Review

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Concepts in monitoring enthesitis in patients with spondylarthritis – the role of musculoskeletal ultrasound

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Abstract

Enthesitis is the key pathological lesion in the spondyloarthritides group and an important element for early diagnosis with a predictive and prognostic value. The recognition of enthesitis on a clinical basis alone remains a challenge and creates unnecessary delays in diagnosis and adequate treatment commencement. Musculoskeletal ultrasound is a valid, reliable, and feasible imaging tool valuable for identifying inflammatory and structural lesions at enthesis level, helpful in establishing a diagnosis, evaluating disease activity and therapy monitoring. This paper focuses on the most relevant aspects of current literature regarding enthesitis and highlights the musculoskeletal ultrasound added value in enthesis assessment.

Keywords: enthesitis, spondylarthropaties, enthesitis scoring system, psoriatic arthritis, ankylosing spondylitis

Introduction

The enthesis defines the insertion region of ligaments, tendons, or joint capsule to the bone. The majority of entheses that are important for clinical evaluation in rheumatologic practice have fibrocartilaginous structure. The term "enthesopathy" designates all pathological abnormalities of ligaments, tendons and capsule insertions including inflammatory and degenerative changes. Enthesitis represents the inflammation involving the enthesis and is regarded as the hallmark for the spondylarthritis group (SpA), including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease related SpA, and undifferentiated SpA.

The inclusion of enthesitis as one of the three main pillars (together with arthritis and dactylits) for the *new* Assessment of Spondyloarthritis Society (ASAS) *classification criteria* for peripheral SpA in 2011, highlights its importance for the clinical practice [1]. Indeed, the European League Against Rheumatism (EULAR) biologic disease modifying drugs (bDMARDs) treatment recommendations for psoriatic arthritis includes active enthesitis as an important finding for treatment commencement if doubled by an insufficient response to nonsteroidal anti-inflammatory drugs (NSAIDs) [2].

The assessment of enthesitis has been performed for a long time through clinical examination and conventional radiography. In the latter years, new imaging modalities such as magnetic resonance imaging (MRI) and ultrasound (US) have been developed, offering a direct visualization of the enthesis and enthesal-related structures. Subsequently, an earlier and a more accurate, inflammatory and structural lesion detection in symptomatic and asymptomatic entheseal areas is expected [3-8].

Concept of enthesis/enthesitis.

The classical concept of enthesis/enthesitis presents enthesitis as a focal disorder of tendon, ligament, or capsule attachment site. The modern concept takes into consideration the "enthesis organ" consisting of the enthesis itself, fibrocartilage, bursa, a pad of synovium covered fat and subchondral bone, components that each contribute to an efficient stress dissipation in the area. Likewise,

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enthesitis refers to a sum of modifications inside these enthesis organ components [9-13].

Clinical evaluation. Clinical scoring systems

Clinical evaluation fails to provide complete information regarding the enthesis involvement. It detects through palpation the presence of local tenderness and global soft tissue swelling. Rarely does it allow a more precise identification of tendon thickening or bursitis. However, acute inflammation cannot be distinguished from chronic changes. Bony changes like erosions and enthesophytes as well as calcifications cannot be identified by clinical evaluation but can be visualized with conventional radiology. However, one important limitation for conventional radiology is the lack of ability to provide information regarding inflammation in the soft tissue structures.

Several attempts to quantify enthesitis in clinical practice has led to the development of validated indices for ankylosing spondylitis (AS) - Mander Enthesis Index (MEI), Maastricht Ankylosing Spondylitis Enthesis (MASES) and Major indices. Gladman and Leeds indices were validated for psoriatic arthritis (PsA) [14-18]. The use of clinical assessment tools for enthesitis has now become widespread in clinical trials despite the fact that there is a persisting debate regarding the choice of an optimal scoring system.

In MEI a total of 66 enthesis (the nuchal crests, the cervical, thoracic, lumbar spinous processes and the costochondral joints- as one group, the manubriosternal joint, the greater tuberosity and the medial and lateral epicondyles of the humerus, the iliac crests, the anterior superior iliac spines, the greater trochanter of the femur, the medial and lateral condyles of the femur, the insertion of the Achilles tendons and plantar fascia to the calcaneus, and the posterior superior iliac spine are evaluated by local pressure and the intensity of pain is graded on a 0-3 scale. The MEI was shown to be sensitive to change in patients treated with NSAIDs but failed to discriminate between different treatment groups in a large placebo-controlled trial of infliximab in AS, possibly due to a low interobserver reliability [19]. The index is time consuming for both patient and doctor, making its feasibility questionable [14].

MASES index was developed to modify MEI to a less time consuming index (more feasible) but with similar validity [15]. It uses a dichotomous 0/1 score for tenderness evaluation. The number of entheses was reduced to 13 (bilateral first and seventh costochondral joints, the anterior and posterior superior iliac spines, the iliac crests, the fifth lumbar spinous process, the proximal insertion of Achilles tendon) after some difficult to localize entheses were excluded. Plantar fascia was not included in the score, thus creating some limitation.

The Major Enthesitis Index is composed of 12 entheses reported to be commonly affected in AS. It includes the iliac crests, the great trochanters of the femur, the medial and lateral condyles of the humerus, the proximal insertion of the Achilles tendon, and insertion of the plantar fascia to the calcaneus [16].

The MEI, the MASES and the Major enthesitis index were all developed and validated for patients with AS.

The Gladman index comprises four enthesitis areas: rotator cuff insertion at the shoulder, tibial tuberosity at the knee, Achilles tendon, and plantar fascia insertions in the calcaneus showing a fair reliability in the assessment of rotator cuff enthesitis, moderate for tibial tuberosity and Achilles enthesitis, and moderate to substantial reliability for plantar enthesitis [17].

The Leeds Enthesitis Index (LEI) consisting of a dichotomus 0/1 quantification system assesses 6 sites: bilateral Achilles tendon insertions, medial femoral condyles, and lateral epicondyles of the humerus. It is the only measure developed specifically for PsA. It has demonstrated the capacity to distinguish between patients with and without active disease and was strongly correlated with other disease activity measures [17,18].

The LEI, MASES, and Major index were proven to be reliable and repeatable tests showing good intra-class correlation coefficients. The MEI, MASES, LEI, Gladman, and Major indices showed a significant response to change at 6 months from baseline [20].

One important limitation of the clinical enthesitis scores under discussion is the questionable specificity for the triggered tenderness in these areas. The assessors' training doubled by a standardized strategy to identify the correct pressure points is obligatory because other conditions may interfere with the accurate examination. Fibromyalgia and the close relationship with some joints may influence the evaluation.

Imaging evaluation

There is currently no gold standard imaging technique to detect enthesitis.

Given the limits of clinical and radiological evaluation, new high resolution imaging modalities, such as MRI and US, have been recently employed to enhance the diagnosis possibility for early and active disease in patients with SpA.

For peripheral enthesis MRI is capable of detecting bone and soft tissue lesions such as diffuse bone marrow edema and perienthesitic edema [21,22]. Unfortunately,

for the soft tissue components modifications, MRI shows lack of sensitivity and specificity generated by the enthesis low water content inside the fibrocartilage, creating visualization difficulties [22,23]. In addition, due to high costs it cannot be performed easily for each patient and even more rarely for the contralateral or for multiple sites.

In the last years, US has been increasingly used in rheumatology settings. Technical advantages such as high resolution real time evaluation and an excellent security profile (non-radiating method, capability to evaluate multiple areas during the same evaluation) doubled by a good reproducibility and feasibility in terms of time, access and economics, have placed US among the preferred imaging methods for enthesis assessment. US evaluation permits the identification of soft tissues inflammatory and structural lesions (grey scale and Doppler mode) and structural bony cortex lesions such as irregularities and erosions [3,4,24-26].

Comparing with clinical evaluation, US is more sensitive and specific in detecting solitary or multiple elementary inflammatory and structural lesions at the level of the enthesis components and identifies subclinical involvement [3,4,27-33]. Indeed, the method has a higher reproducibility in comparison to clinical evaluation [3,4,25,34].

In comparison to MRI, power Doppler ultrasound (PDUS) was suggested to be more sensitive in detecting earlier signs of enthesal involvement having the advantage of contralateral and multiple sites evaluation possibility [35].

The first grey scale enthesis description was published more than 20 years ago by Lehtinen et al, followed in a short time by two other studies [24,36,37]. These studies did not provide an exact description of the different imaging features of enthesitis such as erosion, enthesophyte, and thickness of tendon, ligament, or aponeurosis, nor did they report intraobserver agreement or specificity and sensitivity of the relative examination techniques [3]. The first US extensive descriptions of enthesal involvement in SpA patients were provided by Balint et al (grey scale) and D'Agostino et al (grey scale and Doppler) [3,4]. Of note, the utility of PDUS was highlighted by the capacity to discriminate among SpA and control group and among different types of enthesopathies. Nevertheless, patients with peripheral SpA showed the presence of a more severe enthesal involvement [4,25,38].

Of great value, the presence of PDUS at the enthesis (a landmark feature for SpA) had a high predictive value for diagnosis in SpA in patients with suspected SpA [35].

In clinical practice, the commonest entheseal sites examined by US are: Achilles tendon, plantar fascia, tibialis anterior tendon insertion, greater trochanter, pubis, distal quadriceps tendon insertion, proximal patellar tendon insertion, medial and lateral epicondyles. Entheses of the lower limbs, especially plantar fasciitis and/or Achilles enthesitis, are the most common involved in clinical practice and described as more' specific' for SpA patients [39].

In 2005, the Outcome Measures in Rheumatology (OMERACT) US Task Force defined *enthesopathy* as "an abnormal hypoechoic region with loss of normal fibrillar architecture and/ or thickened tendon or ligament at its bony attachment, seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions or irregularity", describing both findings seen in acute and chronic inflammation as well as in structural damage [40].

New definitions of normal entheses and enthesitis were published recently as a result of a Delphi exercise, having the scope to improve the use of US in identifying the SpA related enthesitis. Therefore, a higher homogeneity in future studies is needed [41]. The US task force group focused on 4 areas of interest as follows: defining a normal US enthesis and other normal anatomis structures, identifying the elementary lesions in B mode and Doppler US to be included in the enthesitis definition after achieving a high expert agreement, defining the elementary lesions, and delineating lesions reflecting inflammation and structural damage.

According to the new published data a *normal enthesis* was defined as an insertion of tendon, ligament, and capsule into bone with regular margin and with the same US appearance and thickness as the corresponding tendons or ligament (fibrillar echotexture or homogenous linear echotexture) and capsule (hyperechoic band). A *normal bursa* was defined as a thin hypoechoic layer surrounded by a hyperechoic line. It was agreed that a normal bursa is visible only in 2 of the considered sites: the patellar tendon insertion on the tibia tuberosity (infrapatellar bursa) and at the calcaneal level, at the insertion of the Achilles tendon (retrocalcaneal bursa); the bursa may contain an iso- or hyperechoic structure corresponding to the echogenicity of the fat pad and therefore, separate definitions for a normal enthesis, normal tendon, and bursa were kept.

The elementary lesions of *enthesitis* included in the definition were: hypoechogenicity, increased thickness of the tendon insertion, calcifications, enthesophytes, erosions, and Doppler activity. Previous OMERACT definitions were preserved except for Doppler activity where a new consensus was elaborated. The Doppler signal at the enthesis was defined as Doppler activity approximately 2 mm near the bony cortex, different from

the reflecting surface artifact or nutrition vessel signal. Hypoechogenicity, thickening, and Doppler signal were considered as *signs of inflammation*, describing acute/active US enthesitis. Erosions, enthesophytes, calcification, and cortical irregularities were included as *signs of structural damage* and therefore suggesting the presence of chronic/inactive US enthesitis. Due to poor agreement, differentiation between acute and chronic enthesitis could not be made [41].

Enthesis assessment technique

Enthesis assessment requires the positioning of the patient acording to the specific enthesis location. High frequency linear or curviliniar transducers are recomended for optimally visualizing these superficial structures [42,43]. The US evaluation (at least in 2 orthogonal planes) is recomended to be performed with the streched tendon or ligament in grey scale, in order to avoid anisotrophy, and with the relaxed structure in color Doppler US. Permanent readjustment of the US machine parameters for depth, frequency, gain, and PRF has to be done [44,45].

Some practical difficulties are worth mentioning: first, for multicenter studies a major challenge is the difficulty in obtaining the settings standardization between different machines and secondly, it is not always easy to find the balance between maximal PD sensitivity and minimal artifacts. Indeed, at baseline evaluation, attention should be given to current therapies, such as NSAIDs, because enthesis vascularization proved to be modified even after one week of treatment [46] .

Ultrasound scoring systems for enthesitis

Different ultrasound scoring systems were developed in the last years in an attempt to standardize the quantitative assessment of the enthesitis. The scoring systems are used for diagnostic purposes [4,25,47] or for responsivness evaluation [48-50]. Some authors proposed semiquantitative grading systems based on grey scale modifications with or without, including PD changes, others developed quantitative scores proposing a cutt off value for differentiating between SpA patients and controls. In some studies, the scoring systems were developed at the enthesal level (mainly at Achilles tendon enthesis) and in some, at patient level allowing the assessment of global enthesal inflammatory activity or structural damage [4,38,51-55]. For PsA, a PD composite score called "Five Targets Power Doppler for Psoriatic Disease" (5TPD) was elaborated by Gutierrez at al and used in a study providing evidence about a multi-target (joint, tendon, enthesis, skin, and nail) monitoring of TNF-a antagonist therapy. It proved to be feasible and reliable and was able to measure globally the perfusion changes induced by TNFalpha blocker [56].

One of the most commonly scoring systems used is the Glasgow Ultrasound Enthesis Scoring System (GUESS) elaborated by Balint et al for the lower limbs in patients with SpA including PsA. It takes into consideration the grey scale elementary components alone, evaluating 5 entheses (18 features, each a score of 1): the superior and inferior pole of the patella, tibial tuberosity, Achilles tendon, and plantar aponeurosis [3].

D'Agostino et al elaborated a five stage classification system relying on grey scale and PD findings at the level of the greater trochanter, pubis, patella (at insertions of the quadriceps femoris and patellar tendons), Achilles tendon, and plantar fascia insertions on the calcaneus, tibialis anterior tendon insertion, and medial and lateral epicondyle [4]. The 5-stage classification was interpreted as follows: stage 1, presumably represented isolated vascular changes occurring during the initial phase of enthesitis, stages 2a and 3a probably reflected increased vascular alterations associated with graded signs of morphologic alterations, stages 2b and 3b, devoid of vascularization, were suggestive of inactive lesions [4].

The Spanish Enthesitis Index (SEI) is a global enthesitis score (at patient level, grey scale elementary components alone) evaluating inflammatory and structural damage at the superior patellar pole (cvadriceps tendon insertion), proximal and distal patellar tendon insertions, Achilles tendon enthesis, plantar aponeurosis at the calcaneus level. This score does not differentiate between the involvement of enthesis, tendon body and bursa. According to the enthesal body concept, the bursa is included in the synovio- enthesal complex [11,13,34].

The Madrid Sonographic Enthesis Index (MASEI) combines abnormalities detected in grey scale and Doppler (PD) at the enthesis level and bursa, bony cortex in both upper (attachment of the triceps tendon on the olecranon) and lower limbs. It is the most complete score system so far and the only one based on the OMERACT definition of enthesopathy. A score >18 demonstrates a high sensitivity and specificity (83.3% vs 82.8%) [25].

At this point, no consensus for the best score to be used in clinical trials and practice has been reached.

OMERACT filter. US validity for assessing enthesitis

Several review papers [5,23,57] demonstrated that face and content validity were found to be generally acceptable. Fewer studies demonstrated the criterion valid-

ity and construct validity [3,4,23-25,34,38,47,51,57-70] where comparators were clinical examination, MRI, X-Ray, and histology. The lack of information is partially explained because of the difficulties in finding the best comparator, the relatively new use of ultrasound in SpA, and a slow rate of disease progression [5,71,72].

OMERACT filter. US discrimination capacity

The reliability of enthesitis US evaluation was tested on static images or acquisition, some of the studies analyzing inter and intra- observer agreement. Generally, the reading reliability was good but with less satisfactory results for acquisition reliability [3,4,23,25,32,34,38,41, 44,47,48, 51,54,55,61,65,73].

There is emerging work demonstrating the sensitivity to change (responsiveness) when examining SpA progression and monitoring response to treatment in grey scale alone or together with PD [48,49,60,74,75].

Enthesitis ultrasound and disease activity monitoring

Monitoring response to therapy using enthesitis assessment is a recent preoccupation. Effective therapeutic options for enthesitis are very limited and include: NSAIDs, local injections, and bDMARDs- TNFalpha blockers.

Two studies have evaluated the sensitivity to change of US in enthesitis evaluation in patients with SpA treated with Sulphasalazine at 6 [36] and 12 months [75], the latter using the GUESS scoring system. Both studies showed no difference suggesting the ineffectiveness of the drug for this condition.

More than 10 years ago, infliximab was proven to be effective in 2 patients with SpA and acute erosive calcaneal enthesitis [60]. Furthermore, the efficacy to TNF-alpha blockers (etanercept, infliximab, adalimumab) at 2 months treatment was reported in 43 AS patients with evaluation at Achilles enthesitis and or retro- calcaneal bursitis (evaluation in grey scale and Doppler) [48]. Naredo et al recently reported the results of a multicenter study performed in 197 patients with different subsets of SpA, showing that enthesal morphologic abnormalities, PD signal, and bursitis were US abnormalities that were responsive to anti-TNF therapy at 6 months and that PDUS can be a reproducible method for multicenter monitoring of therapeutic response in enthesitis of SpA. In contrast, there was no change in calcific deposits at enthesal level or in the cortical abnormalities [26].

However, the study published by De Miguel et al on 68 patients demonstrated that Achilles entheseal erosions in SpA patients are reversible and therefore should not be considered chronic structural lesions. US proved to be sensitive to change when monitoring enthesis erosions at 6 and 12 months and the method is a useful tool for assessing these kinds of modifications [76].

Regarding local CS (iontophoresis), Bethamethasone or Etanercept local US- guided injections, scarce published data is available but showing promising results. SpA patients experienced clinical improvement doubled by a reduction of PD signal [74,77].

Subclinical enthesitis

US has been reported to be more sensitive in comparison to clinical examination in identifying enthesitis. Several published studies have reported significantly higher enthesitis scores in the US assessed groups in comparison to the groups evaluated only by clinical examination. US assessment was made in grey scale alone or combined with Doppler mode, for lower and or upper limbs [3,6,27-31,33,35,62,63,66,69,78] .

The prognostic value of US in subclinical enthesitis was recently assessed in a study by El Miedany et al which concluded that the presence at baseline of synovial thickness, enthesitis, and/or onychopathy associated with positive PD signal and the persistent PD signal over time have relevant prognostic value for the development of articular damage in psoriatic patients [79].

US contrast agents are used in rheumatology clinical research for enhancing the vascularization signal where detection of Doppler signal is hampered due to several factors such as small vessel size, location, slow flow, or Doppler artifacts [46,80]. Regarding peripheral entheses, contrast-enhanced US (CEUS) has already been used to study healthy subjects and it has been demonstrated that normal vascularization of anatomic sites such as Achilles enthesis is not detectable in spite of the enhancement of the vascularization signal, confirming previous results supported by PDUS evaluation [4,81]. So far, CEUS has proved to be useful in confirming a doubtful PD signal or its absence and has improved the detection of enthesitis in SpA patients with a moderate disease.

Conclusions

Enthesitis, a key feature in the clinical picture of the SpA group, has a predictive and a prognostic value and clinical evaluation alone is clearly not sufficient for an accurate enthesis assessment. Early diagnosis of SpA remains a challenge for clinicians because of the poor specificity symptoms and the high frequency of subclinical articular and periarticular structure involvement. In this

scenario, the use of new imaging techniques becomes stringent in order to increase accuracy and sensitivity of clinical and subclinical enthesitis detection. Ultrasound is gaining more and more credibility demonstrating validity, reliability and sensitivity to change doubled by feasibility in terms of access, costs and security profile.

Conflict of interest: none

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