New perspectives in enthesis ultrasound: validation of enthesis fibrocartilage

Evaluation of: Aydin SZ, Bas E, Basci O *et al.*: Validation of ultrasound imaging for Achilles entheseal fibrocartilage in bovines and description of changes in humans with spondyloarthritis. *Ann. Rheum. Dis.* 69(12), 2165–2168 (2010). Enthesitis, the hallmark of spondyloarthritis is underestimated in clinical practice and improving the knowledge of structural damage and inflammation in enthesis is challenging. The results of a study by Aydin *et al.* are put into the context of the recent advances and definitions in the field of enthesis ultrasound and the new contributions of this original paper in the visualization of the enthesis fibrocartilage and its relationship with the histology are discussed.

KEYWORDS: enthesis ■ fibrocartilage ■ spondyloarthritis ■ ultrasound ■ validity

Eugenio De Miguel
Rheumatology Unit, La Paz University Hospital, 28046 Madrid, Spain
eugenio.demiguel@gmail.com

This article aims to evaluate the study by Aydin *et al.*, who introduce new methods to assess and understand the Achilles enthesis using ultrasound [1]. This original paper focuses on peripheral extra-articular enthesitis, at the Achilles level. Inflammation at the entheses, the sites of attachment of the tendon, ligament, fascia or joint capsule to the bone, is a characteristic finding of ankylosing spondylitis and spondyloarthritis (SpA). Historically, enthesis evaluation has been difficult and, as a consequence, enthesitis, the hallmark of SpA, is underestimated in the diagnosis and clinical assessment of SpA. This is an important reason to improve the knowledge in this field.

Enthesitis has been viewed as a focal, insertional problem of soft tissue; however, in the last decade we have come to understand that inflammation also affects the bone, because we have seen osteitis adjacent to fibrocartilaginous enthesis – an important finding on MRI [2,3] – and this supports the concept of a sinovio-entheseal complex proposed by McGonagle *et al.* over the past few years [2–7]. The essential importance of the enthesis in understanding the pathophysiology of inflammation and structural damage in SpA has reemerged in front of the only mechanical overload concept of the pathogenesis of enthesopathy. The link between enthesitis and osteitis in SpA has been clarified in recent studies, which demonstrate a close functional integration of the enthesis with the neighboring bone, with the entheses fibrocartilare playing a central role. Entheseal microdamage and inflammatory cell infiltration has been described; the enthesis architecture was abnormal in the SpA group, with increased vascularity and immune cell infiltration compared with normal subjects [3]. The predominant infiltrating cell at the entheses fibrocartilage was the macrophage, but there was a lack of lymphocytes contributing to inflammation at the insertion point [3,4]. Owing to this, previous concepts that mechanical stress is a central cause of enthesis damage in SpA are being questioned as histology, MRI and ultrasound imaging at the enthesis level demonstrate relevant changes in SpA diseases similar to that of an autoimmune disease.

Until recently, the radiographic features of enthesitis have played an important role in defining enthesitis lesion images in SpA. This includes bone insertion osteopenia, bone cortex irregularity at insertion, erosion, entheseal soft tissue calcification and new bone formation. However, entheseal bone changes appear late in the disease and are also common in mechanical disorders and in crystal-related pathology. Therefore, over the past few years, different image techniques such as MRI and in particular ultrasound have become a valuable source for the understanding and applicability on future diagnosis and clinical management of SpA. Ultrasound has proven to be a highly sensitive and noninvasive tool, especially interesting when assessing enthesis involvement. The importance of ultrasound in SpA occurs because clinical examination lacks sensitivity and specificity, which has been demonstrated by the poor sensitivity to change and by several studies comparing the clinical evaluation with the new imaging techniques [8,9]. Ultrasound, having demonstrated its usefulness in the detection and assessment of synovitis in

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rheumatoid arthritis and other inflammatory diseases, is turning its attention to other fields, one of them being SpA.

Outcome measures in rheumatoid arthritis clinical trials (OMERACT) have defined enthesopathy as abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal, and/or bony changes including enthesophytes, erosions or irregularity [10]. The pathological features that occur in the enthesis are structural damage (hypoechogenicity and loss of the normal fibrillar pattern of the collagen structure of the tendon), thickening of the entheses tendon structure, by edema and other infiltrative and reparative changes, erosion, calcification or ossification of the attachment between collagen fibers in contact with the cortical bone profile as representative of the inflammation and healing of the enthesitis process, and Doppler signal, which can be present or not depending on the activity of the disease in the exploration time. These elemental lesions, included in the OMERACT definition, have been shown to be valid at the patient and entheses level to differentiated SpA patients from the healthy population [11,12] and even from other inflammatory patients [11,13].

The study by Aydin *et al.* offers a new insight on enthesis [1] as it describes an elementary lesion that was not described in the OMERACT definition [10]. This paper provides preliminary evidence supporting the concept that ultrasound can visualize entheseal fibrocartilage and improves our knowledge on enthesis in SpA. The authors describe a new anatomoclinical area of interest in the enthesis, the enthesis fibrocartilage. As the authors demonstrate, the enthesis fibrocartilage can be recognized on enthesis as a thin, uncompressible, well-defined, anechoic layer between the hyperechoic cortical bone profile and the hyperechoic fibrils of the enthesis, both in longitudinal and transverse scans. In my experience this is reproducible (**Figures 1 & 2**), but reliability is yet to be demonstrated. Normal enthesis organs are avascular in their fibrocartilaginous regions; however, tissue microdamage to enthesis is common and appears to be associated with tissue repair responses and vessel ingrowth. From the study being evaluated, we are near to seeing and understanding the anatomopathological lesions described previously, as a structural damage (when we lost the fibrocartilage image), as an inflammatory process when cortical Doppler signal appears (in the fibrocartilage area) – a specific SpA sign previously described [11] – and possibly, in the future, it will be able to make a link with the existence of bone osteitis in MRI.

This description alone has great value, but the authors not only describe this finding, they also attempt to validate this result in two ways. First, by attempting to differentiate whether the lesion described might be an ultrasound device that affected the change of interface between the bone and tendon. In this case the authors are extremely careful to look for the pathologic lesion that could correspond with the ultrasound image and their merit is that they are able to prove, in an animal bovine model, the correspondence between ultrasound and the macroscopic appearance and microscopic histology of the anatomohistological area and proposed definition, and show photos that are able to convince the reader. As a second step, they attempt to see if this finding is clinically relevant; in other words, if ultrasound entheses fibrocartilage identification in humans is able to differentiate between SpA patients and controls. In this case, the results showed statistically significant differences in the loss of the anechoic line over the bone profile, which could be seen in 35.3% of SpA patients and 23.8% of healthy controls ($p = 0.05$); this can be a limitation because fibrocartilage lesions seem to have a low predictive value in the classification of SpA patients. Although imaging of the entheses has improved in the past decade, there are still considerable problems in visualizing entheses fibrocartilage in terms on the resolution limit, and this depends on equipment trade mark, model and settings. The authors worked with a high-quality machine equipped with a broadband 6–18 MHz linear probe that was run by an expert ultrasonographer who knows how to improve image acquisition and settings. I hope that, in the near future, this can be made feasible for other researchers with new and improved equipment.

In summary, at a microscopic level, entheses fibrocartilage is of paramount importance in ensuring that fiber bending of the tendon or ligament is not focused at the hard tissue interface. The study published by Aydin *et al.* is the first systematic and preliminary evidence supporting the concept that ultrasound can visualize enthesis fibrocartilage. This might be relevant in the future because enthesis fibrocartilage is probably the anatomopathological target where the inflammatory entheses lesion occurs. In fact, on ultrasound image we can appreciate

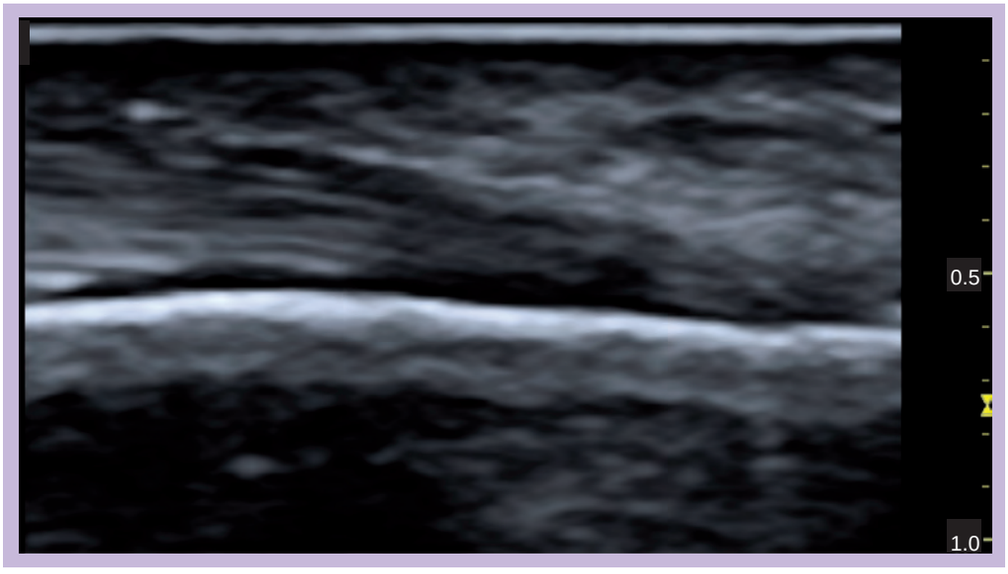

Figure 1. Achilles enthesis longitudinal view. Enthesis fibrocartilage can be seen as a thin, uncompressible, well-defined, anechoic layer between the hyperechoic cortical bone profile and the hyperechoic fibrils of the enthesis.

how, at the fibrocartilage level, it is the origin of the enthesophytes, erosions or bone irregularities and also where the most specific Doppler localization occurs.

In conclusion, understanding the enthesis organ concept helps to explain synovitis and osteitis in spondyloarthropathy. The visualization of the complex anatomy of the enthesis organ will be helpful in understanding and adapting the SpA enthesis concept to clinical practice. The study demonstrates a new ecopathoanatomic observation of entheseal structure that could lead to a new platform for understanding the pathogenesis, diagnosis and assessment of SpA.

Future perspective

Regarding fibrocartilage as an ultrasound elemental lesion with diagnostic and therapeutic implications, several factors must be considered before any generalizability is alleged:

- Interobserver and intermachine reliability;
- Sensitivity to change;

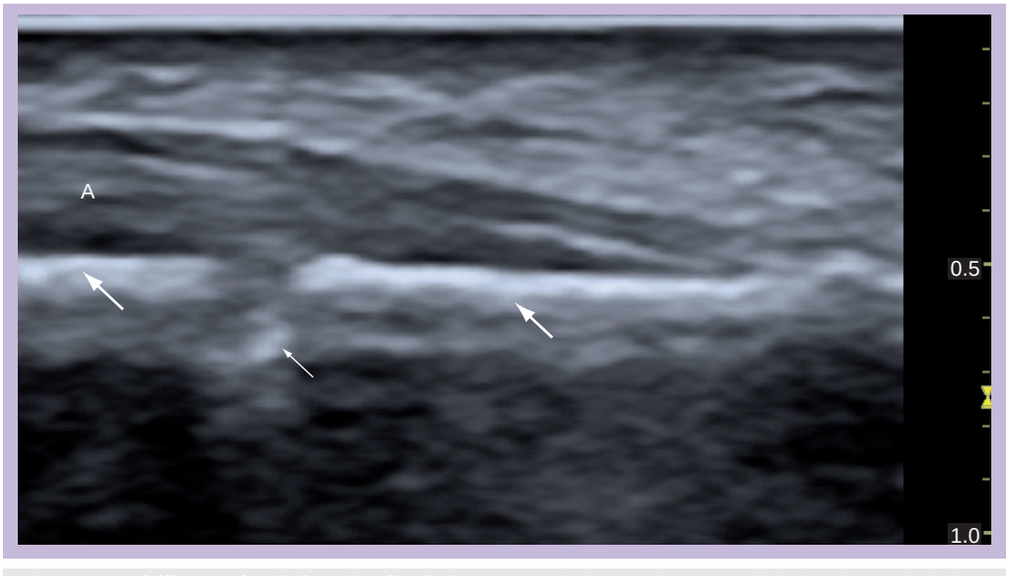

Figure 2. Achilles enthesis longitudinal view. Loss of the continuous well-defined, anechoic layer fibrocartilage. Achilles tendon fibrous connective tissue **(A)**, cortical erosion, with enthesis fibrocartilage disappearance, in a spondyloarthritis patients (thin arrow). Calcaneus cortical bone profile (thick arrows).

- Usefulness in diagnosis classification (isolated or in combination with other ultrasound lesions);
- Link between Doppler signal at fibrocartilage level and the existence of osteitis in MRI;
- Prospective, randomized and controlled studies that confirm the validity of proposed ultrasound lesion.

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Executive summary

- Inflammation at the enthesis is a characteristic finding of spondyloarthritis.
- Historically, enthesis evaluation has been difficult and underestimated.
- Over the last few years, ultrasound has proved to be highly sensitive in assessing enthesis involvement.
- Previous ultrasound enthesis lesions and descriptions are included in the enthesopathy outcome measures in rheumatoid arthritis clinical trials (OMERACT) definition.
- Enthesis fibrocartilage can now be recognized on enthesis ultrasound.
- The correspondence between ultrasound and histology validates the ultrasound fibrocartilage identification.
- Enthesis fibrocartilage Doppler signal can be the next between enthesis inflammation, cell infiltration and osteitis.
- Enthesis ultrasound could lead to a new platform for understanding the pathogenesis, diagnosis and assessment of spondyloarthritis.

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