Limited ultrasound protocol of the Achilles enthesis

A new strategy to inform diagnosis and management of spondyloarthropathies?

This editorial refers to Can we use enthesis ultrasound as an outcome measure of disease activity in spondyloarthritides? A study at the Achilles level, by Sandra Falcao et al., on pages 1557–1562.

Enthesitis is a unifying hallmark in the disease pathogenesis in SpA, which has been proved in several animal models but is obviously more difficult to prove in the case of human disease [1]. Enthesitis is clinically defined as inflammation of an insertion that manifests clinically as pain, stiffness and tenderness, with or without swelling. Unfortunately, physical examination can be inadequate for the assessment of enthesitis for many reasons, including relatively little swelling or inaccessibility of insertions to examination.

The enthesis-centric model for SpA has spawned an increasing number of imaging studies in the past decade including US and MRI [2]. What is clear is that US of entheseal insertions shows a large burden of subclinical abnormalities even in asymptomatic regions [3]. Given the lack of histological validation at these sites, such asymptomatic lesions are best termed enthesopathy, because of the lack of proof that such lesions always cause inflammation.

A new, potentially pivotal study on US and enthesopathy is published in this issue of Rheumatology by Falcao et al. [4]. This study tests the construct validity (i.e. how well a test measures up to its claims) of US on Achilles enthesis by comparing clinical indices and acute phase reactants in an early cohort of SpA; the overarching hypothesis is that US changes at this site may be informative about the more systemic components of the disease. The group showed that the baseline US scores of Achilles enthesis correlated significantly (but weakly) with ESR and CRP, but not with clinical indices [Ankylosing Spondylitis Disease Activity Score (ASDAS) and BASDAI]. On the other hand, when patients were categorized according to the ASDAS, patients with very active disease (ASDAS >3.5) were found to have higher US Achilles enthesis scores. The Achilles tendon has been dubbed the premiere enthesis by Canoso [5] based on its physical size, and the present findings suggest that enthesopathic changes at that site correlate with a more severe systemic enthesopathy in SpA.

The importance of the Falcao et al. study [4] is that it provides data not only about the construct validity of US, but also about its predictive value: patients with higher CRP values had higher US scores at baseline, which also persisted at follow-up. In AS, a high CRP is known to be associated with poor prognosis, in addition to baseline syndesmophytes and smoking [6]. In the case of PsA, high CRP is also associated with a greater likelihood of erosion progression. Given that isolated enthesitis is not typically associated with elevated CRP, it is likely that the link between the positive US enthesopathy findings and CRP reflects a greater burden of systemic disease in those with Achilles imaging findings, irrespective of symptoms at that site. This could be further evaluated by combining US and MRI of the entire body.

Falcao et al. [4] also found that patients with high disease activity had a better chance of improving their entheseal abnormalities after 1 year. The US scores of patients with baseline ASDAS >3.5 fell from 7.8 (s.d. 6.4) to 4.6 (s.d. 4.6), with a larger decrease compared with patients with an ASDAS <3.5 [4.8 (s.d. 3.8) to 3.5 (s.d. 3.8)]. Statistically there was a difference in US scores at baseline [being higher if the ASDAS was >3.5 (P = 0.04)], whereas both groups had similar US scores at the end of 1 year. Although information about treatment subgroups was not given in detail, the authors mention that all patients had NSAIDs and a minority had DMARDs, but none had anti-TNF therapies. This indirectly shows that greater improvement is observed in entheseal US in patients with very active disease. On the other hand, a better response could not be observed according to the CRP values. These data show that US entheseal manifestations of patients with higher ASDAS values at baseline may respond better when a tool such as entheseal US, which focuses on the primary pathology, is used. However, the study was an observational study with the lack of any interventions and randomization, which limits any firm conclusion.

Despite these potentially exciting results, there are still a lot of questions that need to be addressed. In addition to a more accurate assessment of enthesitis, what does entheseal imaging tell us about the disease and how would it shape our treatments? A driving force for work like this comes from axial disease, where positive imaging, namely MRI, is associated with a better response to therapy [7]. Prospective studies will have an important role in determining whether Achilles enthesis US has prognostic value in early SpA. In that respect, when patients with psoriasis were followed up for a mean duration of 3.5 years, those with subclinical US baseline entheseal positivity developed PsA, suggesting that enthesitis may have a predictive value for arthritis [8]. The lack of histological validation for enthesitis is a limitation of US in differentiating it from other forms of enthesopathy, which can be
related to age, BMI and exercise, possibly as a result of mechanical stress. In the study by Falco et al. [4], Doppler positivity seems to be more associated with CRP and ESR (patients having a positive Doppler signal had higher CRP and ESR values) compared with the other US abnormalities, but probably due to the low prevalence, which was not mentioned, it was not predictive of any response.

To summarize, this study suggests that enthesitis may be associated with the severity and course of SpA. The clinically defined role of enthesitis is almost never truly identified, as past history of enthesitis may not be accurate: with recall bias, the patient may misinterpret the signs of enthesitis. Despite the limitations of US, the evidence suggests that entheseal US is a more accurate way to demonstrate enthesitis, excluding the false positivities and negativities of history and physical examination. Subclinical enthesitis in this context appears to have an increasing value as supported by numerous studies [3, 8]. The responsiveness and sensitivity to change of imaging only the Achilles enthesis by US, as well as multiple entheses, has also been shown before, in addition to the construct validity as stated above [9, 10]. Detailed assessment of the enthesis using US in clinical trials will guide investigators to appreciate the role of enthesitis in the pathogenesis of SpA more than physical examination, and focusing on one enthesitic area by US, such as Achilles enthesis, seems to be valuable in AS.

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