# Lessons Learned from Imaging on Enthesitis in Psoriatic Arthritis

Abdulla Watad MD[1,3], Iris Eshed MD[2,3] and Dennis McGonagle MD FRCPI PhD[4]

[1]Department of Medicine B, Zabludowicz Center for Autoimmune Diseases and [2]Department of Diagnostic Imaging, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

**ABSTRACT:** Enthesitis is a term that refers to inflammation at tendon, ligament, or joint capsule insertions. The entheses are increasinlgly considered to be the primary site of joint inflammation in the spondyloarthropathies including psoriatic arthritis (PsA). Great advances have occurred in the understanding of enthesopathy, which has resulted in a better understanding of the etiopathogenesis of PsA. Enthesitis is difficult to assess on both clinical examination and on imaging because of the overlap in features between mechanical, degenerative, and inflammatory pathologies. Ultrasonography frequently detects entheseal abnormalities in patients with psoriasis, despite the absence of clinical symptoms of arthropathy and the longitudinal value of such lesions for PsA prediction remains unknown. The role of magnetic resonance imaging (MRI) in the assessment and monitoring of enthesitis is not fully agreed on but it is clearly superior for the assessment of spinal polyenthesitis and for diffuse peri-enthseal osteitis that can occur anywhere in the skeleton. Nuclear medicine, including conventional positron-emission tomography (PET) and high-resolution PET scan (hrPET), is more of a research tool for enthesitis and can, for example, help distinguish between PsA and osteoarthritis. Entheseal abnormalities are common in osteoarthritis, which creates diagnostic difficulty from PsA. Entheseal changes, especially on imaging, may also occur in rheumatoid arthritis (RA) and likely reflects the extension of the inflammatory process from the adjacent synovium. The nail is anatomically anchored to the skeleton via a mini-enthesis network. An association between ultrasonography determined distal interphalageal joint (DIP) extensor tendon enthesopathy and clinical nail disease was found, which highlights the pivotal role of the enthesis in this PsA risk factor. This review summarizes the relevant insights and implication of imaging for enthesitis, primarily in PsA but also in other arthropathies.

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**KEY WORDS:** imaging, enthesitis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), magnetic resonance imaging (MRI), positron-emission tomography (PET)

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The enthesis is the pivotal connection point or attachment of a tendon, ligament, fascial attachments, or joint capsule onto bone [1]. The adjacent bone is trabecular in nature and consequently the enthesis anchorage also includes the adjacent bone. The "enthesis organ" often includes immediately adjacent synovium that forms a structure called the synovio-entheseal complex. Several inflammatory disorders, formely regarded as autoimmune diseases, are characterized by inflammation at the enthesis, or enthesitis.

The involvement of the enthesis, whether caused by trauma, degeneration, or inflammation or metabolic disease, is termed an *enthesopathy.* The term enthesitis is restricted to inflammatory disease and, in general, refers to seronegative spondyloarthritis (SpA). Indeed, enthesitis is the hallmark of SpA and thus, applies to ankylosing spondylitis, psoriatic arthritis (PsA), reactive arthritis, and undifferentiated SpA. The term, enthesopathy, was originally used by Niepel [2], with Ball triggering the interest of rheumatologists in 1970 with his pathological studies [3]. Ball highlighted that the enthesis was centrally affected in ankylosing spondylitis, in contrast to rheumatoid arthritis (RA), in which it is largely synovial structures that were inflamed. Several years later, the concept of *enthesopathy* was introduced into the clinical terminology of previously undefined conditions such as the syndrome of seronegative *enthesopathy* and arthropathy in children, in addition to a constitutive feature of SpA as defined by the preliminary European Spondylarthropathy Study Group classification criteria [2]. In this mini review, we referred to the general characteristics of enthesits, and to the imaging aspect of *enthesopathy* as well.

## TYPES OF ENTHESIS

Histologically, enthesis can be classified in two types: fibrous and fibrocartilaginous. Most of entheses with relevance for rheumatologists are fibrocartilaginous, characterized by the presence of a small plug of fibrocartilage at the attachment site itself [3]. They are typified by the Achilles tendon and by the tendon of the supraspinatus muscle, and also include those of the digital collateral ligaments and many others. The fibrous entheses are characterized by pure dense fibrous connective tissue that links the tendon or ligament to the bone and are typically anchored a long way from the joint with the most notable example being the

**Figure 1.** A sagittal **[A]** and coronal **[B]** T2w with fat saturation images of the knee showing an inhomogeneous signal of the quadriceps tendon in its insertion (arrows) to the patella . High signal intensity of the adjacent fat pad can also be noted (arrowheads)

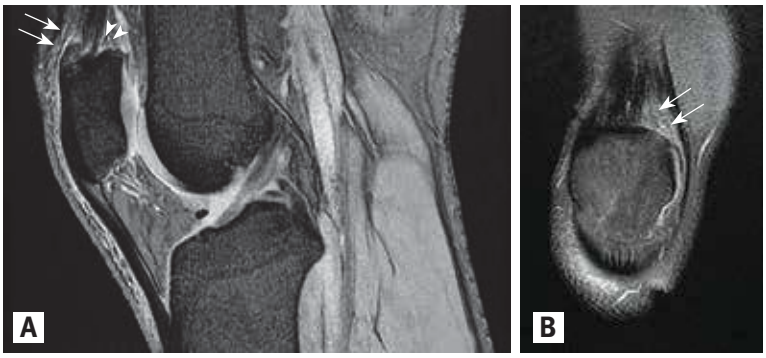
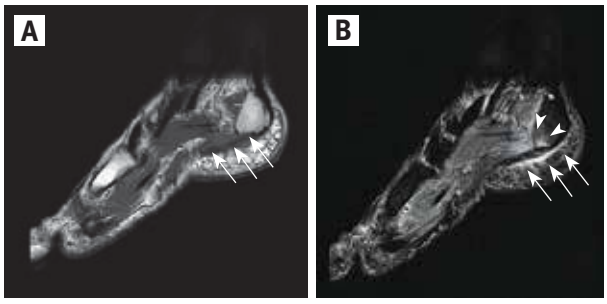



**Figure 2.** Sagittal T1w **[A]** and T2w with fat saturation **[B]** images of the ankle of a patient with plantar fasciitis showing high signal intensity and thickening of the plantar fascia at its insertion to the calcaneus (arrows) as well perientheseal soft tissue edema and insertional bone marrow edema (arrowheads)




deltoid tendon insertion. Virtually all of the inflammation in the SpA group of diseases affects the fibrocartilaginous structures and not the fibrous ones.

### ENTHESOPATHY AND SPONDYLOARTHRITIS: THE COMMON THREAD

Historically, entheseal disease was best recognized in large, clinically accessible tendons and ligaments, including the Achilles tendon and plantar fascia, but the advent of magnetic resonance imaging (MRI) has confirmed that enthesitis is present throughout the skeleton in early stages of SpA and is common at clinically inaccessible sites such as the vertebral bodies, knee joints, hand joints and others [2]. These imaging-based observations resulted in the cytokine mediated enthesitis theory of SpA that drove a secondary synovitis [4].

**Enthesopathy embraces all pathologic alterations at any enthesis, where enthesitis specifically implies that there is inflammation at an attachment site**

Although *enthesopathies* are from the clinical perspective and traditionally viewed as focal, insertional disorders, findings on MRI and ultrasound imaging suggest the presence of more diffuse changes with involvement of the adjacent bone, adjacent synovium as part of synovio-entheseal complex disease and also adjacent soft tissue and fascia. Enthesitis and capsular inflammation were described to be a common finding in the small joints in psoriatic arthritis, but not in RA [5].

Although early RA appears to represent an autoimmune reaction to the synovium, RA-related erosion formation occurs immediately adjacent to the small joint collateral ligament insertions due to enthesis-associated compression of bone at these sites [6,7]. It is believed that in SpA, in contrast to RA, synovitis is secondary to enthesitis but that chronic synovitis in that setting can lead to an RA-like pattern of erosion. Conventional MRI may have some limited diagnostic sensitivity for enthesitis, mainly to those joints already swollen with the inflammatory process then extending to insertions and causing secondary involvement, which is distinct from early primary enthesitis lesions that trigger secondary synovitis [8]. Thus, imaging may not detect enthesitis in every joint with synovitis and its use as a diagnositic tool in routine practice is limited.

### WHAT A RADIOLOGIST NEEDS TO INTERPRET IMAGES OF ENTHESITIS

To know how to interpret images of enthesitis, it is essential to know "when and where" to search for such a finding. As mentioned earlier, enthesitis is typical of all forms of SpA. Such clinically recognizable sites include large tendons and ligaments adjacent to joints and superficial spinal insertions. The entheses of the lower limbs are involved more frequently than those of the upper limbs with plantar fasciitis, Achilles enthesitis, or both being especially common. It is also crucial to know which imaging modality to use for detecting enthesitis. It depends on whether enthesitis is suspected in the axial or peripheral skeleton. Thus, MRI modality is the preferred strategy in the case of suspected axial enthesitis, and ultrasound is more suitable for peripheral enthesitis. MRI is also preferred in large joints including the knee [Figure 1], hip, and others, in which the probe is not accessible [9].

It is essential to know that MRI does not exclude the presence of enthesitis. The reason can be attributed to the possible lack of bone edema in the presence of enthesitis, or to the scarce accumulation of fluid in the enthesis due to its avascular organ. Several studies have shown that fat-suppression MRI, with or without contrast agent administration, is the most sensitive method for identifying active enthesitis at any site. MRI can show peri-entheseal inflammation with adjacent bone marrow edema in fat-suppressed T2-weighted sequences [Figure 2].

Ultrasonography is widely used at times to detect enthesitis. The sonographic features of enthesitis include hypoechoic thickening of the tendon or ligament, erosion and spur formation, and fluid with synovitis in the immediately adjacent bursa, such as the retrocalcaneal bursa associated with the Achilles tendon

[10]. Moreover, radiography can be used in diagnosing enthesitis, even though it detects late features of *enthesopathy*, such as new bone formation and erosions rather than alteration of the enthesis. The best use of radiography in modern times is for the assessment of entheseal new bone formation at spinal entheses termed *syndesmophytosis*.

### THE ENTHESIS ROLE IN THE DIFFERENTIATION OF PSA FROM OTHERS ATHROPATHIES

Enthesitis is one of the archetypical features of PsA and it is reported in 30–50% of PsA patients [11]. The growing use of MRI and ultrasonography as well as improved detection of enthesitis has resulted in the recognition of an even greater burden of entheseal involvement. Risk factors for the development of enthesitis in PsA include higher disease activity, severe synovitis, higher BMI, and younger age at diagnosis [11].

Several clinical tools are used to assess enthesitis including Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Spondyloarthritis Research Consortium of Canada (SPARCC), and Leeds Enthesitis Index (LEI). The SPARCC is not limited for enthesitis in PsA and can be used to determine SpA in general. Despite the usefulness of these scores, imaging, mainly MRI and ultrasonography, is still more sensitive than clinical examination [12].

TNF-alpha blockers are useful in the treatment of enthesitis related to PsA and are known to be effective in the treatment of arthritis in psoriatic patients. In general, the clinical imaging outcomes have shown to be sensitive to change. Unfortunately there is no gold standard for enthesitis assessment because, unlike the synovium where tissue procurement is easy, this is not the case for the enthesis.

### ENTHESIS ORGANS

Enthesitis, a typical finding of SpA, was traditionally viewed as a focal abnormality. Recently, due to greater understating of the role of enthesis and adjacent tissues that produce a functional and structural complex, the term "enthesis organ" has come into frequent use [13]. It seems that the "enthesis organ," comprised of enthesis and two complementary fibrocartilages, represents the primary site of injury. The inflammation of the synovio-entheseal complex (SEC) can lead to the so-called "erosion phase" and thereafter to new bone formation, syndesmophyte as a typical lesion. The SEC highlights the importance of the relationship between synovial membrane and entheses within the enthesis organs [Figure 3, Figure 4]. It also facilitates the comprehension of disease pattern of SpA, mainly PsA [14].

### DIFFERENTIATION OF PSA FROM OSTEOARTHRITIS USING HIGH-RESOLUTION POSITRON-EMISSION TOMOGRAPHY (PET) SCANNING

To better understand the pathogenesis of enthesitis, we used high-resolution fluorodeoxyglucose-PET/CT ($^{18}$F-FDG-PET/CT). The hrPET is a combination of a PET scanner and a high-resolution multi-slice CT, which fuses the functional images of the PET scan and the high-resolution structural images of CT. We conducted a study that used hrPET to examine the determined distal interphalageal joint (DIP) and patients with PsA and osteoarthritis [15]. Among those with PsA, a diffuse pattern of increased bone metabolism involving the entire digit and prominent periosteal involvement and focal hot spots at the entheses was observed. Among osteoarthri-

**Figure 3.** Sagittal T1w **[A]** and T1w with fat saturation after gadolinium injection **[B]** images of the ankle of a patient with Achilles enthesitis demonstrating the concept of enthesis organ. A thickened tendon with high signal at its insertion to the calcaneus (arrows) is detected as well as synovitis in the retrocalcaneal bursa (blue arrowheads) and insertional osteitis (asterix). Synovitis of the tibio-talar joint can also be noted

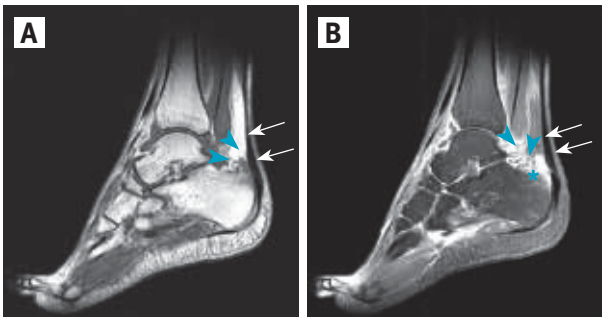
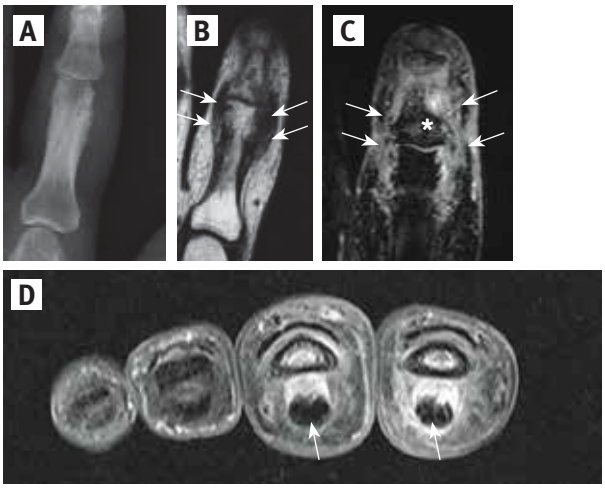



**Figure 4.** An anteroposterior radiograph **[A],** T1w **[B],** and T1w with fat saturation after gadolinium injection **[C]** images of the proximal interphalangeal joint of the hand of a patient with psoriatic arthritis (PsA) demonstrating enthesitis of the collateral ligaments with thickened and hyperintense ligaments as well as insertional osteitis (asterix). Coronal T1w with fat saturation after gadolinium injection **[D]** image of the hand of a different patient with PsA and dactylitis demonstrated tensynovitis of the 2nd and third flexor tendons (arrows) as well as osteitis of the adjacent bones



tis patients, however, hrPET could reveal an uptake pattern that was more subchondral—a site where bone erosions and osteophytes are located.

### DACTYLITIS IN PSA

Dactylitis is a term used to describe the clinical and radiologic diffuse fusiform swelling of a digit due to soft tissue inflammation from underlying arthritis [16]. It is a common feature of PsA and usually causes severe pain. Among those with dactylitis, MRI was able to detect bone edema, flexor tenosynovitis [Figure 4] and, to a lesser degree, extensor tenosynovitis. Indeed, we have also noted 'functional entheses' disease at the extensor tendon and ligament enthesitis of the distal IP joint in cases of dactylitis on high-resolution MRI (hrMRI) [17]. The common presence of enthesitis in PsA dactylitis, and the relation between *enthesopathy* and the flexor tendon, provide an explanation for the involvement of entheses in flexor tenosynovitis that is evident in dactylitis [18]. Therefore, inflammatory changes at digital pulleys and tendons explains the nature of enthesitis in dactylitis.

**MRI imaging and ultrasonography have transformed our recognition of enthesitis at clinically inaccessible sites**

### SUBCLINICAL ENTHESOPATHY MAY PREDICT PSA

The ability to predict the development of PsA in psoriatic patients could have implications for prevention or benefits for early treatment [19]. We presented a questionnaire, "Early Arthritis for Psoriatic (EARP) patients" that can be used in a dermatological setting and provides a simple and fast way to predict PsA in patients with psoriasis [20]. Ultrasonography as an imaging strategy may detect a subclinical involvement of enthesis without any clinical sign of arthritis. Interestingly, ultrasonography was also able to show that the appearance of subclinical enthesitis in psoriasis differs from the subclinical enthesitis in PsA, suggesting the presence of more inflammation in PsA. Therefore, ultrasonography can serve as a very useful tool in psoriatic patients without arthritis aiming to predict the development of PsA in order to initiate an appropriate therapy.

**Enthesitis is the primary lesion in SpA including PsA, and hrMRI has demonstrated a link between dactylitis and digital polyenthesitis**

### NAIL DISEASE AND ENTHESOPATHY

There is a significant role of nail disease in patients with psoriasis with/without PsA. Indeed, the presence of a nail disease among patients with psoriasis can predict the development of PsA with higher prevalence of DIP involvement. Interestingly, nail involvement among these patients is associated with a higher degree of *enthesopathy* [21]. The clinical examination of nails disease is not always useful and therefore ultrasonography and MRI were reported to be more sensitive in the detection of nail disease. We have reported previously the implication of ultrasonography in psoriatic patients with nail disease. An association between *enthesopathy* on ultrasonography and clinical nail disease was reported. This finding was not confined to matrix-specific abnormality (pitting), but was also seen with onycholysis. MRI and histological studies demonstrate that the extensor tendon crossing the DIP is fused with the nail root and matrix, with tendon fibers enveloping the nail root. Subclinical enthesitis may also be responsible for some of the ungual pain experienced by patients with psoriasis without clinical PsA [22]. Therefore, nails are functionally integrated to the skeletal appendage and linked to the enthesis.

### CONCLUSIONS

The term *enthesopathy* embraces all pathologic alterations at any enthesis. However, enthesitis specifically implies that there is inflammation at an attachment site. Imaging studies demonstrate that enthesis itself can be closely integrated with functionally adjacent bone, periosteum, and sometimes synovium. Although enthesitis at sites like the Achilles tendon is readily apparent clinically, its recognition is difficult at inflamed synovial joints owing to soft tissue changes in associated inaccessible sites, including much of the spine. However, improvements in MRI imaging and ultrasonography have transformed our recognition of enthesitis at clinically inaccessible sites. There is a relevant association between nail disease and the involvement of enthesis. Dactylitis, or sausage digits, is a hallmark of PsA and it seems that enthesitis is the primary lesion in SpA including PsA, and hrMRI has demonstrated a link between dactylitis and digital polyenthesitis. Despite the great knowledge accumulated in the last decade concerning *enthesopathy* in terms of etiopathogenesis, imaging implication and effective management, further work needs to be done.

**Correspondance**
**Dr. D. McGonagle**
Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds LS7 4SA, UK
**Phone:** (44-113) 392-4883
**Fax:** (44-113) 392-4991
**email:** d.g.mcgonagle@leeds.ac.uk

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## Capsule

### *Plasmodium* products persist in the bone marrow and promote chronic bone loss

Although malaria is a life-threatening disease with severe complications, most people develop partial immunity and suffer from mild symptoms. However, incomplete recovery from infection causes chronic illness, and little is known of the potential outcomes of this chronicity. Lee and co-authors found that malaria causes bone loss and growth retardation as a result of chronic bone inflammation induced by *Plasmodium* products. Acute malaria infection severely suppresses bone homeostasis, but sustained accumulation of *Plasmodium* products in the bone marrow niche induces MyD88-dependent inflammatory responses in osteoclast and osteoblast precursors, leading to increased receptor activator of nuclear factor kappa-B ligand (RANKL) expression and overstimulation of osteoclastogenesis, favoring bone resorption. Infection with a mutant parasite with impaired hemoglobin digestion that produces little hemozoin, a major *Plasmodium* by-product, did not cause bone loss. Supplementation with alfacalcidol, a vitamin D3 analog, could prevent the bone loss. These results highlight the risk of bone loss in malaria-infected patients and the potential benefits of coupling bone therapy with anti-malarial treatment.

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Eitan Israeli

## Capsule

### A signature event for organoids

Human cancer genomes harbor cryptic mutational signatures that represent the cumulative effects of DNA damage and defects in DNA repair processes. Knowledge of how specific signatures originate could have a major impact on cancer diagnosis and prevention. One approach to address this question is to reproduce the signatures in experimental systems by genetic engineering and then match the signatures to those found in naturally occurring cancers. Drost et al. used CRISPR-Cas9 to delete certain DNA repair enzymes from human colon organoids. In a proof-of-concept study, they showed that deficiency in base excision repair is responsible for a mutational signature previously identified in cancer genome sequencing projects.

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Eitan Israeli