Spondyloarthritis: a journey within and around the joint

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Abstract

Imaging has always been an integral part of the assessment of SpA. This group of diseases involving the axial skeleton and peripheral joints is a particularly intriguing area for sonographers, because it requires the evaluation of both articular and extra-articular regions. Among extra-articular features enthesitis has recently emerged as an area of special interest for both basic science and clinical researchers as well as for those working in the field of musculoskeletal imaging. This review provides information about research in this area focusing on the current concept and definition of enthesitis by US.

Key words: spondyloarthritis, enthesitis, ultrasound, power Doppler.

Introduction

US in the past decade was often used for assessing peripheral involvement of SpA for clinical, educational and research purposes rather than for the assessment of the more frequent axial manifestations of the disease such as sacroiliitis. US can visualize most of the relevant musculoskeletal pathologies associated with SpA, including enthesitis, bone erosions, synovitis, bursitis and tenosynovitis. The exception is osteitis, since the US beam is not capable of penetrating the bony cortex. While conventional radiography allows a clear documentation of the later stages of the inflammatory changes of joint involvement, US (both grey-scale and Doppler) are sensitive enough to also detect early inflammatory lesions.

US features of synovitis, erosion and tenosynovitis in SpA patients generally do not differ from those observed in other inflammatory arthritides including RA or PsA. The main difference is related to the US appearance of enthesitis, i.e. inflammation at the insertion of tendons, ligaments and capsules into the bone.

Enthesitis or enthesopathy?

In the literature, the term enthesitis (i.e. inflammatory involvement of the enthesis) and enthesopathy (i.e. pathological involvement of the enthesis whatever the cause) are often used as synonyms; however, we prefer to use enthesitis only for inflammatory involvement related to SpA. Clinicians and researchers investigated enthesitis as the probable fundamental lesion responsible not only for entheseal involvement in itself, but also as an initial and/or additional process of synovitis, dactylitis and sacroiliitis [1].

In addition to peripheral arthritis and dactylitis, enthesitis is included in several available classification criteria for SpA, including the most recent criteria [2].

Examining the morphology and function of entheses is essential to understanding the process and phenomenon of enthesitis.

We can distinguish two types of enthesis according to their anatomical properties: fibrocartilaginous and fibrous. The two types have different histological features. The fibrocartilaginous enthesis consists of the tendon, non-calcified fibrocartilage, calcified fibrocartilage and adjacent bone. The two layers of fibrocartilage are virtually separated by the tidemark. Defining fibrocartilage remains a challenge since it is considered by many as a sort of half-way structure between cartilage and dense collagenous connective tissue, but is actually closer in its conformation to connective tissue than to cartilage [3]. Most of the histological studies describing this tissue are based on the analysis of lower limb entheses.

Fibrocartilage was described as being within the Achilles enthesis itself (enthesal fibrocartilage); however, analogous tissue may also be found on the surface of the
calcaneus facing the enthesis (periosteal fibrocartilage) and also in the inner surface of the Achilles tendon which faces the calcaneus (sesamoid fibrocartilage) \[3\]. This seems to denote that the retrocalcaneal bursa is only partly covered by a synovial lining, while the rest is covered by fibrocartilage. The same phenomenon may also be observed at other entheses, including the tibial tuberosity enthesis and the deep infrapatellar bursa.

This observation, associated with the clinical symptoms reported by patients, who frequently describe articular pain far from the anatomical entheseal attachment, has led a group of researchers to distinguish between two concepts of entheseal involvement: one strictly localized to the bony interface in which the involved structures include fibrocartilage, subchondral bone and related bone marrow and its respective neural and vascular network; and the other more related to clinical symptoms in which adjacent structures are also included, such as adjacent bursae or synovial membrane-lined fat pads \[3\]. In this sense, this group has suggested that the enthesis should be considered as an organ or unit in which all continuous collagenous connective tissue fibres running over and along a fibrocartilage structure are considered as part of the enthesis, even without the presence of an actual tendon or ligament insertion. Figure 1a shows knee and Fig. 1b shows heel anatomy, including the superior pole, inferior pole of the patella and tibial tuberosity enthesis and the Achilles and plantar aponeurosis enthesis.

Despite considerable developments in US technique, the past 10 years have seen the emergence of more research questions that need to be answered. In the near future, high-end US machines will be capable of depicting fibrocartilage. At this moment ultrasonographic scans of fibrocartilage have only been published using bovine specimens \[4\]. Differentiating between normal and pathological fibrocartilage by US remains a challenge.

One explanation that may provide a link between the two concepts can be related to the duration of disease at the attachment site. If the disease is long-standing or very active, the inflammation transcends the limits of the anatomical insertion to involve the adjacent structures as well.

Demonstrating the presence of local inflammation at the entheseal insertion establishes the enthesitis as a landmark feature of SpA. Examination of the pathological enthesis in SpA has demonstrated local inflammation with CD4⁺ and CD8⁺ T lymphocyte cell infiltration, oedema, angiogenesis, fibrosis, osteitis, erosion and new bone formation \[5\]. Inflammation may occur at any enthesis in SpA, but clinically detected symptoms of enthesitis are more frequently detected in the entheses of the lower limbs, probably for mechanical reasons. The US examination of these entheses confirms the frequency of their involvement \[6\]. However, we cannot exclude that the frequency of enthesitis may be artificially increased and explained by the accessibility of those entheses to

**Fig. 1** Continuous fibres run along the length of the tendon or aponeurosis and may even connect two or three entheses (arrows).
US. In fact, when the entheses of the upper arms are examined, the entheses of the elbow, in particular the Insertion of the common extensor tendon, appears to be frequently involved [6].

**US appearance of enthesitis**

Extensive description of enthesal involvement in SpA patients by US was initially provided by Lehtinen et al. in 1994 [7] followed by the study of Balint et al. in 2002 [8] and that of D’Agostino et al. in 2003 [6]. The first two authors described the grey-scale US abnormalities of lower limb enthesis of SpA, revealing a high frequency of asymptomatic findings, while the third described for the first time corresponding power Doppler findings. Grey-scale US permits us to depict the signs of both acute and chronic inflammation of enthesis as well as structural damage.

Grey-scale scans of enthesitis are characterized by the loss of the normal fibrillar echogenicity of the tendon insertion with or without an increase in tendon thickness or by intralosional focal changes at the tendon insertion, such as calcium deposits, fibrotic scars and periosteal changes (erosions or new bone formation). Additionally, involvement of the body of the tendon far from the enthesis and of adjacent bursae may be observed; however, these two processes can also be observed in the absence of enthesitis in other inflammatory and non-inflammatory diseases.

The anatomical borders of the enthesis should also be taken into account within the framework of new definitions and recommendations. It is still unclear as to what extent the soft tissue part of tendons and ligaments needs to be included in the examination. The principal focus of attention should be directed to the part adjacent to the bone surface; however, we know from clinical experience that thickening of the tendon or ligament is more commonly detected somewhat removed from the bony attachment. It should be noted, however, that moving too far away from the actual entheseal insertion also has its dangers. In our view, mid-portion (fusiform) tendinopathy of the Achilles tendon represents a totally different pathological and imaging entity, wholly distinct from enthesitis.

The elementary US features of enthesitis were listed in a recent systematic review that analysed 48 research papers [9]. Enthesitis was mainly characterized by increased thickness (94% of studies) and hypoechogenicity (83% of studies) of different soft tissue structures. Signs of structural damage, including enthesophytes, erosions, calcifications and cortical irregularity were less representative. Interestingly, 46% of studies included associated bursitis as a characteristic sign among the criteria of enthesitis. Although all recent studies included a pathological Doppler signal among the criteria, altogether only 46% of studies included Doppler US assessment. This systematic review also highlighted the lack of consensus definition for enthesitis. This was also observed for other US studies and defined pathological lesions such as synovitis, tenosynovitis, etc. For this reason the OMERACT task force produced the first preliminary US consensus definitions of the most frequently detected pathologies [10]. The group at that time decided to define enthesopathy (general involvement of the enthesis irrespective of the origin) instead of enthesitis: abnormally hypoechogenic (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 a Doppler signal and/or bony changes including enthesophytes, erosions or irregularity.

Taking into account other aspects such as age and gender may cause considerable problems when attempting to formulate a uniform definition of enthesitis. At age 18, an enthesophyte in grey scale may be accepted as a pathological sign of enthesopathy due to inflammation or to mechanical impact, in view of the frequency of this finding in the general population and its association with pathological conditions. The same phenomenon, however, occurs much more frequently at age 80, probably due only to the ageing process, and should not be considered as a pathological sign in this population.

Moreover, US technique has undergone fundamental changes in the last decade, and Doppler technique has become a fundamental part of the assessment of synovitis and enthesitis and is likely to be included in the new criteria for the US assessment of enthesitis, despite being underrepresented in the studies of the last 10 years as compared with grey-scale features of enthesitis. Before a consensus definition of enthesitis can be reached and subsequently validated, the elementary grey-scale and power/colour Doppler US lesions and their relationship with enthesitis and other forms of enthesopathy, as suggested in Fig. 2, must be evaluated. This review also demonstrated that in addition to the robust variability of accepted US signs of enthesitis, face and content validity were found to be generally acceptable; however, criterion and construct validity results are still missing and need to be evaluated. Only a few studies have compared US and MRI of enthesitis and have led to controversial results [11, 12]. In one study, US demonstrated better sensitivity in detecting enthesitis than MRI; however, other studies have shown opposite results [12]. This is probably due to the fact that the two techniques examine different aspects of the enthesitis and that the definition and border of the enthesis were not defined, leading the authors to put together tendon, bursa and enthesis in the definition of enthesitis involvement. Finally, the review showed the capability of the technique to reliably assess the presence of enthesitis [13, 14].

**How to score activity and severity of peripheral enthesitis by US**

Following the development of the Glasgow University Enthesitis Scoring System (GUESS) [8], new scoring systems have also been formulated. The Madrid and French scores [6, 15, 16] were each evaluated recently; however, large international, multicentre studies assessing validity for sensitivity to change instead for diagnostic purposes.
are still lacking, hindering the routine use of such instruments in both clinical practice and clinical trials. Only a few studies have evaluated the sensitivity to change of US in SpA patients following anti-TNF-\(\alpha\) treatment [17].

**What is the diagnostic value of the technique?**

Several studies have recently shown the impact of US in the early diagnosis of SpA [15, 16, 18]. However, the differential diagnostic capabilities of US should continue to be tested to determine to what extent US can differentiate between enthesitis and local non-inflammatory conditions, e.g. Sinding–Larsen–Johansson disease (patella), Osgood–Schlatter disease (tibial tuberosity) or Sever’s disease (calcaneus).

New US techniques such as elastography, contrast ultrasonography and 4D ultrasonography are currently under evaluation for their use for both adult and paediatric enthesitis. In conclusion, US is an important tool for the evaluation of peripheral involvement of SpA, especially in the diagnosis and follow-up enthesitis.

### Rheumatology key messages

- Power Doppler US permits a complete evaluation of SpA enthesitis.
- Inflammation and structural damage should be differentiated for quantifying enthesitis.
- Further validation is needed as US is an evolving technique.

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