriasis who did not have musculoskeletal diseases than in the healthy control subjects (1). The prevalence of US entheseal abnormalities of calcaneal insertions of Achilles tendon also was demonstrated not to statistically differ in between psoriasis patients with no joint symptoms and PsA patients (61). Finally, Acquacalda *et al*. showed that asymptomatic enthesitis (mostly located at the Achilles tendon) improved significantly after systemic treatment with methotrexate and/or biologic agents given for the skin involvement in psoriatic patients (62). El Miedany *et al*. reported that higher basal values of the GUESS score, as well as the involvement of joints both using GS and PD techniques, predict development of PsA in patients with psoriasis. In addition, nail disease was associated with entheseal thicknening (46). Ash *et al*. found higher enthesopathy scores in patients with nail disease than in patients who had no nail disease, and concluded that nail involvement frequently underlies a systemic subclinical enthesopathy (47). Finally, using the MASEI scoring system, Eder *et al*. (63) found a cut point to classify patients as having PsA or psoriasis, with a low sensitivity (30%) and a high specificity (95% *vs*. healthy subjects and 89% *vs*. psoriatic patients). Even if a sensitivity of 30% could be not clinically fully relevant, this large amount of data cumulatively emphasise the potential value of US identification of abnormalities in patients with psoriasis and entheseal abnormalities to indicate an early diagnosis of PsA. Longitudinal studies are still need to fully understand the role of US in the

subclinical disease and in the definition of a disease in subjects with no symptoms at all.

US and differential diagnosis

To date, it is impossible to distinguish whether a synovitis is due to RA or PsA (or any other arthritis) because the features are the same. In 2006 Fourniè *et al*. demonstrated that erosive synovitis and tenosynovitis were present in RA and PsA, while extra-synovial abnormalities of enthesitis, enthesopathy of deep flexor tendon insertion on the distal phalanx, juxta-articular periosteal reaction and subcutaneous soft tissue thickening of the finger pad or entire finger were found only in the PsA group (31). These findings again emphasise the importance of entheseal involvement, as noted above.

More recently, US patterns than enthesitis have been proposed as possible marker of PsA. De Filippis *et al*. (64) firstly reported the hypoechoic swelling of the soft tissue surrounding the extensor digitorum tendon in psoriatic patients who did not have clinical musculoskeletal involvement; however, 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 RA patients. Therefore, this finding could have potential value in the differential diagnosis between RA and PsA at MCP joint level (65). Ciancio *et al*. described the involvement of the bursa located next to the head of the 5th metatarsal bone in 11.3% of 150 PsA patients, but not in 172 SpA or 95 healthy controls, and concluded that this finding could be useful for the differential diagnosis between PsA and other SpA (66). Furthermore, Sandobal *et al*. (54) showed significantly higher distance between the nail ventral plate and the bone of the phalanx in PsA compared to RA patients (54). Finally, a different US pattern of involvement of the nails has been described between PsA and psoriatic patients with a loosening of the borders of the ventral plate in the first one and focal hyperechoic involvement of the ventral plate without involvement of the dorsal plate in the psoriatic group (54).

US and disease activity monitoring

US has been demonstrated to be of help in the diagnosis of PsA as well as in the assessment of the disease. However, definitive guidelines either alone or combined with clinical assessment still need to be created. A preliminary composite PDUS score for the assessment of blood flow changes induced by anti-TNF-α therapy in PsA patients at five target areas (joint, tendon, enthesis, skin and nail) have been proposed by Gutierrez *et al*. (67). This approach, allowing an 'all-inclusive' evaluation of disease activity follows the already accepted concept of "psoriatic disease" in people with psoriasis. The US follow-up is more sensitive than the clinical examination but it needs a skilled sonographer (for a correct interpretation of the US findings, especially for the enthesis) and a high-end US machine. Real evidence for the prognostic role of US in PsA patients is still lacking. Both of those statements put US examination in a questionable light: should we always perform it for the follow-up of our patients? Considering what has already been demonstrated in RA patients *(i.e*. that US can predict disease progression and flares better than clinical examination and conventional radiology), it seems that the answer could be "yes"; in any case, more evidence is still needed and research work is still required.

Conclusion

In assessing musculoskeletal involvement, US can be of value to evaluate the extent of PsA and in the monitoring of treatment efficacy. However, the potential role of US in diagnosis (PsA *vs*. psoriasis; PsA *vs*. RA) and monitoring needs to be more definitively clarified.

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