

Enthesitis in psoriatic arthritis (Part 2): imaging

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Abstract

Enthesitis is a hallmark finding in PsA and may predate the onset of synovitis. Clinical examination of enthesitis provides no structural information, relies on eliciting tenderness at enthesal sites and may not be sensitive or specific. Soft tissue imaging techniques such as musculoskeletal ultrasound and MRI can depict ultrastructural and inflammatory changes. Although these imaging techniques are complimentary, ultrasound can image superficial entheses with high fidelity and examine vascularity with the use of Doppler but cannot image subchondral bone. MRI depicts bone and can visualize bone marrow edema as well as soft tissue edema. However, due to short relaxation times, enthesal structures are not easily differentiated. There has been increasing recognition of biomechanical confounding, especially since the majority of the entheses examined are in the lower extremity. Imaging enthesal indices are being developed to minimize the effect of body weight and activity. In the following article, contemporary concepts of entheses in relation to imaging will be reviewed as well as important confounders in assessing enthesal alterations. The role and limitations of imaging techniques will be discussed.

Key words: musculoskeletal ultrasound, magnetic resonance imaging, high-resolution computed tomography, enthesitis, psoriatic arthritis, biomechanical confounding

Rheumatology key messages

- Soft tissue imaging of entheses by ultrasound or MRI may be more sensitive than clinical examination.
- There is increasing recognition that biomechanical confounders affect the specificity of imaging of inflammatory enthesitis.
- The choice of entheses and ultrastructural changes impacts the specificity of enthesal imaging outcome measures.

Introduction

Enthesitis is a key manifestation of PsA and, as discussed in the accompanying supplement articles, has a significant impact on patient morbidity and function. Furthermore, in PsA patients, enthesitis is associated with radiographic damage in peripheral and axial joints. As a key manifestation, it has been included in the Classification Criteria for Psoriatic Arthritis (CASPAR) [1] and as a treatment domain for the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment guidelines [2].

Entheses – emerging concepts

Entheses are tendons or ligaments that attach to the bone. There are two main histological types of entheses: fibrous entheses and fibrocartilaginous entheses. Fibrous entheses have fibers that are directly encased in bone. Fibrous entheses such as the deltoid insertion are characterized by having a limited angle of excursion. An essential property of entheses is to dissipate force. A zone of fibrocartilage prior to the osseous margin allows for better dissipation of mechanical energy to allow for a wider angle of excursion [3]. Enthesitis related to SpA occurs at fibrocartilaginous entheses. Examples of fibrocartilaginous entheses include the supraspinatus insertion, patellar ligament attachments and Achilles tendon insertion [4]. Clinical examination of entheses depends on eliciting tenderness on direct palpation of the insertional site and may be not only nonspecific and insensitive [5], but also does not inform of the degree and chronicity of underlying structural changes. Imaging may be used to assess soft tissue and osseous changes associated with

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enthesitis to enable earlier diagnosis of inflammatory enthesitis as well as an opportunity to follow response to therapy.

Plain radiography

Conventional radiography is useful to document articular and periarticular features of PsA, such as erosions or new bone formation [6]. It is also useful in evaluating the spine and sacroiliac joints for evidence of SpA associated with PsA. Calcification at entheses was systematically studied at the hip and heel as well as other available plain radiographs in the CASPAR study [7]. The study enrolled 588 patients with physician-defined PsA (of which 53% had clinical enthesitis) and 525 controls, the majority of which had RA. When compared with RA subjects, PsA patients had a 3 times greater odds ratio for the prevalence of new bone formation at the inguinal ligament, sartorius and rectus femoris muscle attachment to the ilium. Although these findings were specific, the low sensitivity limits using plain radiography of these sites to distinguish PsA from RA. Although the median duration of PsA was 10 years, very few patients were found to have erosions or enthesal bone formation at the heel. The authors concluded that plain radiography for evidence of enthesopathy at major sites could not be reliably used to distinguish PsA from RA.

High-resolution peripheral quantitative CT imaging for entheses

Despite the limitations of plain radiography, there has been considerable interest in characterizing bone formation, particularly at enthesal sites around small joints. High-resolution peripheral quantitative CT can visualize bone microstructure in great detail and has been validated in osteoporosis research [8]. In a study of 30 PsA patients compared with 58 RA patients, high-resolution CT (HRCT) of the hand demonstrated differences in erosion morphology between the two groups [9]. Also, a higher number of 'osteophytes' were seen in the PsA group, which seemed to surround the entire bone circumference as a corona. A later study by the same authors used HRCT to examine 25 PsA patients compared with 25 patients with hand OA and 20 healthy controls [10]. HRCT of the dominant hand revealed that patients with PsA and OA had similar numbers of bone spurs. However, the location of bone formation in PsA patients was mostly at the radial aspect of the second MCP joint, whereas patients with OA had a predominance of bone formation on the dorsal and palmar aspects. Anatomic correlation suggested that bone formation in PsA subjects was prominent in the enthesal regions. Subjects with hand OA had bone spurs at the cartilage–bone margin and the joint margins. Interestingly, HRCT was used to examine 55 psoriasis patients without musculoskeletal complaints and 47 health volunteers. More enthesophytes were found in psoriasis patients

compared with controls [11]. These tended to be larger and occur on the dorsal and palmar surfaces of the metacarpal heads, which the authors suggested to be sites of functional entheses. New bone formation was therefore reported in psoriasis patients before symptoms of PsA developed. Three studies have examined enthesophyte progression in response to therapeutic intervention. Two of them were of 24 week duration, which is not a meaningful period of time to study changes in bone formation [12, 13]. A 1 year study examined MCP joints by HRCT in PsA patients treated with anti-tumor necrosis agents or methotrexate [14]. In both groups, progression of bone formation was seen, suggesting that, as in AS, current therapies may not retard enthesal bone formation.

Dual-energy CT using iodine overlay

Dual-energy CT obtains images using two X-ray tubes of different voltages, and hence energy levels. Tissue differentiation can be depicted with the aid of postprocessing software. The most common use of this in rheumatology is to depict gout deposition. A recent addition to this technique has been to map iodine after iodine contrast material has been administered [15]. The resultant image maps soft tissue lesions over the CT image. Although X-ray radiation is used, the images are acquired rapidly and are of relatively high spatial resolution. At small joints such as the distal IP joints, the resolution may be greater than that of MRI. Preliminary studies in PsA patients have reported the depiction of finger extensor tendon enthesitis, collateral ligament enthesitis, flexor tendon tenosynovitis and extensor tendon paratendinitis [16]. It remains unclear if enthesal structures can be delineated and whether this technique is feasible because of its use of radiation and intravenous contrast.

Sonographic imaging of entheses

In previous sections, the discussion has been mostly about 'damage' due to enthesitis. In order to assess enthesitis disease activity, as well as detailed enthesal alterations, soft tissues need to be imaged. Two common modalities include musculoskeletal ultrasound (MSK-US) and MRI. MSK-US utilizes nonionizing imaging to visualize nonaxial entheses in great detail, as the majority of them are superficial. Also, the vascularity of the entheses can be examined without the use of contrast. MSK-US can provide images in high resolution but cannot image below the bony cortex. MRI, which will be discussed below, can image bone and depict bone edema in addition to soft tissue changes.

In the following section, emerging insights into important biomechanical confounders will be highlighted. Due to significant mechanical loading, fibrocartilaginous entheses are prone to overuse injuries. At single enthesal areas, it may not be possible to distinguish changes due to overuse from those of SpA [17]. This has

important implications for the selection of entheses, especially in PsA, where there are a significant proportion of patients who are obese. Using the Madrid Sonographic Enthesitis Index (MASEI), Eder *et al.* [18] demonstrated that they could not distinguish between healthy controls and patients with psoriasis or PsA when the BMI was >30. Similarly, Wervers *et al.* [19] could not distinguish PsA patients from healthy young volunteers using the MASEI methodology. The main emerging biomechanical factors are therefore mechanical loading due to obesity as well as repetitive physical activity or overloading. Also, distinguishing diseased vs physiologic enthesal changes in physically active adults may be difficult at some entheses.

Sonographic indices were developed in patients with AS or in mixed populations and did not account for these confounders. Of note, most of these indices include lower extremity entheses that are prone to mechanical loading. The ideal balance for an enthesal index is the selection of entheses that are frequently affected in PsA but minimally affected by biomechanical confounders. A summary of the conventional indices is given in Table 1. The GRAPPA ultrasound group [20] has attempted to ameliorate these confounders by using a data-driven approach to select entheses (Table 1). As a result of the regression elimination of enthesal sites from pilot data, more upper extremity entheses were included compared with the other indices, which may minimize the impact of obesity on the proposed GRAPPA ultrasound index. Another approach has been to study entheses of the hand. Zabotti *et al.* [21] demonstrated that ultrasound of the entheses of the hand and finger could differentiate early PsA from early RA. The key discriminative lesions included MCP joint peritonitis and proximal IP joint central slip enthesitis.

Enthesitis ultrastructural changes

Alterations in the enthesis in patients with SpA not only occur at the attachment but also in the surrounding

force dissipation structures. These include the adjacent tendon, bursa and bone. Bony changes on sonography can be seen as superficial erosions. Of note, one drawback of sonography is that it cannot visualize structures below the cortex and hence bone edema cannot be detected. However, changes to the entheses and adjoining tendons, such as thickening and increased hypoechogenicity, as well as bursitis, may be reversible on appropriate treatment. In contrast, enthesophyte formation, intratendinous calcification, intratendinous tears and bone erosions are nonreversible and are considered indications of damage [25]. The OMERACT ultrasound enthesitis group has published a consensus-based definition of enthesitis that includes changes to the enthesis and bone but not adjacent bursa or tendon. Furthermore, the definition restricts the Doppler signal to within 2 mm of the cortical bone margin, which is problematic since it does not account for enthesis size. Also, the group found that the prevalence of Doppler signal was higher with a tendon attachment area at >2 mm [24]. Macia-Villa *et al.* [23] examined the prevalence of Doppler signal at the enthesis in 27 active PsA patients. Doppler signal was present in 81.5% of their patients and always appeared in more than one area of the enthesis complex. The GRAPPA Ultrasound Working Group has proposed a data-driven approach where Doppler signal will be analyzed according to the location within and distal to 2 mm of the bone cortex as well as the bursa [20]. This is keeping with increasing awareness that there are increased inflammatory mediators in insertional tendinopathies [26] that which may overlap with those due to enthesitis.

Role of sonography for differentiating PsA inflammatory disease from central sensitization

One key use of sonography is to provide objective evidence of inflammation when there is patient-evaluator

TABLE 1 Selected ultrasound enthesal indices

Site	GUESS	MASEI	GRAPPA US	OMERACT US
Bilateral Achilles enthesitis	+	+	+	+
Bilateral plantar fascia	+	+	+	-
Bilateral proximal patellar ligament attachments	+	+	+	+
Bilateral distal patellar ligament attachments			+	-
Bilateral quadriceps insertion	+	+	+	+
Bilateral triceps insertion	-	+	+	-
Bilateral lateral epicondyle	-	-	+	+
Bilateral supraspinatus	-	-	+	-
Doppler within 2 mm of the cortex of the enthesitis	-	+	+	+
Doppler >2 mm from the cortex of the enthesitis	-	+	+	-
Doppler at bursa	-	+	+	-

GUESS: Glasgow Ultrasound Enthesitis Score [22]; MASEI: Madrid Sonography Enthesitis Index [23]; GRAPPA US: proposed enthesal sites by the GRAPPA Ultrasound Working Group [20]; OMERACT US: proposed enthesal sites by the OMERACT Ultrasound Enthesitis Working Group [24].

discordance, such as in pain sensitization syndromes. A significant proportion of patients with PsA may have coexisting central sensitization syndrome, which may bias clinical outcome measures. When evaluating newly presenting patients, one question may be to differentiate FM syndrome from PsA. Marchesoni *et al.* [27] reported in a multicenter cross-sectional study that the number of clinical symptoms and tender points had the highest discriminating power in separating these groups. Thirty patients, each with PsA, also underwent sonography. When sonographic signs of enthesopathy were utilized in three or more entheses, the two groups could be separated with moderate discrimination [28]. Marchioni *et al.* [29] found similar findings in a more extensive multicenter cross-sectional study. Of note, the frequency of clinical enthesal tenderness was higher in FM syndrome patients and sonographic features of chronic and inflammatory features were more common in PsA patients. Although the BMI in this group of patients was $<30\text{ kg/m}^2$, age and BMI influenced overall sonographic B-mode structural scores, underpinning the importance of biomechanical factors in the expression of enthesopathy.

MRI for evaluation of entheses

MRI is a sectional imaging technique that produces fat-sensitive (T1 weighted) or water-sensitive (T2 weighted) images. Furthermore, short tau inversion recovery (STIR) sequences suppress fat and are useful to demonstrate bone edema in addition to other water-sensitive pathologies such as synovitis and tenosynovitis. Gadolinium contrast, coupled with T1 weighted imaging, depicts tissue vascularity. Although MRI offers excellent potential in imaging enthesal structures, there are important technical considerations. For example, high-resolution images need higher-strength magnets and coils compared with the low Tesla (0.2 T) equipment available at the point of care [30]. Also, technical details such as slice thickness and the angle of tendons to avoid magic angle artifacts are important considerations that affect image fidelity [31]. Lastly, conventional parameters used for MRI do not adequately characterize tendons and entheses because the enthesis and adjoining tendon have short transverse relaxation times. MR signals from these tissues decay rapidly, and because no information is received, the tissues appear dark. In order to overcome this problem, protocols using ultrashort echo times are being developed [32–34]. In a recent study of cadaveric ankles, the enthesis could be seen separately from the tendon using an 11.7 T magnet and ultrashort echo time sequences [34]. Due to a lack of ultrastructural detail, MRI may not be useful in distinguishing patients with enthesitis from those with other inflammatory arthritides or healthy subjects [35, 36]. Interestingly, in a recent study of heel and knee entheses by both MRI and ultrasound, neither modality could distinguish between peripheral SpA patients and healthy subjects [35]. At the heel, only B-mode changes distinguished

the two groups, and MRI findings were similar. In an earlier study, inflammatory findings by MRI or ultrasound of the heel could not distinguish SpA patients from healthy subjects [37]. Altogether, this is yet further evidence for the biomechanical overlay of findings at the entheses, which has important implications for diagnostic and therapeutic studies.

In a recent systematic literature review on MRI in diagnosing and monitoring enthesitis in patients with SpA, lack of a validated, comprehensive scoring system was recognized but technical limitations were not addressed [38]. The OMERACT MRI group has reported efforts in developing an MRI scoring system for SpA/PsA using the heel as a model [39]. Both inflammatory and structural abnormalities were included in the preliminary heel enthesitis scoring system (OMERACT-HEMRIS). Among all readers, inflammatory changes had good interreader reliability, while structural changes such as enthesophyte formation and bone erosion had poor reliability.

One of the key disadvantages of MRI is the limitation to a single body area for scanning. Whole-body MRI (WB-MRI) is currently being advanced as a technique that can image multiple areas of the body in one scan done in $<1\text{ h}$ [40]. WB-MRI was initially developed to image from the head to the pelvis for metastases. The technique has been adopted to view the whole body. Of note, additional body coils are needed for the extremities and gadolinium may be needed to elicit subtle enthesitis [41]. Two studies using WB-MRI in PsA patients have reported increased sensitivity of detecting enthesitis based on bone marrow edema at enthesal sites compared with clinical exam [41, 42]. However, in one study, signs of enthesitis were also present at several enthesal locations in healthy subjects [42]. These findings further reinforce the contemporary theme of biomechanical confounding at entheses. The OMERACT MRI group is developing scoring systems for WB-MRI. It remains to be seen if the specificity of findings at the entheses can be improved.

Future directions

Sonography and MRI can image many of the peripheral entheses and provide ultrastructural information as well as relative vascularity of the structures. Given the significant biomechanical confounders, further research needs to be done to establish a candidate set of entheses that can be used across diverse populations. Similarly, the choice of ultrastructural elements, as well as the region of vascularity, needs to be examined across populations with a wide range of BMIs and physical activity. Finally, imaging of enthesal and force dissipating structures is providing an anatomical backstage for understanding the interplay between innate and adaptive immunity in daily life as well as in patients with PsA.

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