Enthesitis: A Hallmark of Psoriatic Arthritis

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Enthesitis: A hallmark of psoriatic arthritis

Gurjit S. Kaeley, MBBS, MRCP, Lihi Eder, MD, PhD, Sibel Z. Aydin, MD, Marwin Gutierrez, MD, Catherine Bakewell, MD

Introduction

Psoriatic arthritis (PsA) is a form of chronic inflammatory arthritis affecting nearly 30% of patients with psoriasis [1]. Although PsA may present at any point in a patient’s life, it most commonly occurs between the ages of 30 and 50 years [2,3]. In almost 85% of patients, psoriasis will develop before PsA, but in 10–20% of patients, the symptoms will either appear concomitantly or the symptoms of PsA will precede those of psoriasis [4].

Moll and Wright originally divided PsA into 5 broad categories based on clinical characteristics: (1) predominant involvement of distal interphalangeal (DIP) joints, (2) arthritis mutilans (with digital telescoping or the doigt en lorgnette deformity), (3) symmetric arthritis only distinguished from rheumatoid arthritis by negative serology, (4) mono- or oligoarthritis, and (5) predominant ankylosing spondylitis [5].

The CLASSification criteria for Psoriatic Arthritis (CASPAR) was developed in 2006 as a means to standardize the classification of PsA for clinical trials and observational studies and help differentiate it from other forms of arthritis [6,7]. These criteria demonstrate that musculoskeletal inflammation of the joints, spine, or entheses is central to the recognition of PsA. More recently, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has highlighted 6 commonly accepted clinical domains of PsA—peripheral arthritis, axial disease, enthesitis, dactylitis, skin disease, and nail disease— that should be considered when treating patients [8].

Objective: To describe the growing importance of enthesitis in patients with psoriatic arthritis (PsA) and discuss the advantages and disadvantages of clinical and imaging methods currently used to assess enthesitis.

Methods: PubMed literature searches were conducted using the terms psoriatic arthritis, entheses, enthesitis, pathology, imaging, ultrasound, magnetic resonance imaging, clinical, and indices. Articles were deemed relevant if they provided insight into the pathology, monitoring, and/or diagnosis of enthesitis in PsA, or if they discussed clinical or imaging indices used to assess enthesitis.

Results: Enthesitis is an early manifestation of PsA that is associated with increased disease activity and reduced quality of life. A variety of clinical indices exist to assess enthesitis in PsA; however, the Leeds Enthesitis Index and Maastricht Ankylosing Spondylitis Enthesitis Score index have been the most frequently used indices in recent clinical trials. Limitations of these indices include an inability to discern structural involvement, risk of missing subclinical enthesitis, and lack of sensitivity in detecting enthesitis, especially in patients with central sensitization and/or pain amplification. Such limitations have led to the emergent importance of imaging techniques in the assessment of enthesitis. Although there have been recent advances in magnetic resonance imaging, ultrasound (US) appears to be the preferred method for detecting enthesitis because it allows for accurate assessment of the soft-tissue components of entheses and also for new bone formation. Hypoechogenicity, increased thickness of tendon insertion, calcifications, enthesophytes, erosions, and Doppler activity have been identified as important US characteristics of enthesitis.

Conclusion: Enthesitis is thought to be integrally involved in the pathogenesis of PsA and is associated with worse prognostic outcomes in patients with PsA. A validated US index with entheses that are less confused by mechanical factors and obesity would be the most effective measure of enthesitis in PsA. As imaging techniques continue to advance, our understanding of enthesitis and its involvement in PsA will also improve.

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An enthesis is a location where the tendon, ligament, or joint capsule inserts into the bone to facilitate joint motion [9,10]. Entheses are considered either fibrous or fibrocartilaginous, depending on the tissue present at the attachment site [9]. While enthesopathies can result from metabolic syndrome, these tend to occur at membranous entheses [11]. Inflammatory enthesal changes associated with spondyloarthritis almost always occur at fibrocartilaginous attachments [9,12]. As suggested by the CASPAR criteria as well as GRAPPA recommendations, inflammation of the entheses (enthesitis) is important to the identification, diagnosis, and treatment of PsA [7,8].

Enthesitis has been reported to occur in 35–50% of patients with PsA and is more common in PsA than other forms of arthritis such as rheumatoid arthritis, ankylosing spondylitis (AS), and osteoarthritis [2,13–16]. Further, enthesitis has recently been associated with radiographic damage in the peripheral and axial joints of patients with PsA [58]. When all these factors are taken together, enthesitis is emerging as an important marker, necessary both for differentiating PsA from other forms of arthritis and identifying the severity of the disease.

Clinically identifying enthesitis in patients with PsA can be challenging. Enthesitis may be asymptomatic or mimic symptoms of other conditions such as mechanical injury and tendinitis [17]. Although several indices have been established to measure enthesitis, many of these indices were developed specifically for patients with AS [17]. Additionally, the close proximity of entheses to the synovium often makes clinical diagnosis problematic [17].

Clinical limitations have led to the emergent importance of imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI), which are capable of detecting soft-tissue and osseous inflammatory changes. Recently, whole-body MRI has shown potential for identifying subclinical enthesitis in the greater trochanter and Achilles tendon [18]. Although there have been recent advances in MRI, US appears to be the preferred method for detecting enthesitis because it allows for accurate morphostructural assessments of entheses, including identification of new bone formation as well as functional evaluation of vascularization using Doppler technology. Additionally, US can be more sensitive than MRI in detecting early changes to the enthesal fibers of the heels and knees [19]. Finally, US is cost-effective and allows real-time evaluation by the clinician [20]. To date, different US indices to evaluate enthesitis in patients with PsA have been proposed. Despite this, there is no consensus on which indices should be used in clinical trials and daily practice [21].

In this review, we discuss the prognostic value of diagnosing enthesitis, clinical indices used to monitor enthesitis, and the growing role of imaging techniques such as MRI and US in the identification of enthesitis in PsA.

**Methods**

Relevant literature in the field published in the last 20 years was screened. We included original articles published between January 1996 and December 2016. A targeted literature review was performed in PubMed using the following search terms in all possible combinations: psoriatic arthritis, entheses, enthesitis, pathology, imaging, ultrasound, magnetic resonance imaging, clinical, and indices. Titles, abstracts, and full reports of the identified articles were screened for relevance. Search results were supplemented based on the reference citations in articles identified in initial searches and based on the authors’ familiarity with the published literature. Articles were deemed relevant if they presented data or provided insight into the pathology, monitoring, and/or diagnosis of enthesitis in PsA, or if they discussed clinical or imaging indices used to assess enthesitis. Articles were omitted if they were case reports, letters to the editor, and/or not published in English.

**Basics of entheses and enthesitis**

Entheses are commonly categorized as fibrocartilaginous (occurring at the apophysys or epiphyses of bones) or fibrous (characteristic of attachments to the metaphyses or diaphyses), and as previously described, are defined as the locations where the tendon, ligament, or joint capsule inserts into the bone to facilitate joint motion [9,12,22]. More recently, entheses have also been classified as part of a larger anatomical group known as the enthesis organ, rather than merely the anchoring location of tendons or ligaments [23]. This organ consists of surrounding structures—fibrocartilage, bursa, fat pad, adjacent cancellous bone networks, and investing fascia—that functionally adapt in order to dissipate stress at the soft- and hard-tissue interface [23,24]. The concept of the enthesis organ has been important in understanding enthesopathies, including enthesitis, as well as explaining sonographic changes observed at entheses [23,25].

The relationship between the pathophysiology of enthesitis and PsA

Currently, 2 models exist to explain the pathogenesis of PsA. Traditionally, PsA was thought to be initiated by an autoimmune reaction driven by an adaptive immune response [26]. Recently, it was proposed that an innate immune response to an autoinflammatory reaction at predisposed sites is the triggering mechanism for PsA [26].

According to the traditional model, T-cell directed autoimmunity against a common skin and joint autoantigen leads to chronic inflammation in patients with psoriasis and PsA [26]. Although no such common antigen has been found [26], some studies have demonstrated that autoimmunity against fibrocartilage proteins (such as aggrecan and the proteoglycan versican) may result in enthesitis and spondylitis [24]. Further, the microbiota has also been implicated in the development of joint disease [24]. Although this model has appeal, specific features of PsA such as new bone formation, bone edema, periostitis, and dactylitis are not dependent on synovitis and are, instead, centered on enthesitis [26].

The enthesis organ, of which the synoviointhesal complex is a part, is critically important in dissipating the stress resulting from repetitive forces on entheses (Fig. 1).

This stress has been suggested as the triggering mechanism of enthesitis and more broadly, PsA [26]. According to this theory, biomechanical stress at an enthesis results in cytokine production. These cytokines then enter the nearby synovial tissue resulting in an articular inflammatory response [24]. Further supporting the concept of enthesitis as a hallmark of PsA, new bone formation in the Achilles tendon and planter fascia often appears in close proximity to entheses. Tumor necrosis factor (TNF) is overexpressed in the enthesis region in this mouse model [27]. These models suggest that enthesitis is an early feature of arthritis and is dependent upon

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**Fig. 1.** Representative changes at the Achilles enthesis organ.
The presence of higher sonographic scores of enthesitis in PsA [30]. Studies have to assess when treating patients with PsA [8]. The importance of identifi
outcome in many of these studies. Progression and improve long-term morbidity [36]. The arrival of IL-23 exposure to entheseal tissue results in the upregulation of cytokines such as IL-17 and IL-22, and mouse models have shown that inhibition of either IL-17 or IL-22 results in decreased paw swelling scores—the greatest decrease occurring when IL-17 and IL-22 were inhibited simultaneously [33]. Generally, the effects of IL-23 are mediated by downstream biomolecules involved in the pathogenesis of specific arthropathies has led to an emphasis on early diagnosis of rheumatic diseases. Identifying enthesitis is thought to be important for early diagnosis and treatment of PsA as McGonagle and colleagues have put forth a model for PsA-associated synovitis, whereby inflammation starts at entheses and then triggers secondary joint synovitis [37]. The importance of enthesitis is highlighted by its inclusion as a baseline characteristic of patients with PsA in clinical trials (Table). Moreover, enthesitis has also become an important secondary outcome in many of these studies. In addition to being an important marker of PsA, GRAPPA identified enthesitis as 1 of the 6 major disease domains necessary to assess when treating patients with PsA [8]. The importance of treating enthesitis is further highlighted by a recent study in patients with PsA in which a higher Madrid Sonography Enthesitis Index (MASEI) score was associated with more peripheral joint damage, greater axial damage, and a greater chance of patients developing joint ankyloses and/or arthritis mutilans [58]. An analysis of data from the Corrona registry showed that PsA disease activity is significantly greater in patients with enthesitis compared to those without enthesitis [59]. Further, in patients with PsA, enthesitis is significantly correlated with patient quality of life and sleep disturbance [60,61]. Patients with enthesitis have also demonstrated significantly poorer functional status as well as greater patient-reported pain and fatigue and were significantly more likely to experience overall impairment and impairment while working [59].

Enthesitis, therefore, is an important clinical domain of PsA that may be detected early in disease progression and serve as an indicator of disease severity. The ability of therapies that effectively treat enthesitis and potentially improve patients' long-term outcomes makes accurate diagnosis and characterization of enthesitis increasingly important [54,55,62].

### Clinical diagnosis and scoring of enthesitis

The CASPAR criteria and GRAPPA guidelines demonstrate that the identification of enthesitis is critically important for classification, diagnosis, and treatment of PsA. Clinically, enthesitis is perceived as tenderness at entheses [63]. Several indices, including the Mander/Newcastle Enthesitis Index (MEI), the Maastricht Ankylosing Spondylitis Enthesitis Score; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis index; TNF, tumor necrosis factor.

### Table

<table>
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<tr>
<th>Inhibitor</th>
<th>Study published (year)</th>
<th>Measure</th>
<th>Prevalence of enthesitis (%)</th>
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<tr>
<td>Biologic TNF-α inhibitors</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infliximab [38]</td>
<td>2005</td>
<td>Enthesopathy</td>
<td>35–42</td>
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<tr>
<td>Etanercept [39]</td>
<td>2010</td>
<td>4-point</td>
<td>36–40</td>
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<tr>
<td>Adalimumab [40–42]</td>
<td>2005</td>
<td>4-point</td>
<td>38</td>
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<tr>
<td>Certolizumab pegol [43]</td>
<td>2014</td>
<td>Enthesitis at the heels</td>
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<td>Biologic IL-12/23 inhibitor</td>
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<tr>
<td>Ustekinumab [45,46]</td>
<td>2013</td>
<td>PsA-modified MASES</td>
<td>69–76</td>
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<tr>
<td>Biologic IL-17A inhibitors</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Secukinumab [47,48]</td>
<td>2015</td>
<td>LEI</td>
<td>56–69</td>
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<tr>
<td>Ixekizumab [49,50]</td>
<td>2017</td>
<td>LEI</td>
<td>58</td>
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<tr>
<td>Biologic IL-6 inhibitor</td>
<td></td>
<td></td>
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<tr>
<td>Clazakizumab [51]</td>
<td>2016</td>
<td>SPARCC/LEI</td>
<td>76–83</td>
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<tr>
<td>Biologic T-cell signaling inhibitor</td>
<td>Abatacept [52]</td>
<td>2017</td>
<td>63–66</td>
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<tr>
<td>Small-molecule JAK inhibitor</td>
<td></td>
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<tr>
<td>Tofacitinib [53,54]</td>
<td>2016</td>
<td>LEI</td>
<td>62–72</td>
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<tr>
<td>Small-molecule PDE4 inhibitor</td>
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<td>2016</td>
<td>MASES</td>
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<td></td>
<td>2016</td>
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<td>57–67</td>
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IL, interleukin; JAK, Janus kinase; LEI, Leeds enthesitis index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis index; TNF, tumor necrosis factor.
the 4-point enthesitis index, and the Leeds Enthesitis Index (LEI), have been developed to aid clinical recognition and quantification of enthesitis [17]. As shown in the Table, the frequency of assessment of entheses in clinical trials has risen considerably in recent years and while there is no consensus index, the LEI, MASES, and SPARCC indices have been used most frequently over the past 2 years (6, 2, and 1 trials, respectively).

**Comparison of clinical indices for enthesitis**

The MEI, MASES index, Berlin enthesitis index, and UCSF enthesitis index were all primarily developed to assess enthesitis in patients with AS, while the SPARCC index and LEI were developed for patients with spondyloarthritis [17,64]. The MEI is the most comprehensive of these indices and encompasses 66 enthesis sites and scores each site from 0 (no pain) to 3 (severe tenderness causing withdrawal). As a result of the extensive time needed to perform the MEI, the MASES index selected the 13 most specific and sensitive sites from the MEI in order to assess the entheses of patients with axial spondyloarthritis using a score of 0 (absence of tenderness) or 1 (presence of tenderness) [17,64]. The SPARCC index is slightly different from the other indices because the 16 analyzed sites were selected based on the most frequent sites of enthesitis from published data of power Doppler US and MRI studies [64]. Although the development of these indices was heavily influenced by patients with axiale spondyloarthritis, most have also been tested on patients with PsA. The intraclass correlation coefficient (ICC) for the MASES index was greater for patients with AS than those with PsA, and the SPARCC index had a higher ICC for patients with PsA compared with the Berlin enthesitis index [64]. However, the MEI, MASES index, Berlin enthesitis index, UCSF enthesitis index, and the 4-point enthesitis index have not been validated for patients with PsA.

The PsA-modified MASES index and LEI were developed or modified to assess enthesitis in patients with PsA [17,64]. Similar to the MASES index, tenderness at entheses was assessed as absent (0) or present (1) in the PsA-modified MASES index [44,64]. The LEI (which measures 6 entheses) has been utilized in several PsA trials and is unique in that it was developed and validated specifically for PsA [64]. This index was developed by clinically identifying the 6 most commonly involved enthesis sites in patients with PsA, including both the left and right lateral epicondyles, medial femoral condyles, and Achilles tendon insertions [65]. These entheses are scored based on the dichotomous 0/1 system (absence/presence of tenderness) [64]. The LEI is reliable, and when compared with the MEI, MASES, SPARCC (8 sites), and Berlin indices, LEI correlates most consistently with the clinical parameters of disease activity in patients with PsA [64]. Further, LEI is capable of distinguishing between patients with and without active PsA [65]. In general, effective indices are easy to perform, maintain reliability among clinicians, provide information on the activity of the disease, and help to differentiate the effect of treatment versus placebo in clinical trials [17]. Regarding ease of performance and reliability among clinicians, LEI is the most effective index for assessing enthesitis in patients with PsA.

**Challenges of clinically identifying enthesitis in patients with PsA**

Clinical evaluations of entheses can detect tenderness and general soft-tissue swelling, but often are unable to identify more specific disease characteristics often associated with the pathology of enthesitis, such as tendon thickening, bursitis, bone erosions, entheseal scarring, and calcifications [21,66]. Although clinical indices have been created as a means to quantify enthesitis, and these indices are often used in clinical trials, there is no clearly recognized or universal index for PsA. Reproducibility may be challenging because tenderness is assessed by applying ~4 kg/cm² of pressure to each enthesis, which is hard to measure [64]. Further, clinical indices may not be specific, especially when there is overlap with fibromyalgia, mechanical injury, or tendinitis [17,21].

The increased use of imaging techniques to assess entheses has further demonstrated the limitations of clinical indices in diagnosing enthesitis. US is considered to be more sensitive than clinical examination for the identification of enthesitis because studies have reported higher enthesitis scores in patients assessed with US than in patients assessed only through clinical examination. In a study by Perrotta and colleagues, enthesal abnormalities were detected clinically in 42.9% of patients compared with 95.5% of patients using US, and agreement between clinical findings and US findings at individual entheses was generally low [67]. US has also aided in the identification of subclinical enthesitis in patients with psoriasis [68–71]. In these studies, patients with psoriasis were found to have a higher prevalence of enthesopathy or more severe enthesitis than healthy controls. The identification of subclinical enthesitis in patients with psoriasis is becoming increasingly significant; results of one study suggested that subclinical enthesitis detected by US may be predictive of the development of PsA and/or osteoarthritis in patients with psoriasis [72]. Another US study has demonstrated that patients with PsA have more frequent vascular changes including calcification at entheses, compared with patients with psoriasis, and this observation has led to the concept that switching to a vascular phenotype in psoriasis may play a role in the development of arthritis [70]. In contrast, a study by Freeston and colleagues in patients with new-onset PsA found that clinical examination, compared with US examination, overestimated enthesis activity in 13% of the entheses studied [73]. Overall, studies have shown poor correlation between clinical assessment and US assessment of enthesitis. Recent clinical trials have mostly used clinical indices to assess enthesitis. However, as the importance of enthesitis to the prognosis of patients with PsA is realized, more attention should be given to imaging methods that can be used to accurately diagnose and characterize enthesitis.

**Imaging in the diagnosis of enthesitis**

Early recognition and treatment can result in favorable outcomes for patients if PsA is diagnosed correctly [74]. A 6-month delay in the diagnosis of PsA has been linked with worse long-term radiographic and functional outcomes [75]. Enthesitis is an early sign of PsA and persistent enthesitis has been linked with the development of arthritic damage in psoriatic patients [69]. As previously discussed, enthesitis, specifically subclinical enthesitis, is challenging to identify using traditional clinical examination indices. In the past, imaging in rheumatology consisted of conventional radiographs to confirm arthritic damage, but these radiographs were not useful in identifying early signs of inflammatory arthritis such as enthesitis [36]. Conventional radiography identified bone cortex irregularities, erosions, entheseal soft-tissue calcifications, and new bone formation as signs of enthesitis [76,77]. These changes, however, do not appear early in the development of enthesitis and are associated with mechanical disorders and crystal-related pathology [76,77], thus making early identification and diagnosis of enthesitis and PsA challenging. Over the past 2 decades, advances in imaging techniques such as MRI and US have enabled rheumatologists to more accurately assess early signs of inflammatory diseases, and thus treat patients in a timely manner with the proper biologic agents [36].

**MRI and enthesitis**

MRI is a powerful imaging tool that is commonly used to identify early axial involvement in spondyloarthritis [78–81].
Additionally, MRI has been used to evaluate peripheral entheses and has helped to identify a link between enthesitis and synovitis [82]. Enthesitis, as viewed by MRI, usually involves soft-tissue inflammatory changes outside the joint capsule, which is seen as tendon enlargement, loss of flattened hypointense appearance, focal thickening, and rounded configuration at the insertion site, as well as perienthesal bone marrow edema [24,83]. Bone marrow edema, however, is not specific to enthesitis and can be the result of rheumatoid arthritis, osteoarthritis, or a variety of other conditions [84].

Despite the usefulness of MRI, many limitations still exist, especially for the identification of enthesitis in peripheral entheses. For example, visualization is limited if enthesitis lacks bone marrow edema. Additionally, MRI signals can be low in areas where there is bone attachment because water accumulation is low. Finally, MRI is less practical than other techniques because of cost, availability, and the time taken to image each joint. Recently, efforts have been made to reduce the time needed to image each individual joint through the use of whole-body MRI [18]. This technique has shown promise in imaging the entheses at the shoulder, pelvis, and hip. However, sites such as the elbow are not visualized properly [18], and evaluation of chosen entheses could not differentiate between healthy subjects and pooled individuals with spondyloarthropathy and PsA [85]. Additional work needs to be done before this technique is optimized for entheses at the elbow, knee, and foot [18].

**US and entheses**

US, like MRI, is a useful technique for identifying enthesitis—it does not utilize ionizing radiation and is noninvasive (Fig. 2) [86]. Additionally, US has the ability to image tendons under different levels of stress in a dynamic examination, it can scan all peripheral joints from a variety of angles, and it is relatively low cost [71,86]. US has also been employed to monitor patient response to drug treatment. In an open-label study, the efficacy of TNF inhibition in treating Achilles enthesitis in patients with AS has been shown in as little as 2 months [87]. Other studies have used US to demonstrate that Achilles entheseal erosions in patients with spondyloarthritis are reversible and changes could be seen at 6 and 12 months [88]. Recently, an effort was made to properly define enthesitis visualized using US by the Outcome Measures in

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**Fig. 2.** US imaging of enthesitis. Images (A and B) courtesy of Dr. Marwin Gutierrez and images (C–F) courtesy of Dr. Catherine Bakewell. (A) Longitudinal scan of the Achilles tendon by Doppler ultrasound showing Achilles enthesitis. Note the loss of fibrillar pattern of the tendon and the presence of enthesophytes (arrowheads) and intratendinous power Doppler signal, as well as Doppler signals at the entheseal level. (B) Longitudinal scan of the Achilles tendon by Doppler ultrasound showing Achilles enthesitis. The main ultrasound findings are the presence of active bone erosion (arrow) and retrocalcaneal bursitis with intense power Doppler signal. (C) Ultrasound depicting enthesitis of the extensor tendon at the dorsal aspect of the distal interphalangeal joint. Note the enthesophyte (single asterisk) at the extensor tendon insertion onto the distal phalanx and enthesopathy of the extensor tendon (double asterisk; thickened, hypoechogenic, loss of fibrillar architecture) and Doppler signals (D, single asterisk, enthesophyte on distal phalanx; double asterisk, extensor tendon). (D) Doppler ultrasound of metacarpophalangeal joint with extensor mechanism involvement; dorsal aspect (double asterisk, extensor tendon). (E) Doppler ultrasound of distal interphalangeal joint; dorsal aspect, transverse scan (double asterisk, extensor tendon). (F) Doppler ultrasound of metacarpophalangeal joint with extensor mechanism involvement; dorsal aspect (double asterisk, extensor tendon). AT, Achilles tendon; C, calcaneus; DP, distal phalanx; MC, metacarpal; MP, middle phalanx; PP, proximal phalanx.
Rheumatology (OMERACT) group [89]. A Delphi exercise identified and agreed that “hypoechogenicity, increased thickness of tendon insertion, calcifications, enthesophytes, erosions, and Doppler activity” are important components of enthesitis [89].

**US indices for enthesitis**

To date, several methods—the Glasgow Ultrasound Enthesis Scoring System (GUESS), Spanish Enthesitis Index (SEI), MASEI, and a 5-stage classification system relying on gray-scale and power Doppler findings that was created by D’Agostino et al.—have been developed as a means of standardizing the assessment of enthesitis [90–93]. These indices are used for either diagnosis or evaluation of enthesal response to treatment. One of the most common scoring systems, GUESS, evaluates 18 total features of 5 entheses using gray-scale US [92]. Although the current OMERACT consensus definition does not include bursitis, MASEI includes the retrocalcaneal bursa as part of the synovio-enthesal complex [89,91]. MASEI also incorporates the presence or absence of Power Doppler into its scoring system, unlike GUESS, which is purely B-mode based. High MASEI scores (>18) are consistent with high sensitivity (83.3%) and specificity (82.8%) in diagnosis of spondyloarthropathy [91]. In patients with a body mass index (BMI) of < 30 kg/m², MASEI can successfully differentiate healthy patients from those with psoriasis or PsA [94]. However, in patients with a BMI > 30 kg/m², MASEI was unable to differentiate these patient groups. Despite the success of MASEI scores in this study, current US enthesitis indices are not designed to specifically identify enthesitis among patients with PsA, SEI, MASEI, GUESS, and the D’Agostino index were all developed based on a majority of patients with AS versus PsA [90–93]. Additionally, 2 US composite scores that evaluated 22 bilateral joints/entheses (psoriatic arthritis-specific score “PsASon13”) or 13 unilateral (PsASon13) joints/entheses have been developed to feasibly assess PsA-specific inflammatory and structural lesions in the clinic [95].

**Future directions and the role of imaging in understanding enthesitis**

Our understanding of the exact pathophysiology of enthesitis and its role in PsA is evolving. Clinical evaluation alone assesses only tenderness and, therefore, does not give a clear picture of the structures affected by enthesitis. Imaging techniques, however, play an important role in the elucidation of this pathway, as well as newer and related concepts such as the enthesis organ and functional entheses. Enthesitis in spondyloarthropathy is known to be associated with changes in the surrounding tissues [23]. Such changes are accounted for by scoring indices such as MASEI, which currently includes the bursa as part of enthesitis scoring [91]. The Delphi exercise, however, demonstrated that there is not complete agreement among rheumatologists over the inclusion of adjacent tissues in scoring indices [89] because these tissues are not disease specific and are involved in other diseases such as rheumatoid arthritis.

Looking forward, a validated US scoring system specific for enthesitis that is not confounded by mechanical factors or obesity needs to be developed. This scoring system may include smaller entheses around peripheral joints that are commonly affected by PsA. One of the challenges of visualizing entheses is the tendency of researchers to choose the large lower-limb entheses for screening [92,96]. This is understandable because of the ease and feasibility of screening the large entheses. The BMI of patients with PsA, however, is higher versus the general population [97], and BMI is known to have a major impact on enthesal findings. For instance, both increased MASEI and GUESS scores correlate with increased BMI [68,94]. More specifically, thickness of the Achilles tendon and enthesophyte scores are correlated to BMI [98,99]. BMI is also a marker for ongoing biomechanical stress, and may have implications on disease pathogenesis as well. Research by Zabotti et al. has demonstrated that US findings of the synovial-enthesal complex of the small joints in the hand can be used to differentiate between early PsA and early rheumatoid arthritis [100]. Specifically, imaging of the metacarpophalangeal joints revealed that only 2.5% of joints in patients with early rheumatoid arthritis, compared with 54.1% of joints in patients with early PsA, displayed the presence of peri tendon extensor digitorum tendon inflammation. Further, at the proximal interphalangeal joints, central slip enthesis was observed only in patients with PsA [100]. Enthesis scoring at the level of the phalanges, for example, may be much more specific for inflammatory arthritis activity (Fig. 2C–F) and recent advances in musculoskeletal US (e.g., higher-resolution capabilities, better image processing) will allow use of non-BMI-dependent areas such as the phalanges for enthesis scoring systems, in addition to the triceps, which are already included in MASEI [91].

In addition, the visualization of the enthesis can improve our understanding of disease pathogenesis. For example, there is a well-known relationship between nail involvement and DIP joint involvement in PsA. Following this, the link between nail disease and the adjacent enthesitis has been demonstrated through MRI and US studies [101,102]. Additionally, histological studies have shown that the extensor tendon, attached to the terminal phalanx, extends distally to connect with the nail root, thereby making the fascia of the nail root an extension of the enthesis [103]. Inflammation of the enthesis may, therefore, give rise to nail disease [103]. Patients with psoriasis and nail disease have higher enthesitis scores at remote sites than patients without nail disease, suggesting that enthesitis is not only a focal response in patients with nail disease but more suggestive of a systemic enthesal response [104]. Thus, psoriatic nail lesions can potentially help identify the presence of enthesitis [103], and evolving thoughts on nail psoriasis indicate that it may represent enthesal disease.

Sensitive imaging techniques also need to be developed to measure the differential response of enthesitis to varying biologic agents and to help identify the biologic targets that induce a faster response to enthesis complex inflammation, as well as postinflammatory changes such as calcification. Such techniques will improve treatment monitoring of patients receiving biologics and expand research related to the involvement of adjacent tissues and structures (bone, tendon, bursa, adjacent fat, synovia, etc.) in the enthesis organ, so that the pathophysiology of enthesitis can be further explored.

Finally, US imaging techniques and indices should be developed with the aim of detecting and quantifying subclinical enthesitis in patients with psoriasis because these patients have a higher prevalence of enthesopathy [68–71]. A validated US index for enthesitis could be used to diagnose early PsA and thereby improve patient outcomes.

**Summary**

Enthesis is a hallmark of PsA. It is considered by some to be integrally involved in the pathogenesis of PsA, it is linked to nail pitting (a critical feature of PsA), and patients with enthesitis generally have worse prognostic outcomes. Although clinical trials have largely used clinical indices to assess enthesitis in PsA, these indices do not provide insight into structural damage and are inaccurate in assessing the level of disease activity. US indices exist; however, none of them have been validated in patients with PsA. A validated index that is not confounded by mechanical factors—which may include smaller peripheral joints—could be a more valuable tool for the assessment of enthesis in patients with PsA. As imaging tools such as MRI and US continue to
improve, the role of the enthesis organ in enthesitis will likely become clearer, which will greatly build upon the current understanding of enthesitis and its involvement in PsA, as well as aid the treatment of patients with PsA.

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