Clinical and imaging assessment of peripheral enthesitis in ankylosing spondylitis

Enthesitis, defined as inflammation of the origin and insertion of ligaments, tendons, aponeuroses, annulus fibrosis and joint capsules, is a hallmark of ankylosing spondylitis. The concept of entheseal organ prone to pathological changes in ankylosing spondylitis and other spondyloarthritis is well recognized. The relevant role of peripheral enthesitis is supported by the evidence that this feature, on clinical examination, has been included in the classification criteria of Amor (heel pain or other well-defined enthesopathic pain), European Spondiloarthropathy Study Group and Assessment in SpondyloArthritis International Society for axial and peripheral spondyloarthritis. Nevertheless, the assessment of enthesitis has been improved by imaging techniques to carefully detect morphological abnormalities and to monitor disease activity.

KEYWORDS: ankylosing spondylitis ■ clinical assessment ■ enthesitis ■ MRI ■ spondyloarthritis ■ ultrasound

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In primary ankylosing spondylitis (AS) the frequency of peripheral enthesitis has been found to be between 25 and 58% [1], however, the real prevalence of this feature depends on the type of assessment (i.e., clinical, imaging or histological). Peripheral enthesitis can be revealed by clinical findings, such as localized pain, tenderness and swelling, but there are no definite clinical criteria for the diagnosis of this manifestation, which may even be asymptomatic. Thus, the clinical assessment of enthesitis has a low sensitivity, may often underestimate the presence of enthesitis, and requires a careful diagnostic work-up with other joint and soft tissue disorders, such as fibromyalgia [2–4]. Histological examination of the enthesis is the potential gold standard for the evaluation of enthesitis, but is rarely obtained owing to ethical and practical constraints. Imaging techniques include conventional radiography, bone scintigraphy, MRI, ultrasonography (US) and, recently, PET/CT scans [1,5]. Conventional radiography may show erosions and bone proliferation changes (ill defined and finely speculated), but only in more advanced phases [1]. Technetium-99m methylene diphosphonate scintigraphy has been shown to be a sensitive indicator of heel enthesitis, but its specificity has not been determined. MRI may show the swelling of the enthesis and the peritendinous soft tissue, the distension of adjacent bursae by fluid collection and edema of the bone near the insertion. On the other hand, the study of entheses with MRI is limited owing to its reduced availability and high costs [6]. US has proven to be a highly sensitive and noninvasive tool to assess the presence of enthesitis, characterized by hypoechogenicity with loss of tendon fibrillar pattern, tendon thickening, local calcifications, enthesophytes and bony erosions. Moreover, the use of power Doppler US (PD) allows the detection of abnormal vascularization of soft tissues, entheses, tendons and joints [7,8]. Recently, PET/CT scans have been considered as a new tool to assess enthesitis in spondyloarthritis (SpA) [5].

Clinical assessment of enthesitis

Many clinical indices to assess enthesitis in AS and other SpA have been employed in previous years. A scoring system was developed by Mander *et al.*, based on the patient's response to firm palpation over 66 entheses. The Mander Enthesis Index (MEI) was significantly correlated with visual analog scale for pain and stiffness, but it was time consuming [9]. The modified MEI, however, considered only 17 entheses in the spine and lower limbs [10].

In 1995, the 'Assessment in Ankylosing Spondylitis' working group selected a core set for outcome assessment in AS, including physical function, pain, spinal mobility, patient global assessment, peripheral joints/enthesis assessment, x-ray of the spine and acute phase reactants [11], but there was no specific instrument to measure enthesitis. Braun *et al.* used an enthesis index (Berlin index) in a study on infliximab in AS, composed of 12 entheses that are reported to be commonly affected in the inflammatory process

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in AS [12]. This index included the iliac crest, the great trochanter of the femur, the medial and lateral condyle of the femur, the proximal insertion of Achilles tendon and insertion of the plantar fascia to the calcaneus. In this study, the enthesitis index showed a significant change after anti-TNF treatment. In 2003, Heuft-Dorenbosch *et al.* validated a new clinical index to assess enthesitis involvement in AS: the Mastricht Ankylosing Spondylitis Enthesitis Score (MASES). The MASES considers the palpation of only 13 entheseal sites (e.g., first costochondral joint, seventh costochondral joint, posterior superior iliac spine, anterior superior iliac spine, iliac crest, fifth lumbar spinous process and proximal insertion of Achilles tendon). The MASES correlated with the MEI and with the Bath Ankylosing Spondylitis Disease Activity Index, and seemed to be a good alternative to the MEI with much better feasibility [13]. Gladman *et al.* assessed four entheseal sites bilaterally (rotator cuff insertion at the shoulder, tibial tuberosity at the knee, Achilles tendon and plantar fascia insertions in the calcaneus) to determine the reliability in a cohort of psoriatic arthritis (PsA) patients. In this study, authors only found good interobserver agreement for the detection of plantar fascitis [14]. Healy and Helliwell developed the Leeds Enthesitis Index in a cohort of 28 PsA patients based on bilateral palpation of three entheseal sites (lateral epicondyle, medial femoral condyle and Achilles tendon insertion). They showed strong correlation with measures of disease activity; furthermore, the enthesis index showed a significant change after 6 months of therapy with disease-modifying antirheumatic drugs. The authors reported that the MEI, Leeds Enthesitis Index and Berlin index were able to distinguish between patients with active disease and those without active disease as defined by the Disease Activity Score. This finding suggests that these measures relate to an assessment of inflammation on a more general scale and, probably, represent localized inflammation at the entheseal points [15]. Recently, Maksymowych *et al.* validated a new enthesitis index in AS patients: the Spondyloartrhritis Research Consortium of Canada enthesitis index, which is based on palpation of eight entheseal sites (great trochanter, quadriceps tendon insertion on the patella, inferior pole of patella, Achilles tendon insertion and plantar fascia insertion on the calcaneus, tendon insertions on medial and lateral epicondyle of humerus and sopraspinatus insertion into greater tuberosity of the humerous). The authors showed that the enthesitis index was feasible and reproducible and correlated with disease activity and functional index [16].

Imaging assessment of enthesitis

Historically, the radiographic features of enthesitis have played a pivotal role in defining enthesitis lesions of SpA. Conventional radiography can show bone erosions and new bone formations at sites of insertion of tendons and ligaments [17]. Frequency of erosions at the insertion of the Achilles tendon and enthesopathy in both the Achilles and plantar fascia insertions were observed radiographically in 33–58% of cases [18]. Entheseal radiographic changes are the result of chronic inflammation that led to an irreversible damage. Thus, radiography is not useful in identifying bone lesions at an early stage and does not provide information regarding the status of soft tissues. However, it may be useful in differential diagnosis between the various forms of enthesopathy: a study by Gerster on heel pain showed how the bony erosions are present particularly in patients with rheumatoid arthritis (RA) and AS, while, generally, the erosions are not present in patients with osteoarthritis. Similarly, in the two patient groups enthesophytes had different characteristics: linear and regular in patients with osteoarthritis; irregular and ill-defined margins in patients with AS or RA [19]. Several studies considered bone scintigraphy in the diagnosis of sacroiliitis and to assess lower back pain, but assessment of peripheral enthesitis with this technique is rarely used. Technetium-99m methylene diphosphonate scintigraphy has been shown to be a sensitive indicator of heel enthesitis in a study on 38 consecutive patients with Reiter's syndrome, but its specificity was not determined [20].

In recent years, MRI has played a key role not only in early diagnosis of axial SpA [21], but also in the assessment of peripheral enthesitis. In fact, MRI has a higher sensitivity compared with other radiological modalities and may show swelling of the enthesis and the peritendinous soft tissue, distension of adjacent bursae by fluid collection, erosions, enthesophytes and bone edema near the insertion [22]. MRI bone edema can be detected at the entheseal and subchondral level, but diaphyseal involvement seems relatively specific to PsA [23]. Nevertheless, bone edema is not specific for SpA. In fact, McGonagle *et al.* reported that mechanically induced and inflammatory enthesitis had similar MRI appearances with soft tissue and bone marrow edema at the plantar fascia insertion. However, patients with SpA showed more severe bone marrow edema, and its degree correlated with the presence of HLA-B27,

suggesting that the effect of the *HLA-B27* gene may be mediated in the bone adjacent to entheseal insertions [24]. Studies on knee entheses showed that MRI can recognize entheseal inflammatory involvement in patients with SpA in a subclinical stage, demonstrating the primary involvement of this structure in SpA [25].

However, the study of entheses with MRI is limited because of its reduced availability and high costs [6], as well as the evidence that the normal features of enthesis cannot be recognized with conventional sequences [6,26]. In fact, 'transverse relaxation times' of the fibrocartilaginous enthesis are very short, resulting in absent or low signals with all conventional MRI techniques. To overcome these limitations two new techniques have been recently developed: ULTRASHORT echo time and magic angle imaging [26].

Among imaging techniques, musculoskeletal US, using both grayscale and PD modalities, has an increasing and relevant role in the assessment of SpA, mainly for its capacity to detect enthesitis that may be clinically asymptomatic [2,8,27,28]. In the assessment of entheseal involvement, PD US has been shown to provide the visualization of abnormal vascularization and hyperemia of soft tissues [8,27]. In particular, abnormal vascularization was present only in the SpA patients, while this finding was not observed in the healthy controls [8]. Other findings that can be detected are enthesophytes, thickness and hypoechogenicity of tendon and enthesis, calcifications, bursitis and erosions (FIGURE 1) [29,30]. These features are more present significantly at entheseal sites in SpA patients compared to RA patients [31]. In osteoarthritis, enthesopathy is characterized by gross and well-marginated enthesophytes in fibrocartilaginous entheses, with poor evidence of inflammatory changes of the entheseal tract, a hallmark of SpA [31,32]. Studies on athletes (runners and jumpers) show a high percentage of entheseal abnormalities, such as hypoechogenicity, thickness and calcifications, however, erosive changes have not been reported [33,34]. Thus, US could be a useful tool in differential diagnosis.

Moreover, PD US has been demonstrated to be more sensitive than physical examination in the detection of enthesitis in AS, although there is a discrepancy between clinical and US examination [8,27]. Balint *et al.* found US abnormalities (using Glasgow Ultrasound Enthesitis Scoring) in 56% of five entheseal sites of the lower limbs (superior pole and inferior pole of patella, tibial tuberosity, Achilles tendon and plantar aponeurosis) of 35 SpA patients (27 with AS), suggesting that US is better than clinical examination in the detection of entheseal abnormalities [27]. De Miguel *et al.,* using B-mode and PD US, developed the Madrid Sonographic Enthesis Index in a cohort of 25 patients (19 with AS) compared with healthy controls. This index evaluated, bilaterally, six entheses sites: proximal plantar fascia, distal Achilles tendon, distal and proximal patellar tendon insertion, distal quadriceps tendon and distal brachial triceps tendon. This study confirmed the high sensitivity and specificity of US evaluation in assessing entheseal abnormalities [28]. Borman *et al.* reported pathological US abnormalities at the insertions of Achilles tendon and plantar fascia on the calcaneum in 56.8% of 44 SpA patients, whereas 37% showed signs of entheseal involvement by clinical examinations [35]. D'Agostino *et al.* reported that 161 (98%) of 164 patients with SpA (104 patients with AS) had at least one abnormal enthesis by grayscale combined with PD, demonstrating how US of enthesis is an important tool to assess entheseal involvement in AS and to determine disease activity. The sites most commonly affected were the distal portions of the lower limbs [8]. Lehtinen *et al.* reported that enthesopathic abnormalities were more frequently (66%) found at the distal part of lower limbs (i.e., at patella insertion, Achilles tendon and plantar fascia insertions) compared with the proximal part of the lower limb (i.e., ischial tuberosity and great trochanter, insertion of adductor muscles) in 31 patients with SpA [36]. Kiris *et al.* showed that changes in gray scale combined with PD were more prevalent in lower-extremity entheses, in a group of 30 AS patients [37]. The reasons for predilection of the distal part of lower limbs by the enthesitic process is unknown, but anatomic and physiological factors, such as the major length of the tendon, may play a role. In fact, the major length of the Achilles tendon or its movement on the adjacent bursa may be responsible for a more relevant mechanical injury at this entheseal

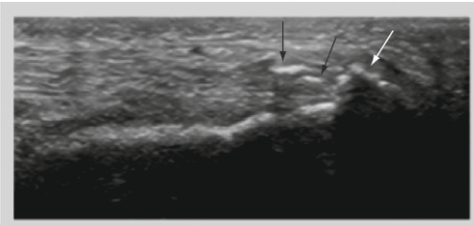

Figure 1. Ultrasound assessment of Achilles tendon. Presence of calcifications (black arrows) and enthesophyte (white arrow) at entheseal sites.

site [8,26]. However, no clear agreement exists on the definition of enthesitis, on the number and which entheses to examine and on US technique, and, as seen for clinical assessment, different sonographic indexes were developed to evaluate enthesitis. Furthermore, US index does not seem to correlate with clinical evaluation and clinical indices. Alcalde *et al.* developed the Sonographic Enthesitis Index in a cohort of 44 patients with AS. In comparison with clinical examination using the MEI, this index did not show correlation with clinical examination and other activity or severity parameters [38]. These results were confirmed by the lack of correlation between presence of erosion, hypoechogenicity, thickness and presence of PD signal at six entheseal sites examinated bilaterally, and clinical evaluation of the same enthesis [2]. Nevertheless, in a recent study Hamdi *et al.* evaluated five entheseal sites (patellar insertion of the quadriceps tendon, proximal and distal insertions of the patellar tendon, and calcaneal insertions of the Achilles tendon and superficial plantar fascia) by clinical indices, radiography and US in 60 AS patients. The sonographic score developed by the authors for enthesitis correlated with the clinical indices [39]. US assessment is also a useful tool to help physicians in joint injection and to detect changes during therapy, such as the response to treatment with anti-TNF [40–42]. Naredo *et al.* evaluated 14 peripheral entheseal sites in 197 SpA patients and showed significant morphological and PD changes after 6 months of anti-TNF therapy [42].

Another interesting tool to assess enthesitis for its capability to combine morphological and metabolic study is PET/CT scans: Taniguchi *et al.* have shown how PET/CT scans can detect enthesitis in a group of SpA patients. In this study eight patients with SpA and seven patients with RA were retrospectively examined, with specific focus on joints and enthesis; furthermore, sensitivity and specificity of PET/CT was compared with MRI and gadolinium scintigraphy. Results show how PET/CT scans can detect accumulation of fluorodeoxyglucose at the entheses in SpA and in the synovium in RA patients. Comparing the data with information derived from MRI evaluation, PET/CT scanning may, at least, have sensitivity and specificity that are equivalent or superior to MRI in the SpA group [5,43].

Conclusion & future perspective

In conclusion, evaluation of enthesitis is essential in AS and other SpAs, especially to monitor disease activity and response to therapy; however, clinical indices need to be validated and standardized. MRI is the only imaging method capable of detecting bone edema, but it was difficult to compare the pathology of both sides or to perform a dynamic examination of the tendons [31]. US appears to be a valid (especially for face and content validity) and reliable tool for enthesitis evaluation, but consensus on enthesitis definition is required in order to improve the quality of studies and the value of US in SpA management. US is a quickly evolving diagnostic technique and advances in US technology, such as the increased availability of high-speed computers and the development of high-resolution transducers, will facilitate physicians in management of AS.

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Executive summary

- Enthesitis, the typical pathological feature of spondyloarthritis, may assume variable aspects.
- However, owing to the low sensitivity of clinical assessment in the detection of inflammatory musculoskeletal changes, peripheral enthesitis is frequently mixed up with other joint and soft tissue disorders by physical examination and its presence may often be underestimated.
- Clinical assessment of entheses have been performed with heterogeneous scoring methods.
- Despite its limitations owing to high cost and availability, MRI represents a significant advance for the early diagnosis of enthesitis-related arthropathies.
- MRI is the only radiological instrument capable of detecting bone marrow edema at entheseal sites.
- Ultrasonography evaluation seems to be a useful tool to evaluate peripheral enthesitis in patients with ankylosing spondylitis and other forms of spondyloarthritis, by detecting abnormalities and inflammation at the entheseal site and to differentiate enthesitis due to spondyloarthritis from other clinical conditions, such as rheumatoid arthritis or mechanical disorders. Thus, ultrasonography evaluation plays a relevant role in the diagnosis of, in the follow-up during therapy and in guiding joint infiltration. Moreover, ultrasonography shows low cost, feasibility and interobserver agreement.

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