Enthesitis: from pathophysiology to treatment

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Abstract | Entheses are the insertion sites of tendons and ligaments to the bone surface and are essential structures for locomotion. Inflammation of the entheses (enthesitis) is a key feature of psoriatic arthritis and spondyloarthritis. To date, our conceptual understanding of enthesitis remains limited. This Review provides an insight into the pathophysiology of enthesitis, addressing the role of biomechanics, prostaglandin E2-mediated vasodilation and the activation of innate immune cells in the initiation phase of enthesitis, as well as the role of entheseal IL-23-responsive cells that augment inflammation by producing pro-inflammatory mediators such as IL-17A, IL-22 and TNF. In addition, the molecular steps that translate inflammation into resident tissue responses, resulting in new bone formation, are discussed. The second part of the article summarizes the clinical features of enthesitis, and the role of clinical and imaging instruments in detecting enthesitis are discussed together with their challenges and limitations. Finally, the Review summarizes the current treatment possibilities for enthesitis based on the aforementioned pathophysiological concepts, focusing on the role of cytokine-blocking agents.

Inflammation of the tendon insertion sites into bone (enthesitis) is an important and frequent manifestation of inflammatory musculoskeletal disease. Traditionally, enthesitis has received only limited scientific and clinical attention. However, this unfavorable situation has substantially changed in the past few years. In particular, the ongoing progress in the molecular characterization of diseases such as psoriatic arthritis (PsA) and spondyloarthritis (SpA), which share enthesitis as a hallmark clinical feature, have fostered our knowledge and understanding of enthesitis. In this Review, we reflect on these developments and address the latest insights concerning the pathophysiology, clinical manifestations and treatment of enthesitis. We introduce a mechanistic disease concept of enthesitis that highlights the specific pathways involved in mounting entheseal inflammation and in triggering local tissue responses. Based on this concept, we then discuss the clinical presentations as well as the diagnostic and therapeutic possibilities in enthesitis.

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Definition and function of entheses

The term enthesis derives from the ancient Greek word for insertion. In medical terminology, enthesis describes the insertion of tendons and ligaments into the bone surface[1]. Entheses are essential structures for the transduction of mechanical forces from muscles to bones and hence are the basis for locomotion. Whereas joints enable the mobility of the skeletal system by constituting natural 'breaks' between the bones, entheses transduce mechanical forces to the skeletal system (in the case of tendons) and provide stability (in the case of ligaments). Entheses are usually localized outside the joints, either inserting into the periarticular bone (as with the flexor tendon insertions of the phalanges or the biceps tendon insertion) or distant from any synovial joint (such as the Achilles tendon or annulus fibrosus insertions at the vertebral bodies). Exceptions to this rule are the entheseal region inside the knee joint, where the intra-articular cruciate ligaments of the knee insert, and dominant entheseal compartments within some distinct joints such as the sacroiliac, sternoclavicular and acromioclavicular joints. In addition, the term 'functional entheses' has been coined to describe regions where the tendon is wrapped around bony protrusions (for example, the peroneus tendons)[2]. Overall, more than one hundred entheses can be found in the human body, linking 'soft' connective tissue with the 'hard' tissue of the skeleton.

Knowledge of the anatomical features of entheses is important for understanding the process of inflammation of the entheses, which is fundamentally different from synovitis. Whereas enthesitis usually occurs outside the joint, synovitis describes an intra-articular process characterized by inflammation of the synovial

Key points

- Entheses are predominantly extra-articularly localized structures that represent a key target of musculoskeletal inflammation in diseases such as psoriatic arthritis (PsA) and spondyloarthritis (SpA)
- Entheses contain a specific immune microenvironment, which is activated by a combination of factors that include mechanical stress, genetic susceptibility and microbial-triggered immune activation
- Enthesitis arises from robust activation of prostaglandin E2 and the IL-23–IL-17 axis, leading to the influx of innate immune cells and homing of inflammation into the entheses, which is followed by mesenchymal tissue responses and new bone formation
- Clinical and imaging instruments have been developed that enable the reliable detection and monitoring of enthesitis in patients with PsA and SpA
- Inhibition of the key effector cytokines of enthesitis — IL-17, IL-23 and TNF — has shown to be effective in supporting the resolution of enthesitis in PsA and SpA

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membrane (FIG. 1). Notably, enthesitis and synovitis can occur separately or concomitantly in diseases such as PsA and SpA.

Structure of entheses

Entheses are distinct anatomical structures that are sometimes also termed entheseal complexes[3]. These structures have to enable not only the stable anchoring of the tendon or ligament into the bone surface, but also the smooth transduction of mechanical forces. These functions are made possible by the unique tissue properties of entheses, which arise from a gradual transition from tendon or ligament tissue to bone tissue as well as from specific features of cortical bone that allow a robust connection. Key insights into the microanatomy of these structures have been gained in the past 10 years, such as the appreciation that the distinct orientation of fibres in the inserting tendon allows for the physiological transduction of force[4] and the definition of a critical 500 µm-thick transition zone between the tendon and bone, where the alignment of these fibres is lost and collagen content decreases[5,6]. This region is unique in that it contains intermingled fibre-rich areas with interspersed fibroblasts and areas of chondrocytes with cartilagenous matrix[5,6]. Accordingly, collagen type I content is low in these areas, whereas collagen type II and hyalectan-type proteoglycans, such as aggrecan and versican, are increased[6]. The tissue in this transition zone between the tendon and the bone is also known as fibrocartilage[7,8]. This mixture of fibrous with cartilaginous tissue elements provides at the same time both stiffness and elasticity, which are required to fulfil the high mechanical demands on entheses. In close vicinity to the bone surface, fibrocartilage is then mineralized before transitioning into bone. Furthermore, bone at entheseal sites is thin and porous with blood vessels emerging from the neighbouring bone marrow, enabling the supply of the entheses with nutrients[2].

Pathophysiology of enthesitis

Enthesitis can result from repeated mechanical overloading, such as that which occurs during sporting activities, in otherwise healthy individuals. 'Tennis elbow' or 'golfer's elbow' is a typical example of an isolated enthesitis resulting from mechanical overload. In such cases, enthesitis usually affects only one enthesis, also involves the body of the tendon and usually resolves spontaneously. However, enthesitis is also a pathognomonic feature of PsA and SpA, where it occurs frequently, often affects more than one enthesis and shows a remarkable degree of chronicity[8]. The reason why patients with PsA or SpA are susceptible to the development of enthesitis is not fully clear. There is no conclusive evidence that enthesitis that occurs in conjunction with PsA and SpA involves a fundamentally different process than enthesitis resulting from mechanical overloading. It can be hypothesized, however, that the threshold for triggering entheseal inflammation is substantially lower in patients with PsA and SpA, which allows the development of enthesitis with little or no mechanical force — resembling an excessive reaction to low-level mechanical strain. Similar processes are known to occur in psoriatic skin disease. The well-known Koebner phenomenon describes an exaggerated and persisting inflammatory reaction of the skin to mechanical irritation in patients with psoriasis. Translated to the musculoskeletal system, enthesitis in patients with PsA and SpA might represent a pathologically exaggerated bodily response to stress. The cause for the apparently low threshold for the development of enthesitis in patients with PsA and SpA, however, remains speculative. Potential explanations include genetic factors, such as MHC class I genes and polymorphisms in *IL23R* (encoding IL-23 receptor (IL-23R)), which lead to enhanced and prolonged immune activation[9,10], and the possibility of disturbed epithelial barrier function due to concomitant clinical or subclinical psoriasis (in PsA) and colitis (in SpA), which result in increased exposure to microbial stress and prolonged immune responses[11].

Induction and inflammation

Enthesitis seems to be triggered predominantly by an innate immune response; B cell activation, follicular reactions and autoantibody formation are absent. Clinical observations suggest that mechanical stress is a central

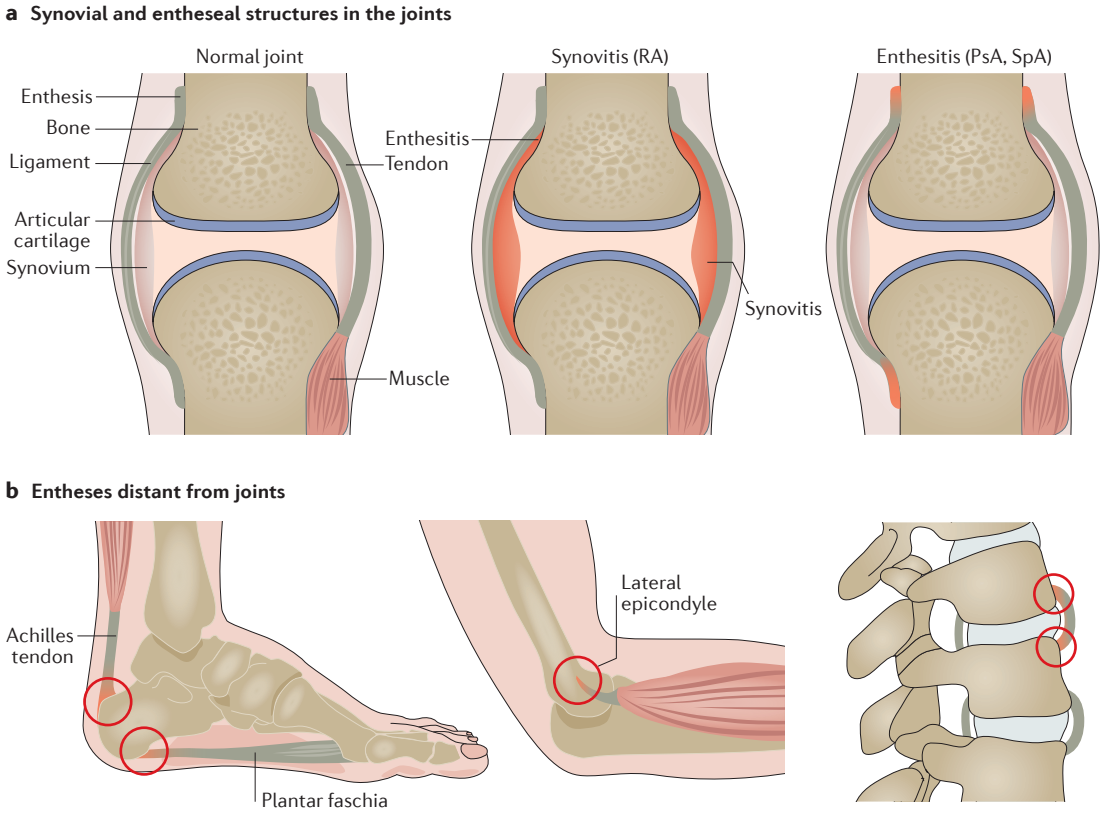

Figure 1 | **Enthesitis versus synovitis. a** | Schematic drawing of a diarthrodial joint showing the joint caspsule with the synovial membrane and tendons inserting into periosteal bone. Synovitis is characterized by inflammation of the synovial membrane. Enthesitis is defined as inflammation of the entheses, the insertion sites of tendons and ligaments to the bone surface. Enthesitis can occur with secondary synovitis. **b** | Enthesitis is usually periarticular but can also occur at sites distant from the joints (indicated by red circles), such as the Achilles tendon, the plantar fascia, the epicondyle or the anterior longitudinal ligament insertion at the vertebral edges. PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.

factor in the induction of enthesitis. Thus, enthesitis primarily affects the lower limbs, which are exposed to higher mechanical forces than the upper limbs[12]. In support of this concept, mechanical unloading in mice is sufficient in reducing Achilles tendon enthesitis[13]. The exact molecular process by which mechanical stress elicits enthesitis, however, remains to be determined.

An important early mediator of enthesitis is prostaglandin E2 (PGE2) (FIG. 2a). The role of PGE2 in enthesitis is supported by the remarkable responsiveness of axial and peripheral enthesitis to treatment with NSAIDs. Local PGE2 production might enable a rapid stress response to mechanical overload or other triggers in the entheses. Resident mesenchymal cells, for instance, express inducible prostaglandin G/H synthase 2 (also known as cyclooxygenase 2), which explains the site-specific production of PGE2, which is the main enzymatic product of cyclooxygenases[14]. PGE2 triggers vasodilatation, which might also widen the transcortical vessels and facilitate neutrophil recruitment from the bone marrow into the entheseal compartment. Such a process would explain the development of an inflammatory reaction in the neighbouring bone marrow (osteitis), which is observed on MRI scans of patients with PsA and SpA and is usually associated with pain (discussed further below). Furthermore, PGE2 fosters the production of IL-17 by T cells and thereby links initial inflammatory responses to activation of the IL-23–IL-17 pathway[14].

Mechanistic studies in mice have suggested that IL-23, a cytokine derived from macrophages and dendritic cells, has a key role in enthesitis. Hence, overexpression of IL-23 *in vivo* triggers enthesitis, seemingly bypassing the need for mechanical overload[15]. Notably, entheses harbour IL-23-responsive cells[16]. In mice, T cells that express IL-23R reside at entheseal sites[15,17]. Rigorous phenotyping of these cells revealed that most do not belong to the classical αβ T cell receptor-bearing group of T cells but are, in fact, γδ T cells[17]. γδ T cells are at the crossroads of innate and adaptive immunity and are instrumental in mediating host defense. γδ T cells are known to represent a major cellular source of IL-17 and TNF[18]. Whether other IL-23R-expressing cells populate entheseal sites remains to be confirmed. Some evidence suggests that innate lymphoid cells (ILCs) are interesting candidates in this respect[19]. These cells do not express a T cell receptor but share cytokine activation pathways with specific T cell lineages. Type 3 ILCs, for instance, express IL-23R, produce IL-17A and can be found in normal human entheses[20]. A functional role of these cells in enthesitis, however, remains to be determined.

The production of IL-17 seems to be a crucial step in augmenting the inflammatory response in the enthe-ses. IL-17 fosters neutrophil migration and activation, a process that is also observed in psoriatic skin disease and links IL-23–IL-17 activation with the effector phase of inflammation[21] (FIG. 2b). IL-17 acts as an amplifier of enthesitis and induces the production of a variety of cytokines and mediators by resident mesenchymal cells, which can trigger neutrophil migration and activa-tion[15,22–25]. Among these products are pro-inflammatory cytokines such as granulocyte-macrophage colony stim-ulating factor, IL-6 and IL-8, the last of which is a major chemoattractant for neutrophils. Neutrophils seem to be important effector cells in entheseal inflammation. In the enthesis, neutrophils further augment the inflam-matory response by releasing proteases and reactive oxygen species, which aggravate pain responses during enthesitis. Very few histopathology studies have been done in human enthesitis. These studies suggest that also macrophages infiltrate into the entheseal tissue[26]. The activation state of neutrophils and macrophages is critical in determining the development of enthesi-tis. For instance, uncontrolled activation of signal transducer and activator of transcription 1 (STAT1) in myeloid cells has been shown to trigger enthesitis by promoting cytokine release. In the absence of A20 pro-tein, a negative regulator of STAT1, enthesitis develops spontaneously[27].

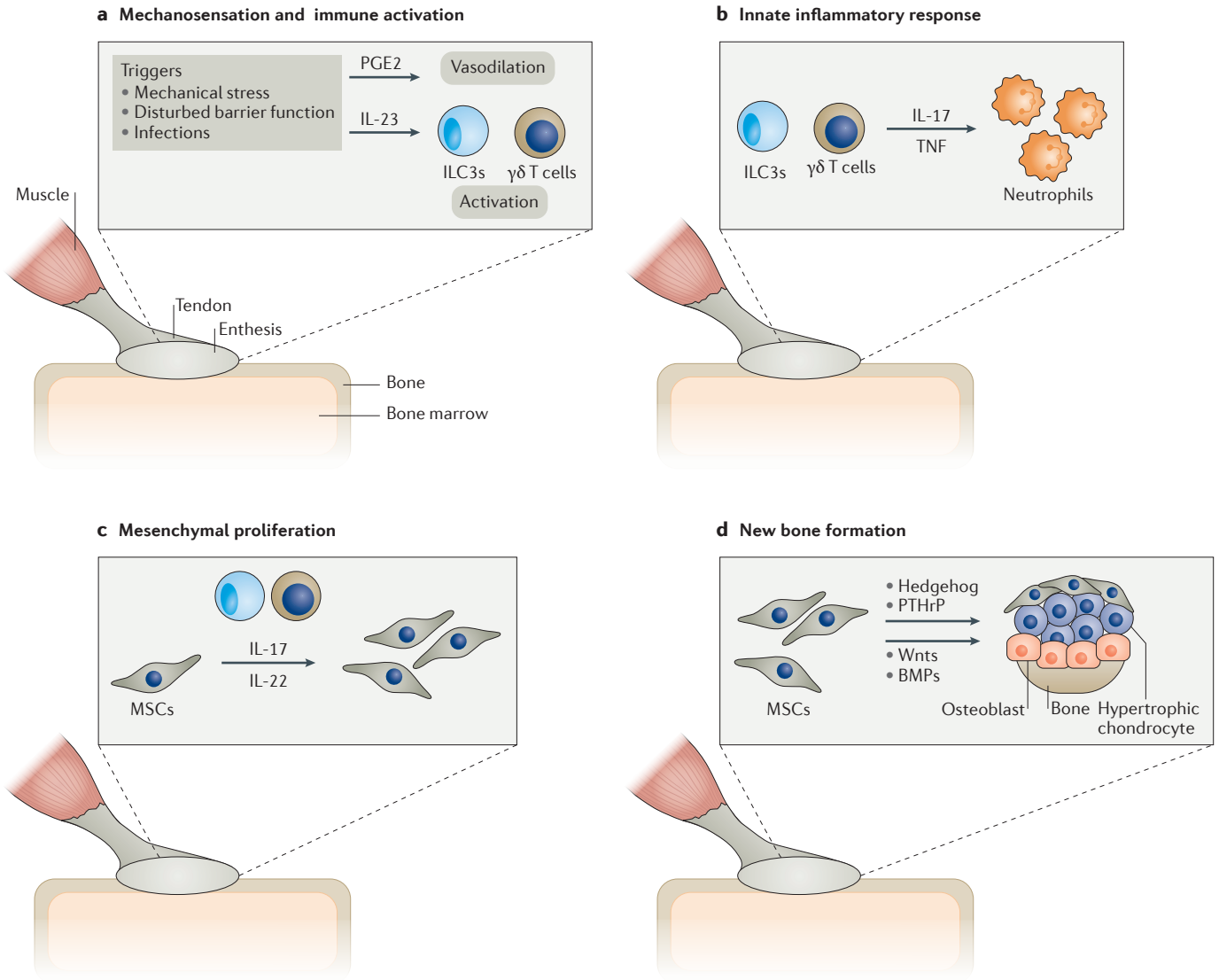

Figure 2 | **Functional model of enthesitis. a** | Enthesitis is initiated during a mechanosensation and immune activation phase involving mechanical and/or infectious stress that leads to the activation of prostaglandin E2 (PGE2) and IL-23, followed by vasodilatation and activation of resident γδ T cells and type 3 innate lymphoid cells (ILCs). **b** | The subsequent innate inflammatory response is characterized by the release of TNF and IL-17, leading to the influx of immune cells such as polymorphonuclear neutrophils (PMNs). **c** | Mesenchymal proliferation elicited by IL-17 and IL-22 is characterized by the activation and proliferation of resident mesenchymal stem cells (MSCs) from the perientheseal periosteum. **d** | New bone formation at entheseal sites (enthesophyte growth) is triggered by hedgehog signalling and parathyroid hormone related-peptide (PTHrP), which contribute to the mineralization of fibrocartilage; bone morphogenic proteins (BMPs) and Wnt proteins induce osteoblast differentiation and enable new bone apposition.

Tissue proliferation and bone formation

Entheseal inflammation is characterized by remarkable tissue responses (FIG. 2c). Central to these architectural changes is local new bone formation. Although spurious erosions can occur in the context of enthesitis, the net effect of entheseal inflammation is the gain of new bone, which is often characterized by excessive local apposition of periosteal bone at entheseal sites (enthesophytes)[28,29]. In the spine, the anterior and posterior parts of the vertebral bodies are affected, which leads to syndesmophyte formation and subsequent spinal ankylosis[30]. At peripheral sites, entheses such as the plantar fascia are affected by new bone formation (calcaneal spurs). Furthermore, entheseal sites at peripheral joints such as the hand joints give rise to new bone formation in PsA[29]. Remarkably, the first sign of musculoskeletal involvement in patients with psoriasis is enthesophyte formation in the peripheral joints, highlighting the role of enthesitis as an early feature of diseases such as PsA and SpA[28].

Mechanistically, new bone formation is speculated to represent a tissue response process that starts after the peak of entheseal inflammation has been reached. This process is probably initiated by resident mesenchymal cells, which have the potential to proliferate and differentiation into chondroblasts and osteoblasts to form cartilage and bone, respectively. In some respects entheseal new bone formation resembles fracture repair, which is characterized by a rapid and robust mesenchymal tissue response following an initial inflammatory phase[31]. The molecule(s) linking the inflammatory phase with the tissue response in enthesitis are as yet unknown but IL-17, IL-22 and PGE2 have been implicated in this process. IL-17, for instance, has shown to effectively activate mesenchymal cells[32,33]. Furthermore, although epithelial cells are the key targets of IL-22, other resident entheseal cells, such as mesenchymal cells, also respond to this cytokine and IL-22 might therefore support new bone formation[34]. Finally, PGE2 is a robust activator of osteoblast differentiation and hence might link entheseal inflammation with new bone formation[35]. By contrast, TNF seems to be primarily anti-anabolic through its induction of Dickkopf-related protein 1 (DKK1) and sclerostin, both of which effectively block bone formation[36,37]. Although there is experimental evidence that the absence of TNF retards fracture repair, the clinical relevance of this observation remains unclear[38].

In contrast to the initiation process of enthesophyte growth, the factors required for chondroblast and osteoblast differentiation are well characterized (FIG. 2d). Hedgehog proteins activate a specific cell population in the enthesis (cells expressing the hedgehog-regulated transcription factor GLI1), which are different from the tendon fibroblasts[39,40]. These GLI1$^+$ cells are critical for building mineralized fibrocartilage and their activity seems to be controlled by muscle loading. Accordingly, inhibition of smoothened homologue (SMO), a key component of hedgehog signalling pathways, has been shown to block enthesophyte formation[41]. Furthermore, parathyroid hormone-related peptide is also expressed in the entheses and probably supports the recruitment and/or activity of underlying bone cell populations[42].

Osteoblast differentiation and new bone formation are facilitated by bone morphogenic proteins (BMPs) and Wnt proteins. Increased BMP and Wnt expression has been associated with excessive new bone formation and the generation of bone spurs. For instance, BMP2 is expressed by mesenchymal cells of the entheses and BMP6 and BMP7 are expressed during the later stages of chondrocyte differentiation[43]. Similarly, both murine and human entheses show activation of SMAD1–SMAD5 during inflammation, indicative of active BMP signalling[44]. Inhibition of the BMP signalling pathway by noggin retards new bone formation in male DBA1 mice, a model of enthesitis characterized by enthesophytes[44]. Thus, BMPs seem to essentially promote the proliferation of mesenchymal precursors, which are required to form hypertrophic chondrocytes. These cells build the scaffold for the later apposition of new bone by osteoblasts, which form the enthesophyte. Wnt proteins and their inhibitors, DKK1 and sclerostin, are key effector molecules for osteoblast activity and enable new bone apposition at entheseal sites[36,37]. The balance between Wnt proteins and their inhibitors is also crucial for the amount of new bone formed at entheseal sites. For instance, blockade of the Wnt inhibitor DKK1 is associated with more pronounced differentiation of mesenchymal stem cells into hypertrophic chondrocytes, resulting in bony spur formation at peripheral joints as well as ankylosis of the sacroiliac joints[36,45].

Detection and assessment of enthesitis

Prevalence and clinical presentation

In a 2016 publication, Polachek and colleagues provided a detailed analysis of the prevalence and clinical presentation of enthesitis in >800 patients with PsA[46]. Enthesitis was defined as pain at specific tendon insertion sites (such as the Achilles tendon or the plantar fascia) using established clinical instruments, which are described below. The prevalence of enthesitis in patients with PsA in this study was 35%, with the Achilles tendons, plantar fasciae and lateral epicondyles being the most commonly involved sites. Additional studies have suggested that enthesitis can be among the first symptoms of PsA and SpA[47,48]. High body mass, more active joint disease and young age are factors associated with the appearance of enthesitis. The association of young age with enthesitis might indirectly implicate mechanical load as a trigger of entheseal inflammation, as physical activity is usually higher in younger individuals than older individuals[46].

Whereas the prevalence of enthesitis (defined as pain at defined sites) seems to be between 30% and 50% in patients with PsA, the overall burden of enthesitis might in fact be higher for two reasons. Firstly, entheseal sites are more abundant than those assessed in standard clinical examinations. Because entheses are also found in direct conjunction with the joints, arthralgia in PsA and SpA can sometimes result from enthesitis rather than from synovitis, hence the attribution of joint pain to synovitis can lead to an underestimation of the prevalence of enthesitis. This concept is supported by MRI studies in patients with SpA, which showed enthesitis

underlying the clinical manifestation of 'arthritis' (REF. 49). Secondly, the application of imaging rather than palpation of entheses yields a substantially higher prevalence of enthesitis, with ~70% of patients with PsA affected by enthesitis[50,51]. Hence, the overall clinical burden of enthesitis in patients with PsA and SpA is high and possibly still underestimated[52].

Clinical assessment

Traditionally, the presence of enthesitis is ascertained by clinical examination. Clinically, the only way to assess the presence of enthesitis is to assess tenderness at the entheseal site. However, it is not clear whether tenderness always denotes inflammation, nor it is clear whether the absence of tenderness rules out enthesitis. In contrast to synovitis, where swelling in addition to tenderness is an important discriminator between inflammation and pain, swelling is absent in enthesitis with the exception of bony enlargement resulting from enthesophyte formation or occasional entheseal enlargement (TABLE 1). Hence, the question of whether tenderness at entheseal sites is related to hyperalgesia alone or indeed is also related to an inflammatory process is difficult to answer by clinical examination alone.

Despite these challenges, reliable clinical instruments have been developed to assess enthesitis, which add up tender entheseal points[53]. The Spondyloarthritis Research Consortium of Canada (SPARCC) index covers the 16 most relevant peripheral sites affected by enthesitis such as the Achilles tendon, plantar fascia and femoral trochanter as well as entheseal sites at the knees, elbows and shoulders[54]. The Leeds enthesitis index (LEI) is also focused on the assessment of peripheral enthesitis but is confined to only six entheses (Achilles tendon, lateral distal humerus and medial distal femur on each side of the body)[55]. The third index for clinical evaluation of enthesitis is the Maastricht ankylosing spondylitis enthesitis score (MASES), which focuses primarily on the axial entheses such as those along the ribs and the iliac crest; the Achilles tendon is the only peripheral entheseal site included in this score[56]. MASES largely replaced the rarely used and hardly feasible Mander enthesitis index (MEI), which assesses a total of 66 entheses in the spine and peripheral skeleton[57]. To date, the SPARCC, LEI and MASES indices are mostly used in clinical trials to assess the efficacy of DMARDs for enthesitis, whereas their use in clinical practice is limited. This situation might seem surprising since these easy-to-use instruments are the only clinical tools available for assessing enthesitis and because joint counts have been used successfully for many years in the clinical assessment of synovitis.

Imaging of enthesitis

The acknowledged limitations in the clinical assessment of enthesitis have prompted clinicians to search for better instruments for its detection and monitoring. Although pain is an important, if not the most important, clinical sign of enthesitis, it is not specific and hence does not prove the presence of enthesitis. Therefore, different imaging modalities have been applied to better detect enthesitis and to distinguish it from mere pain

Table 1 | **Comparison of the features of enthesitis and synovitis**

Feature	Enthesitis (PsA and SpA)	Synovitis (RA)
Anatomical localization	Extra-articular	Intra-articular
Tissue composition	Fibrocartilage	Synovial membrane
Mechanical trigger	+++	+
Aetiopathogenesis	Danger response	Autoimmunity
Resident immune cells	γδ T cells, type 3 innate lymphoid cells	Tissue-resident macrophages
Resident non-immune cells	Periosteal and fibrocartilage MSCs	Fibroblast-like synoviocytes
Type of immune activation	Innate (mostly polymorphonuclear neutrophils)	Mixed
Genetic associations	MHC class I genes, *IL23R*	MHC class II genes
Clinical symptoms	Pain	Pain, swelling
Pre-clinical phase	Subclinical enthesitis	Autoantibodies, tenosynovitis
Bone marrow involvement	+++	+
New bone formation	+++	–
PGE2 dependence	+++	+
Clinical effect of methotrexate	–	++
IL-17–IL-23 dependence	+++	+
IL-6 dependence	–	+++
TNF dependence	+++	+++
Associated organs	Gut, skin	Lungs

–, absent; +, minor; ++, moderate; +++, strong; MSC, mesenchymal stem cell; PGE2, prostaglandin E2; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis-,

or the involvement of adjacent structures[58]. Assessment of enthesitis by imaging reflects the pathophysiological processes underlying enthesitis, demonstrating either the inflammatory phase or the tissue response phase of the disease.

Imaging the inflammatory phase of enthesitis. The inflammatory phase of enthesitis can bedetected by visualizing the hyperaemia and vasodilation that precedes and facilitates both immune cell migration and the deposition of an inflammatory infiltrate. A 1998 study by McGonagle *et al.* marked the first use of MRI for demonstrating the link between enthesitis and arthritis, confirming the hypothesis that enthesitis is the landmark lesion of SpA[49]. MRI is particularly useful in detecting perientheseal osteitis, which appears as soft tissue 'oedema' on short tau inversion recovery (STIR) images and fat-suppressed contrast-enhanced T1-weighted images in the bone marrow adjacent to entheses (see also the schematic drawing in FIG. 3). Detection of perientheseal osteitis by use of MRI is also of importance in the assessment of axial disease associated with PsA and particularly in SpA. MRI has revealed that osteitis is a hallmark of inflammation in axial fibrocartilagenous joints such as the sacroiliac and sternoclavicular joints as well as in the vertebral bodies in patients with axial SpA or ankylosing spondylitis[59]. Furthermore, MRI studies have also shown that extensive osteitis sometimes accompanies peripheral enthesitis, such as enthesitis adjacent to the plantar fascia, in patients with peripheral SpA[60]; similar, although less extensive, lesions have also been observed in mechanical enthesitis[60]. A study using whole-body MRI revealed the coexistence of perientheseal osteitis at axial and peripheral sites in patients with PsA and SpA[61]. Overall, MRI studies support the concept that the entheses and the perientheseal bone marrow form a functional unit. The porous cortical bone, which is characterized by multiple transcortical vessels, enables intensive communication between the bone marrow and the enthesis. In fact, the bone marrow might serve as a 'recruitment pool' for immune cells such as neutrophils entering the entheses through transcortical vessels. Vasodilatation in the perientheseal bone marrow, which appears as a water-rich signal on MRI and is probably triggered by PGE2, might facilitate this process (FIG. 3). Such a concept is strongly supported by ultrasonography studies demonstrating enhanced blood flow based on the vascularization of the enthesis–bone junction[62].

Assessment of vascularization by measuring the power Doppler signal can, to a certain extent, differentiate inflammatory enthesitis from mechanical enthesitis: whereas inflammation is directly localized at the bony insertion in the inflammatory enthesitis of PsA and SpA, the changes in mechanical enthesitis are more distant from the bone and sometimes represent tendinitis rather than enthesitis[58,60]. Ultrasonography studies have shown that enthesitis is an early feature of PsA but is not found in patients with rheumatoid arthritis[63]. Subclinical enthesitis has been detected by ultrasonography in patients with psoriasis without a history of PsA[64–66] and is more common in patients with psoriasis who have clinical nail involvement[64]. The concept of the nail–entheseal

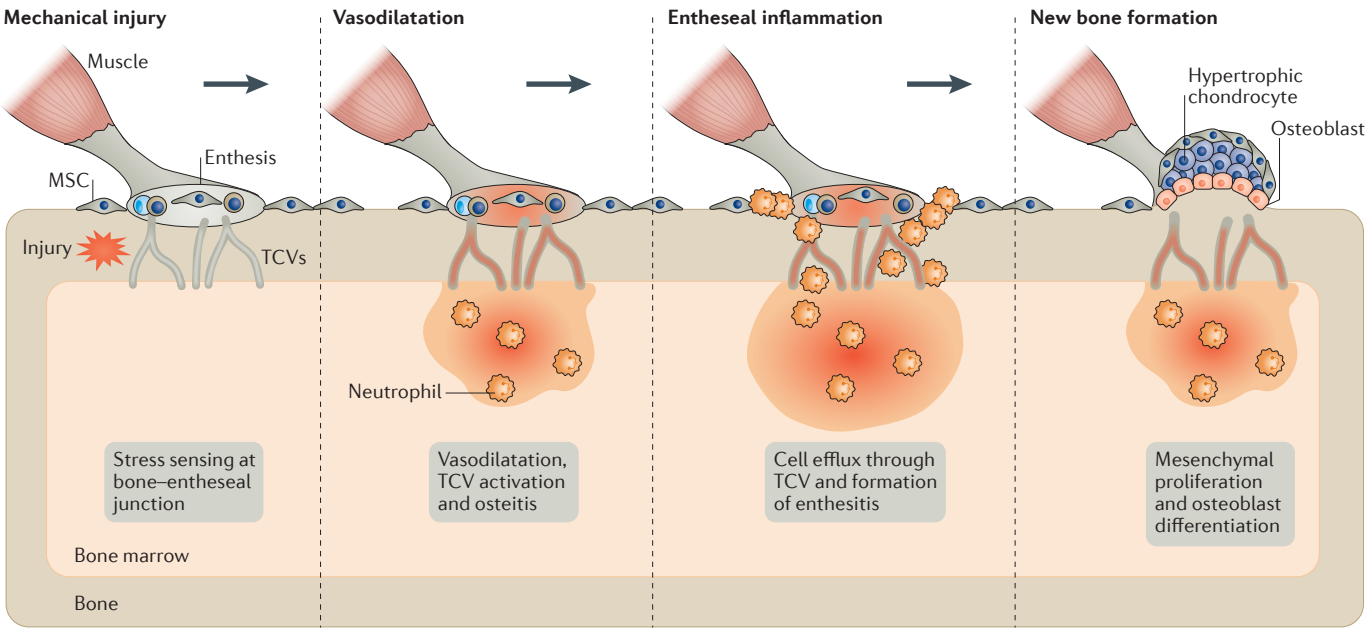

Figure 3 | **Microanatomical changes in enthesitis.** In a normal enthesis, a tendon inserts into a porous trabecularized bone, which is characterized by a high number of transcortical microvessels (TCVs) that enable communication between the bone marrow and the enthesis. The bone–entheseal junction is subject to mechanical stress (red star). Following mechanical stress at the enthesis, TCVs are activated and an inflammatory reaction (osteitis) forms in the adjacent bone marrow. TCV widening via vasodilatation facilitates the efflux of immune cells (such as neutrophils) from the perientheseal bone marrow into the enthesis.

complex is further supported by ultrasonographic signs of enthesitis in the distal interphalangeal joints of patients with psoriasis and PsA[66]. Finally, and supporting the concept of initially PGE2-induced and later cytokine-induced vasodilatation in enthesitis, several studies have shown the responsiveness of entheseal inflammation to treatment with NSAIDs and TNF inhibitors by demonstrating a decrease in the power Doppler signal[67–70].

Imaging the tissue response phase of enthesitis. The anatomical changes related to the considerable tissue responses associated with enthesitis were the focus of imaging research even before the depiction of inflammatory changes. Until 1990, conventional radiography was the only technique commonly available; therefore, the radiographic features of enthesitis have played a pivotal role in defining entheseal lesions in SpA. These features include periarticular osteopenia (most likely related to bone marrow inflammation), cortical bone irregularities and erosions at insertion sites (most likely linked to enlarged transcortical vessels), and signs of calcification and new bone formation, which are pathognomonic for enthesitis. Instruments developed to score new bone formation, such as the Stoke ankylosing spondylitis spine score (SASSS) and Rathingen score, were later used to enable the quantification of tissue responses in axial and peripheral entheseal disease, respectively[71,72]. In addition to conventional radiography, ultrasonography is particularly instrumental to investigating structural pathology in the peripheral joints, with the first study of this approach dating back to 1994 (REF. 73). Ultrasonography can depict structural lesions such as bone erosions, bony spurs and thickening of the tendon or ligament insertion[74]. Scoring instruments such as the Glasgow ultrasound enthesitis scoring system (GUESS)[75] or the Spanish enthesitis index (SEI)[76] have been developed to assess the presence and severity of enthesitis on the basis of such morphological changes, even though these findings are also commonly found in mechanical pathologies. More recently, high-resolution peripheral quantitative CT (HR-pQCT) was introduced to define structural lesions in enthesitis, in particular the quantification of new bone formation in PsA. Studies using HR-pQCT showed that entheseal new bone formation is a very early sign of musculoskeletal involvement in patients with psoriasis[28]. Furthermore, enthesophytes represent the dominant structural feature in established PsA but are virtually absent in rheumatoid arthritis. These data suggest that a large component of the structural changes seen in PsA is driven by entheseal inflammation[29]. Moreover, HR-pQCT showed that TNF inhibition arrests the progression of bone erosions but does not halt the progression of enthesiophye formation, indicating essential differences in the pathophysiology of bone erosions and enthesophytes[77]. Taken together, imaging studies using conventional radiography, ultrasonography and HR-pQCT have been essential to understanding the tissue responses associated with enthesitis that escape detection by physical examination.

Treatment of enthesitis

The most stringent proof that a certain pro-inflammatory mediator has a pathophysiological role in a disease process is that a compound inhibiting that mediator has therapeutic efficacy[78]. Notably, current knowledge on the treatment of enthesitis is limited. Remarkably, to date no study has been specifically designed to evaluate the treatment of enthesitis. DMARDs have not been studied in enthesitis and clinical trials of cytokine-blocking agents in which enthesitis instruments were applied (in those patients who actually demonstrated enthesitis) were not powered to assess enthesitis. Nonetheless, the observations on the apparent therapeutic efficacy of drugs in the treatment of enthesitis largely support the pathophysiological concepts introduced in the first part of this Review.

In clinical practice, the treatment of enthesitis aims to resolve inflammation and prevent subsequent inflammation-induced tissue responses. To date, all drugs used for treating enthesitis aim to stop entheseal inflammation and relieve symptoms. The concept that resolution of entheseal inflammation might also affect the related tissue response is, however, not well developed. Enthesitis and related osteitis often respond to NSAIDs, which are widely used in rheumatic diseases associated with enthesitis such as PsA and SpA. As mentioned, ultrasonography studies have confirmed the effects of NSAIDs on vasodilatation and inflammation at entheseal sites[68]. In fact, clinical observations suggest that enthesitis is much more sensitive to NSAIDs than is synovitis, pointing to a more dominant role of PGE2 in enthesitis than in synovitis. The effects of NSAIDs in enthesitis might rely on the inhibition of vasodilatation of transcortical and bone marrow vessels as well as the limitation of PGE2-associated pain responses. Furthermore, NSAIDs suppress tissue responses associated with enthesitis, as PGE2 is a potent inducer of osteoblasts[35]. In axial SpA, the use of NSAIDs might also retard new bone formation, although the data are not always consistent[79,80].

If enthesitis becomes chronic, NSAIDs often do not adequately control disease and additional drugs are required. Unfortunately, methotrexate does not show efficacy in inhibiting entheseal inflammation, in contrast to its well-documented action in synovitis. Similarly, other conventional DMARDs, such as leflunomide and sulfasalazine, do not seem to work in enthesitis. By contrast, the phosphodiesterase 4 inhibitor apremilast, which has been approved for the treatment of PsA, is currently the only orally available DMARD with proven efficacy in enthesitis. Apremilast inhibits the production of several cytokines involved in entheseal inflammation, such as IL-17A, IL-23 and TNF[81], and also limits the migration of neutrophils to sites of inflammation[82], thereby interfering with the key cytokines and cells involved in the onset of enthesitis. About half of the patients with PsA treated with apremilast show complete resolution of enthesitis as measured by MASES after 1 year of treatment[83]. Although these results are encouraging, further data in peripheral enthesitis is needed for apremilast as MASES focuses largely on axial rather than peripheral enthesitis, whereas other indices (such as SPARCC and LEI) better discriminate peripheral enthesitis[84].

The role of TNF inhibitors in controlling enthesitis is reflected by their well-documented efficacy in improving spinal pain in axial SpA and ankylosing spondylitis[85,86]. Spinal pain in axial SpA and ankylosing spondylitis is presumed to originate from inflammation of fibrocartilagenous entheseal joints such as the sacroiliac joints and the ligament insertion sites at the anterior and posterior bodies of the vertebrae, which are usually associated with substantial osteitis. In addition, TNF inhibitors also improve the signs and symptoms of peripheral enthesitis, such as in the heels of patients with axial SpA and peripheral entheseal involvement[87]. Accordingly, results from several clinical trials in PsA provide substantial evidence that TNF inhibitors are efficacious in controlling peripheral enthesitis: after treatment with infliximab, the number of patients with symptoms of enthesitis in the feet declined by 50% in one trial[88]; improvements in all three aforementioned enthesitis indices (SPARCC, LEI and MASES) have been reported following treatment with adalimumab[84,89]; and etanercept, golimumab and certolizumab[90–92] have proven efficacy in the treatment of peripheral enthesitis.

MRI studies have confirmed the concept that axial and peripheral entheseal inflammation are responsive to TNF inhibitors. In particular, peri-entheseal osteitis along the sacroiliac joints and in the vertebral bodies in ankylosing spondylitis resolved after TNF inhibition[93]. Furthermore, studies on peripheral enthesitis in PsA have shown that TNF inhibition improves peri-entheseal osteitis detected by MRI[94] and increased vascularization measured by power Doppler ultrasonography[62,70]. Taken together, these clinical and imaging data provide robust evidence that TNF is an effector cytokine in enthesitis.

Apart from TNF inhibition, newer data have revealed a striking responsiveness of enthesitis to inhibition of IL-23 and IL-17A. Ustekinumab, an antibody against the p40 subunit common to IL-12 and IL-23, has shown to effectively treat enthesitis in slightly more than 50% of patients with PsA after 6 months of treatment[95]. Considering that <20% of patients with PsA treated with ustekinumab achieve a high-level response (that is, ≥70% improvement in ACR response criteria) in their joint symptoms, the improvement in enthesitis is remarkable and strongly supports a central role of the IL-23–IL-17 axis in entheseal inflammation. This concept is also supported by data on IL-17A inhibition in PsA and ankylosing spondylitis: treatment with the IL-17 inhibitors secukinumab and ixekizumab results in improvements in enthesitis scores with resolution of enthesitis in ~50% of the patients treated with secukinumab and 30–40% of those treated with ixekizumab[96,97]. Overall, the remarkable clinical efficacy of inhibitors of the IL-23–IL-17A pathway in enthesitis, and the ability of these therapeutic agents to control the symptoms of axial disease in ankylosing spondylitis, supports the pathophysiologic concept of an IL-23–IL-17A pathway-dependent inflammation of entheseal structures.

Conclusions

Experimental and clinical observations reveal remarkable differences between entheseal and synovial inflammation with respect to their pathogenesis, diagnosis and treatment. Enthesitis is a distinct disease process, which can occur independently of arthritis. It relies on a multistep process consisting of initiation and augmentation of inflammation followed by local tissue responses leading to new bone formation. Mechanical stress, innate immune activation and mesenchymal tissue modelling and remodelling are hallmarks of the process of enthesitis and are guided by distinct molecules and cells. Despite the development of this mechanistic framework, which is supported by findings showing the effects of drugs targeting entheseal inflammation, there are still substantial limitations in our knowledge of how enthesitis works. Experimental modelling of enthesitis is in its infancy, especially when compared with the modelling of arthritis. Furthermore, the accessibility of human entheseal tissue is very limited, which has retarded progress in defining the key cellular and molecular players of enthesitis in human disease. Some, but not all, of these hurdles can be overcome by applying modern imaging techniques. However, further insights into the molecular and cellular players of enthesitis are also needed. We anticipate that modern immunologic research will be able to tackle some of these open questions.

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