

# Enthesitis – a review on the ultrasonographic assessment

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## ABSTRACT

The potential benefit gained from ultrasonography examination of the enthesis been extensively studied. Enthesitis plays a key role in pathogenesis of spondyloarthritis and thus, understanding the diagnostic and therapeutic implications has shaped the way clinicians view its importance in clinical practice. The development of high-quality imaging technologies offered a great opportunity to obtain more detailed analysis of the enthesis structure and also differentiate acute from chronic lesions. Several taskforce groups, including OMERACT, highlighted the diagnostic performance of ultrasonography for the detection of enthesitis. Panels of experts have also provided consensus-based definitions of elementary lesions in order to standardize the approach of US-defined enthesitis. Enthesitis is considered one of the main clinical domains in psoriatic arthritis patients and several trials have adopted its use as a potential outcome measure, although research carried out until now, still lacks uniformity between methods used to assess enthesitis. Multiple semiquantitative scoring systems of enthesitis using ultrasonography have been developed in the last two decades and these may provide a more standardized approach in future research.

**Keywords:** enthesitis, ultrasonography, scoring, spondyloarthritis

## INTRODUCTION

Ultrasound (US) examination plays an important part in the evaluation of patients with spondyloarthritis (SpA) with peripheral involvement and is especially useful in patients with clinical features of enthesitis. US can confirm a clinical suspicion of enthesitis and can also detect a subclinical inflammation of the entheses which could otherwise be overlooked. When seeing a patient with enthesitis pain, it is particularly important to know if it's due to active or chronic lesions. This can further guide appropriate patient management. US can also aid the physician in this respect and also help guide local treatment if needed. It is an accessible imaging tool, it's fairly inexpensive and lacks contraindications. The major drawbacks would be the long learning curve and the time-consuming evaluation of multiple accessible enthesis sites, but the last one can be limit-

ed by adopting a more targeted examination to specific enthesis areas. Research has been carried out in order to offer a more standardized approach to ultrasound examination of the enthesis by establishing basic pathologic definitions and main sites of interest. Similar to clinical enthesis scores, ultrasound indices have been developed in order to provide a more accurate outcome measure for SpA treatment. This review aims to provide insight into research that supports the potential benefit of US assessment of the enthesis as an accurate tool for diagnostic and monitoring of SpA patients.

## ULTRASONOGRAPHY FEATURES OF ENTHESOPATHY

Ultrasonography examination of the enthesis is performed using a high-resolution linear transducer with a working frequency of up to 18 Mhz. Because the enthesis sites commonly examined by US are su-

perforial structures, higher frequencies can be applied, and this will enable the examiner to obtain clear images of the tendon insertions. B-mode is used to depict structural features of the enthesis, while Doppler mode, either colour- or power-Doppler (PD), is used to detect presence and degree of vascularity a feature related to active inflammation (1).

Upon examination, the enthesis should be in tension for B-mode evaluation, for a clearer image the fibrillar pattern of the tendon, and in a more relaxed position, when using Doppler mode to assess the vascular pattern. For example, the quadriceps and patellar tendons should be examined with the knee flexed at 30 degrees in B-mode and with the knee in neutral position in Doppler mode. The Achilles tendon should be scanned with the patient in prone position and feet overhanging the edge of the examination table. Dorsal flexion of the foot will generate tension in the Achilles enthesis for a better view of the tendon structure.

Enthesis sites are evaluated bilaterally in both long and short axis (1,2).

During the US examination, certain features are of particular interest. These include bone irregularities, calcifications, enthesophytes, erosions, enthesis hypoechoogenicity, thickened enthesis and Doppler signal at enthesis (1). In order to provide more uniformity in the approach of US examiners for the identification of enthesis lesions, the OMERACT task-force group has developed standardized US definitions of enthesis pathologic features (1), as seen in Table 1.

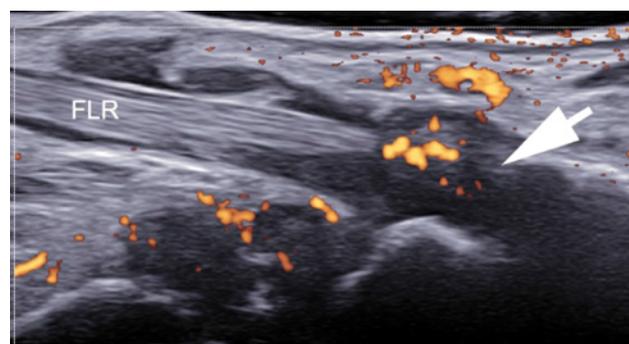
In most research on the topic of enthesis US, there is a strong agreement regarding the differentiation of acute and chronic lesions. Doppler signal, hypoechoogenicity at the level of the enthesis and increased thickness are considered features of acute enthesitis. Chronic lesions on the other hand are more related to structural damage such as bone erosions, calcification or enthesophytes.

Following the OMERACT recommendations, US-detected enthesitis is defined as a thickened insertion of the tendon and/or hypoechoic area adjacent to bone (< 2mm from bone cortex) which can feature Doppler signal, if it is active (Figure 1), or additional structural lesions (1). An earlier definition of PD enthesitis was used by Miguel et al in the development of the Madrid Sonography Enthesitis Index (MASEI) ultrasound enthesis score (2) and implied the presence of the Doppler signal at the cortical bone profile, intratendon, paratendon or in the bursa on the enthesis insertion.

Both definitions reached excellent inter-reader reliability (kappa= 0.92 for OMERACT PD, 0.86 for MASEI PD) reported by Collada et al. in a recent multicenter study in patients with axial SpA and psoriatic arthritis (PsA) (3).

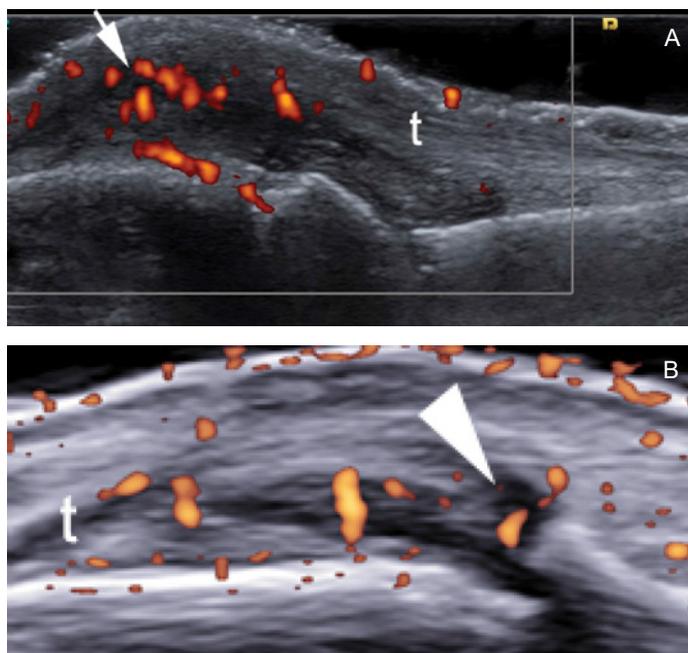
**TABLE 1.** OMERACT task-force group standardized US definitions (1)

Lesion	Definition
Bone irregularity	Bone profile changes not including definite enthesophytes nor bone erosions.
Enthesophyte	Step-up bony prominence, seen in two perpendicular planes at the end of the bone contour of the enthesis.
Erosion	Cortical break with a step-down contour defect, seen in two perpendicular planes, at the insertion of the enthesis.
Hypoechoogenicity at the enthesis	Lack of the homogeneous fibrillar pattern in the enthesis (<2mm from the cortical bone) with loss of the tightly packed echogenic lines after correcting for anisotropy.
Thickened enthesis	Increased thickness of the tendon insertion into the bone (<2mm from the cortical bone) as compared with the body of tendon, with or without blurring of the tendon margins.
Calcification	Hyperechoic foci, with or without acoustic shadow, detected at the enthesis (<2mm from the cortical bone).
Doppler signal at enthesis	Doppler signal seen at bone insertion (<2mm from the cortical bone), different from reflecting surface artefact or nutrition vessel signal, with or without cortical irregularities, erosions or enthesophytes.
Doppler signal outside the enthesis	Doppler signal far from the enthesis (>2mm from the cortical bone, within the body of tendon) and clearly different from nutrition vessel signals.



**FIGURE 1.** Ultrasound image showing both tenosynovitis and enthesitis of the flexor radialis carpi (FLR), with thickened, hypoechoic area near bone cortical, loss of fibrillar aspect of the tendon and Doppler signal (arrow)

Apart from the classical enthesis structures which constitute insertions of tendons, ligaments and joint capsules, US can be used to identify changes also in functional enthesis. They form proximal to the at-



**FIGURE 2.** A. Peri-extensor tendon inflammation (PTI pattern) at the level of the A1 pulley, showing hypoechoic area and Doppler signal surrounding the tendon. B. Inflammation of the finger extensor central slip, at the level of the proximal interphalangeal joint, showing a hypoechoic aspect of the tendon at the insertion, with loss of the fibrillar pattern and Doppler signal. t -tendon, arrow – PTI pattern, arrow head – insertion of the central slip

tachment sites, where tendons and ligaments wrap around bony pulleys. These areas are sites of significant mechanical stress, which in turn generates fibrocartilage differentiation (4), like in the A1 pulley area (Figure 2A). Another important enthesis site with particular interest for PsA is the finger extensor central slip insertion (Figure 2B). Zabotti et al. established in a 2016 study that central slip enthesitis is a key discriminative lesion when differentiating PsA from rheumatoid arthritis patients (5).

While the aforementioned US lesion may be restricted only to the enthesis, it is not unusual to see concomitant inflammatory features in the surrounding soft tissue. Close anatomic structures like the fat pad, synovial tissue of adjacent bursa or joint, together with the enthesis form the so-called “entheseal organ” (4).

## DIAGNOSTIC APPLICABILITY OF ENTHESIS ULTRASONOGRAPHY

Ultrasonography has become a well-established examination tool for the rheumatology practitioner and has proved good diagnostic performance and reliability in the assessment of enthesopathies (6–9). Semiquantitative assessment using US scoring systems which apply certain cut-off values can further increase the diagnostic capabilities of enthesis US (1,2,9–11). Most studies focused on the sensitivity and specificity of PDUS-defined enthesitis in distinguish-

ing SpA from non-SpA patients. Enthesial involvement is part of the CASPAR (CLASSification for Psoriatic ARthritis) (12) and ASAS classification criteria (Assessment of SpondyloArthritis international Society) (13). Moreover, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) included enthesitis as one of the main clinical domains to be considered when treating PsA patients (14). One important advantage of applying US to the screening of enthesis involvement stems from its capacity to detect subclinical enthesitis which could be otherwise overlooked. This can have important implications on the management of patients. In an earlier study by Balint et al. on SpA patients (15), prevalence of enthesitis increased significantly from 22% on clinical examination to 56% when assessed using US. Importantly, the study failed to detect any correlation between US score of enthesitis and acute phase reactants levels. More recently, Zuliani et al. studied the role of musculoskeletal US in psoriatic patients in order to identify cases of subclinical PsA. They observed features of active enthesitis in 20% of psoriatic patients and this occurrence was correlated with a higher PASI score (16).

Multiple studies have obtained promising results regarding the positive predictive value of PDUS for patients with SpA and while sensitivity tends to vary between studies, PDUS-defined enthesitis regularly achieves high specificity rates in SpA patients (6–9). Drawing data from the DESIR cohort, Poulain et al reported an 83% specificity for PDUS-defined enthesitis in patients meeting ASAS classification criteria (8). In a 2020 study, Fujukawa et al. studied the significance of enthesitis in at least one site. Enthesitis detected by PDUS alone achieved high diagnostic accuracy and likelihood ratio of 4.88 when differentiating SpA from non-SpA patients. Moreover, combining PDUS findings with well-established classification criteria could increase the specificity of the latter (6). A follow-up study on patients with early SpA which featured initial PDUS-defined enthesitis in at least one site reported good predictive values for SpA diagnosis with an OR of 14.1 (9).

In patients with PsA, the US examination of the distal interphalangeal (DIP) joint and, more specifically, of the enthesis of the digital extensor tendon are of particular interest. Nail psoriasis disease can associate subclinical enthesitis of the extensor tendon and this can be explained by the close anatomical relation of this enthesis with the nail matrix. This frequent occurrence has led to the idea that initial inflammation occurs in the nail and progresses proximally to the distal phalanx where it generates enthesitis and DIP arthritis (17,18). Nail abnormalities could be thus included in the broader entheseal complex of the distal phalanx.

There is significant evidence to support the role of US-defined enthesitis in distinguishing SpA patients, especially on the basis of acute lesions. Still, an important limiting factor is the inability to accurately differentiate between chronic lesions caused by an inflammatory disease or mechanical stress. In fact, there is still no consensus regarding a specific definition for non-inflammatory enthesopathy (19). Surely, when faced with this question, the practitioner will rely on the clinical setting and additional tests in order to establish a diagnosis.

## ENTHESITIS SCORING SYSTEMS

Development of US-defined enthesitis scoring systems addressed a need for a more standardized approach for this particular manifestation of SpA patients. Multiple semiquantitative scoring systems have been published in the past two decades and each was aimed to provide the examiner a more focused assessment and a guide for grading the observed US lesions (3). A selection of common US enthesitis scoring systems widely used in clinical research is detailed in Table 2. In general, inter-reader reliability is good among examiners involved in the original studies on scoring system development (1,2). In a recent 2021 study on use of Doppler enthesitis as a potential useful outcome, Collada et al. also reported high interreader reliability for both MASEI and OMERACT defined enthesitis with a kappa of 0.92 and 0.86, respectively (3). Nail US has also gained interest for achieving of a more detailed assessment taking into account its close relation with the enthesial organ. The Brown University Nail Enthesis Scale (BUNES) developed by Cunha et al. includes 3 domains: nail plate changes (yes/no), abnormal or thickened nail beds and/or matrix (yes/no) and Doppler signal of the nail bed and nail matrix (graded 1-3) (17).

## ENTHESITIS ULTRASONOGRAPHY EVALUATION USED AS OUTCOME MEASUREMENT

Enthesitis is recognized as an important target in the management of patients with PsA. Recommendations published by both GRAPPA (14) and OMERACT (20) research groups include enthesitis in the list of core domains to be addressed when treating patients with PsA. Although multiple trials have used enthesitis evaluation as an outcome measure, there are still considerable differences between instruments used to evaluate the enthesitis, between cut-offs and timing of reported outcomes (21).

Assessment of enthesitis through US has proven high sensitivity to change and this motivates its use in the treatment follow-up (22). Besides local treatment with glucocorticoids, improvement of enthesitis can also be obtained with systemic treatment. US

**TABLE 2.** Ultrasonography scoring systems for enthesitis

Score	Year	Enthesis sites	Scoring system (lesions and grading)
GRAPPA Tom et al.	2019	CETLA, SS, AT, PF, PL (P, D)	hypoechoogenicity, thickening, bone erosions and irregularities, calcifications, bursitis (0 or 1); enthesophytes, Doppler signal (0–3)
OMERACT Balint et al.	2018	CETLA, AT, PL (P), QT	hypoechoogenicity, enthesophytes, calcifications, erosions, Doppler signal (0 or 1)
MASEI de Miguel et al.	2009	TT, AT, PF, PL (P, D) QT	calcification (0–3), Doppler (0 or 3) and erosion (0 or 3); tendon structure, tendon thickness and bursa (0 or 1)
SEI Alcalde et al.	2007	AT, PF, PL (P, D), QT	acute lesions - thickening, hypoechoogenicity of tendon, peritendinous oedema, bursitis (0 or 1); chronic lesions - tendon tear, loss of thickness, tendon calcification, bone erosion (0 or 1)

GRAPPA - Group for Assessment of Psoriasis and Psoriatic Arthritis; OMERACT - Outcome Measures in Rheumatology; MASEI - Madrid Sonography Enthesitis Index; SEI - Spanish Enthesitis Index; AT - Achilles tendon; CETLA - common extensor tendon of lateral epicondyle; CFTME - common flexor tendon of medial epicondyle; GT - greater trochanter; PF - plantar fascia; PL - patellar ligament; QT - quadriceps tendon; SS - supraspinatus tendon; TT - triceps tendon; P - proximal; D - distal; scoring values - binary (0 - absent, 1 - present) or weighted (0-3 scale).

responsiveness of enthesitis at 3 and 6 months has been evaluated in studies on patients with SpA treated with anti-tumor necrosis factor agents (22–24). Aydin et al. observed US improvement of Achilles enthesitis in SpA patients at 2 months after start of anti-TNF therapy (25). Even earlier enthesitis response is reported in a study using SPARCC enthesitis index which showed significant changes in common extensor tendon of the elbow at 6-week US follow-up (26). Interestingly, US improvement of enthesitis does not always correlate with patient-reported outcomes (22). Moreover, in a large study by Naredo et al. on 327 patients with active SpA started on anti-tumor necrosis factor (TNF) therapy, responsive enthesitis proved to be a relevant marker of disease activity, independent of clinical and laboratory outcomes (23). More and more studies seem to support this asynchrony between the response of clinical and US-detected enthesitis and also between response of joint and enthesitis inflammation (4).

As expected, responsiveness is reported in most studies at the acute lesions, such as enthesitis Doppler signal and bursitis, while structural damage proves to be mostly non-responsive (23). However, data from a study by Miguel et al. proved that erosions could display responsiveness (27) and this raises the question if they should be labeled as chronic structural lesions as a whole or more stratification is needed. Finally, severity of enthesitis involvement can further predict joint damage, both peripheral and axial. A 2017 study on 223 PsA patients, showed a correlation of higher MASEI US scores with peripheral and axial radiographic pro-

gression, with arthritis mutilans and joint ankylosis (28).

## CONCLUSIONS

Enthesis involvement is the central pathological process in spondyloarthritis. Ultrasonography is an accessible and reliable tool for the clinician and provides several benefits in regard to enthesitis diagnosis, follow-up and guided local treatment. Consensus-based definitions of ultrasound pathologic features and development of ultrasound scoring systems aim to provide more uniformity between examiners and better-quality assessments of the enthesitis.

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