
Enthesitis detection by ultrasound: where are we now?

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ABSTRACT

Over the last 25 years, ultrasound has been used to evaluate involvement at the entheses in spondyloarthritis (SpA) and psoriatic arthritis (PsA). Several studies have been reported indicating its value in detecting active inflammation at enthesal sites using both gray scale and Doppler findings. This review explores the recent literature and appraises the current knowledge and the unmet needs of enthesitis detection by ultrasound in the management of both SpA and PsA.

Introduction

Enthesitis is usually defined as an inflammation of the insertion of tendons, ligaments and capsules into the bone, and it is considered a pathological hallmark of the spondyloarthritis (SpA) group of conditions, including psoriatic arthritis (PsA) (1-3). Recent knowledge regarding the function, anatomy and pathophysiology of the enthesitis (4, 5) has improved our understanding of the involvement of this anatomical structure in the course of such diseases, and has confirmed initial observations concerning the relevance of enthesitis to the pathogenesis and clinical manifestations of SpA and PsA. Enthesitis is characterised by pain and stiffness at tendon insertions, such as the Achilles tendon, the plantar fascia or the common extensor tendon insertion at the epicondyle of the elbow. Clinical assessment of enthesitis has been based traditionally by recognition of tenderness elicited by the palpation of the enthesal site. Whereas the prevalence of clinically-detected enthesitis (*i.e.* pain at specific sites) appears to be between 30% and 50% in patients with PsA and SpA (6), the overall burden of enthesitis might be higher using more sensitive tools such as imaging techniques.

Enthesitis is sometimes the primary clinical manifestation of active SpA disease. The Assessment of Spondyloarthritis International Society (ASAS)

and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have recommended enthesitis as one of the outcome domains for assessing disease activity and response in both axial and peripheral SpA and PsA (7, 8). The introduction of new pharmacological therapies with improved trial designs incorporating enthesal outcomes, magnetic resonance imaging (MRI) and ultrasound, as well as increased use of these sensitive modalities in research and clinical practice, also have contributed to recognition of a pivotal role of enthesitis in both diagnosis and management of SpA (axial and peripheral) and PsA.

In this context, European League Against Rheumatism (EULAR) and GRAPPA in their management recommendations for PsA, have clearly highlighted the importance of specific recommendations for predominant enthesal disease. Somewhat different in their recommendations, ultrasound evaluation is an accepted method for detecting enthesitis in both sets (8-10).

The clinical assessment of enthesitis by physical examination may be challenging as the tenderness at the enthesal site, is a non-specific finding: presence of such tenderness does not always denote inflammation, nor does its absence exclude enthesitis.

Considering the value and importance of imaging to detect this characteristic lesion, the objective of this review is to summarise current knowledge and the unmet needs concerning the use of ultrasound for the detection of enthesitis in diagnosis and management of SpA and PsA.

Ultrasound of enthesitis where we are now?

The comprehensive description of ultrasound involvement of entheses in SpA patients was made for the first time by Lehtinen and colleagues in 1994 (11, 12) and then by Balint and colleagues in 2002 (13). Both authors described,

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using grey scale (GS), ultrasound abnormalities of lower limb entheses in SpA patients, revealing a high frequency of asymptomatic findings. Enthesitis in GS is characterised by the loss of normal fibrillar echogenicity of tendon insertion, especially in the acute inflammatory phase, which appears as hypoechoic, with an increase in thickness and/or intralesional focal changes at the tendon insertion, such as calcific deposits, fibrous scars, and periosteal changes (erosions or new bone formation). The latter are commonly seen during chronic inflammation or in longstanding focal disease. Additionally, involvement of the body of tendon, distant from the entheses, and of the adjacent bursae may also be observed.

Thus, GS ultrasound permits depiction of both signs of acute and chronic inflammation of the entheses as well as structural damage. In 2002 and 2003, for the first time, D'Agostino and colleagues described the capacity of Doppler ultrasound, in addition to GS changes, to detect active inflammation at entheses as abnormal vascularisation at their bony insertion. They also showed the discriminative capacity of adding Doppler information in differential diagnosis and monitoring of treatment response (14, 15).

Since then, several studies have been reported supporting the capacity of ultrasound in GS combined with Doppler (in particular, power Doppler) to evaluate enthesitis in SpA and PsA (16-22). In a range of studies from those focused on the diagnostic value of the technique to those exploring sensitivity to change, all have shown that ultrasound can improve the management of the SpA diseases through accurate detection of the presence of enthesitis.

Detection of enthesitis improves the diagnostic evaluation

The importance of ultrasound to enhance the diagnostic evaluation have been noted previously, particularly on the adding value of an earlier diagnosis of axial and peripheral SpA, or mixed SpA diseases including PsA (16, 19, 20). Most of the published scoring systems were developed for diagnostic purposes. More recent studies have

been primarily focused on PsA and on the capacity of ultrasound to enhance early or differential diagnosis (23). Marchesoni and colleagues (24) in a recent report, expanded on a previous observation (23) concerning the incremental value of using power Doppler ultrasound to differentiate polyenthesopathic forms of PsA from fibromyalgia (FM). Sometimes the differential diagnosis between the two diseases may be difficult, when the only symptom is pain. This is in part due to the fact that FM tender points may overlap with enthesal sites, particularly when there is diffuse enthesitis involvement. In addition, some PsA patients can present with concomitant FM symptoms together with active disease. In their first cross-sectional study, they observed that ultrasound findings of enthesitis in GS were more frequent in PsA than in FM, and, furthermore, that power Doppler findings were exclusively present in PsA-detected enthesitis (23). In their 2018 article they suggest a possible diagnostic algorithm which included the use of power Doppler ultrasound in case of difficulty in making the diagnosis (24). Ultrasound of enthesitis also appears useful to detect SpA in ASAS-negative patients, as documented by a recent longitudinal study reported by Poulain and colleagues (25).

The incremental value of ultrasound to detect enthesitis was explored in a study of psoriasis patients with musculoskeletal complaints by van der Ven and colleagues (26). The authors reported that adding ultrasound evaluation to the clinical assessment of enthesitis in these patients from a primary care setting, demonstrated that 36% of those with clinical enthesitis had active ultrasound inflammation, while structural changes were seen in the vast majority of patients, independent of clinical signs and symptoms.

A recent publication by Michelsen and colleagues on PsA patients, confirmed once again the discordance between clinical and ultrasound evaluation of entheses, in particular for Achilles enthesitis (27). In this cross-sectional study none of the clinical characteristics of active enthesitis were statistically significantly associated with ul-

trasound inflammatory activity at the Achilles, as well as none of the usual biological parameters (C-reactive protein and erythrocyte sedimentation rate) used to evaluate PsA disease. However, ultrasound structural damage was statistically significantly associated with age, body mass index, regular physical exercise and current use of biological disease-modifying anti-rheumatic drugs, suggesting an increased prevalence of structural damage with increased duration of disease, and increased age. These results, along with those from previous studies, raise a question of whether inflammatory findings should be more weighted than structural damage in the development of an ultrasound enthesitis score. The absence of correlation between clinical and ultrasound evaluation of enthesitis, as well as the different ultrasound definitions of enthesitis used, have generated discordant data about the capacity of the technique to clearly differentiate between entheses involvement in SpA or PsA and in other conditions (28). This discordance is related to several factors, but in particular to the absence in some of these studies of a clear definition of ultrasound-detected enthesitis, including which components were evaluated for defining its presence (29). Although GS scale components are important for detecting pathology at an enthesal site, they cannot be used as the only information to differentiate between mechanical and inflammatory involvement.

The absence of discriminant capacity of GS findings has already been reported (15, 16) and recently confirmed by Wervers and colleagues and Lanfranchi and colleagues (30, 31). The former group reported that the MASEI (MAdrid Sonographic Enthesitis Index) (20), which includes GS structural changes and Doppler signal at 5 enthesal insertions, could not be used to distinguish between PsA and young healthy subjects, except when thickness of the patellar tendon was excluded, and the Doppler was weighted. They observed that increased thickness and PD signal in knee entheses, as defined by the score (in the body of the tendon and perientheses), were common for

patients and healthy volunteers, while changes at other locations occurred predominantly in patients only (and not in normal subjects). They therefore suggested excluding knee tendons from this index and to weight more heavily the Doppler findings. By contrast, Lanfranchi and colleagues observed that the MASEI could be used to discriminate between SpA patients and athletes and healthy subjects. These reports confirm previous observations that structural changes may be too common in some settings, to allow differentiation between diseases or between healthy controls and diseased patients, especially in PsA. Nonetheless, a recent study from Polachek and colleagues confirmed the severity of enthesitis measured by the MASEI is associated with radiographic damage in PsA (32).

Which ultrasound scoring system should be used?

In recent years, several enthesitis scoring systems have been published (29, 33), including the MASEI. However, each system is different and incorporates different ultrasound elementary lesions, and their validity, both discriminant and diagnostic, may vary according to the elementary components included in such scores. These differences render comparisons across studies difficult, and the use of ultrasound as outcome measurement instrument of enthesitis in multicentre studies remains problematic (33).

Within the Outcome Measures in Rheumatology (OMERACT) ultrasound Working Group, a sub-task force for enthesitis was created in order to produce a standardised, agreed definition of enthesitis, and a reliable scoring system. The group previously had published a systematic literature review highlighting the great variability in the definitions of enthesitis applied in the ultrasound studies since 1994, in particular the great variability of the definition of its constituent elementary components (33). Following a standardised step-wise consensus-based approach, the group initially agreed on the definitions of each potential elementary component and then on which of them should be included in the global defi-

nition of ultrasound-detected enthesitis for both SpA and PsA (34).

Recently, the group finalised this process by testing the intra and inter-observer variability of this scoring method (35). The definition of enthesitis validated by the OMERACT ultrasound group is: "hypochoic and/or thickened insertion of the tendon close to the bone (within 2 mm from the bony cortex), which exhibits Doppler signal if active and that may show erosions, enthesophytes/calcifications as a sign of structural damage". The definition highlights the mandatory presence of inflammatory findings for defining the presence of SpA- or PsA-related enthesitis, whereas the structural findings may not always be present. In this case, the scoring of each lesion is made binary for facilitating detection, and some structural findings are scored together (as osteophytes and calcifications) in order not to increase, artificially the weight of these components in the final definition (and scoring). The sensitivity to change of this proposed score is under evaluation in several multicentre randomised and open label studies in PsA.

Conclusions

Since 1994, ultrasound has played an important role to detect enthesitis in SpA and PsA. Ultrasound has been incorporated into the management of these patients in both clinical research and practice. With the latest study, the OMERACT group has finalised the process of development of a reliable and unanimously- defined definition of enthesitis by ultrasound, including each elementary component. This is an important step towards ensuring a higher degree of homogeneity between studies and a facilitation of the daily clinical work.

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