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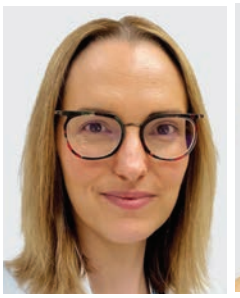
Editorial



New Advances in the Knowledge of Elemental Enthesis Lesions: Doppler, Erosion, and Thickness

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The entheses are more than a point of anatomical attachment for tendons, ligaments, joint capsules and fascia to bones; its involvement in the pathophysiology of spondyloarthritis (SpA) and psoriatic arthritis (PsA) is the cornerstone of these diseases. In 1971, the relevance of the enthesis as the primary pathological site of seronegative SpA was clearly defined.[1] In 1999, McGonagle et al highlighted this central role with the concepts of the "enthesis organ"[2] and the "synovio-entheseal complex,"[3] in which the multiple enthesis components (eg, tendon fibers, paratenon, bursae, sinovium, fibrocartilage, specific cells, and cytokines) shape the physiopathological basis and the primary inflammatory location both in SpA and PsA, even leaving synovial involvement a secondary role.[4] The term enthesis *organ* should be taken into special consideration, as it is very significant and was surely chosen to translate not only its complexity but also the systemic character of this affectation (leaving again the local boundary) and its capacity for remote connection with other distant disease domains.

The Assessment of SpondyloArthritis international Society (ASAS), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), and European Alliance of Associations for Rheumatology (EULAR) recommend evaluating the enthesis as one of the outcome domains for assessing disease activity and response in SpA and PsA.[5] Globally, enthesis is the epicenter of these diseases, and experts suggest its evaluation as a main outcome. However, in clinical practice, only indirect data of enthesis status in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) are used, as physical entheses examination is associated with a lack of sensitivity, specificity, and reliability that limit its use.[6] For this reason, ultrasound (US) indices have emerged in recent years as an attempt to improve the evaluation of the enthesis, with the Glasgow Ultrasound Enthesitis Scoring System (GUESS)[7] and the Madrid Sonographic Enthesis Index (MASEI)[8] being the most widely used. US is a cardinal enthesis evaluation technique, as it accurately detects both vascular and structural abnormalities, turning it into a first-line imaging method in this field.[9,10] Moreover, in the study of entheses, US has been demonstrated to be a valid and sensible tool that is sensitive to change.[11] However, nowadays, the enthesis is probably the most underestimated domain in SpA and PsA, perhaps due to the general criticism of the low reliability and accuracy of entheses physical examination in clinical indices[6] and the low use of US in clinical practice. Added to this is the idea that US is an operator-dependent technique, resulting in the more widespread use of other subjective surrogate markers of activity.

Today, however, the evidence is changing. Accordingly, the Outcome Measures in Rheumatology (OMERACT) US Task Force, after more than a decade of experience in the field of enthesis US, published in 2018 the reliability of a consensus-based US definition and scoring for enthesitis in SpA and PsA[5] based on the following elementary enthesis lesions: inflammatory or active lesions (enthesis tendon ecostructure or hypoechogenicity, thickening, and power Doppler [PD]), and chronic or structural lesions (erosions, enthesophytes/calcifications). Additionally, in recent years, the number of studies focused on entheses has increased exponentially. In this issue of *The Journal of Rheumatology*, 2 new studies help deepen the knowledge and relevance of entheses in SpA and PsA.[12,13]

Smerilli et al[12] share the results of a joint and entheses US study performed in 104 patients with PsA, exploring the association between enthesis involvement and peripheral joint damage measured by US joint erosions, demonstrating how enthesis US findings have become a biological marker of surrogate structural joint damage in PsA and reinforcing the central role of enthesis inflammation in PsA and its association with other outcomes and domains in this disease (joints, in this case). In this study,[12] joint erosions were found to be associated in the univariate and multi-

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See Entheseal thickening MSK US, *page 70, and* Enthesitis and erosive damage, *page 66*

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variate model and in the logistic regression analysis with enthesis PD (β 0.51, $P < 0.001$ and odds ratio [OR] 1.74, 95% CI 1.17-2.59, $P < 0.01$), enthesis erosion (β 0.20, $P = 0.02$ and OR 3.17, 95% CI 1.30-7.77, $P = 0.01$), and greyscale joint synovitis (β 0.42, $P = 0.03$ and OR 2.59, 95% CI 1.16-5.78, $P = 0.02$). The results of Smerilli et al[12] are also consistent with the results obtained by other authors, who point out that the enthesis PD is the main US lesion for enthesis evaluation in SpA and PsA,[14] even suggesting that it is sufficient to define enthesitis not only as an isolated elemental lesion.[15] In their cohort of patients with PsA, Smerilli et al[12] found PD present in 55.8% of patients and 10.6% of entheses, similar to previous findings (66.7% of patients and 10.2% of entheses),[16] although a proper comparison seems complex due to the different selection of explored entheses and disease activity states of the included patients. Another series also reported high percentages of enthesis PD (81.5-96%),[16-18] and Mease et al[19] proposed that the enthesis domain could be associated with greater PsA disease activity, globally supporting the association between the enthesis domain (highlighted by PD) and the systemic activity in SpA and PsA, thereby emphasizing the importance of introducing new methods to improve the evaluation of entheses.

Other authors have previously explored the relationship between the erosive behavior of PsA and the enthesis. In 2017, Polachek et al[20] published a study in patients with PsA demonstrating an association between radiographic damage (sacroiliitis, modified Stoke Ankylosing Spondylitis Spine Score [mSASSS], joint ankylosis and arthritis mutilans) and MASEI (total score and both structural and inflammation subscores). In 2021, other authors also published an association between the MASEI-inflammation subscore and sacroiliac joint X-ray affectation.[21] El Miedany et al[22] also evaluated potential structural joint damage predictors in an early PsA cohort and reported peripheral and sacroiliac X-ray damage after 1 year, demonstrating an increased probability for structural progression related to PD at entheses using the GUESS. To our knowledge, Smerilli et al[12] is the first study to evaluate structural damage in terms of peripheral erosions by US, and not by X-ray, and its association with the presence of enthesitis; however, the results led to the same conclusions. Erosion appears in this study as the other elementary lesion of the enthesis related to joint damage in the multivariable analysis, which is very interesting since the evidence in this field is scarce but in agreement with previous studies.[21]

The second article of interest related to enthesis is published by Keenan et al[13] in this issue of *The Journal of Rheumatology*. In this case, the topic is entheseal thickness, another OMERACT enthesis elemental lesion. In recent years, this specific topic has been a pending task to improve the accuracy of enthesis imaging assessment. Enthesis thickening is categorized as an active lesion assuming (as human in vivo histological evidence is nonexistent) that the inflammation of the enthesis causes local edema and, consequently, an increase in its size. However, for some authors, enthesis thickening can also be considered a chronic or structural lesion, as this inflammation can evolve to a state of local fibrosis, which also implies enthesis thickening. Both thoughts are correct according to the time and evolution of the disease. The results shown by Smerilli et al[12] demonstrated how entheses thickening was related to structural joint damage in the univariate analysis but not in the multivariate analysis, such that the thickening is also relevant in the association of the enthesis with other disease domains. The problem is that in the aforementioned OMERACT reliability exercise,[5] thickening achieved the worst results, with a κ of 0.1 (95% CI 0-0.7), and this needs to be improved, highlighting the importance of the article by Keenan et al published in this issue.[13]

Three options can be chosen to define entheseal thickening, as the authors mention[13]: comparing with the contralateral side (which does not seem appropriate in inflammatory patients, since the possibility of bilateral pathological findings increases), comparing the enthesis insertion with the body of the tendon, and using cut-off values (probably the most time-consuming option but increasing reliability and improving lesion assessment). The use of cut-offs has been the most employed method to date in the literature, but the accepted values were based on small sample studies, with heterogeneous cohorts (patients, healthy people, cadaveric samples), and most of the studies were published in the 1990s based on the low-quality US machines available at that time.[23,24] Moreover, current cut-off values[7] have been demonstrated to be influenced by older age, male sex, higher BMI, physical activity, and metabolic syndrome. Even their discriminant validity between inflammatory patients and healthy subjects is poor.[25] The study by Keenan et al[13] is of interest due to the proposal of updated higher enthesis US thickening cut-off values in front of current margins[7,8] in patients with axial SpA. They found in both cases that only triceps tendon enthesis thickening discriminates healthy people from patients with SpA (cut-off > 4.2-4.3 mm). These results are likely to help improve the reliability and assessment of thickness and enthesis.

In summary, the study by Smerilli et al[12] adds to the previous studies a further step toward the confirmation of the association between enthesitis (based on enthesis PD) and peripheral radiographic damage in PsA, as well as an understanding of the connection of the enthesis with other distant domains, with a holistic explanation of interconnected PsA domains. The work by Keenan et al[13] will likely improve the reliability and demonstrate that having evaluation standards is highly desirable not only to improve knowledge in this field but also for the future accuracy of enthesis studies. Both studies published in this issue of *The Journal of Rheumatology* contribute new pieces to the complex puzzle of knowledge of the entheses. Day by day, the final picture becomes clearer, increasing our knowledge and understanding of this key piece in SpA and PsA: the enthesis.

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