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Diagnosis and Management of Enthesopathy

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ABSTRACT

Enthesopathy is inflammation of the enthesis. Outcome Measures in Rheumatologic Clinical Trials (OMERACT) defined enthesopathy as abnormal hypoechoic (loss of normal fibrillar architecture) and/or tendon or ligament thickening at the site of bone attachment (sometimes containing hyperechoic foci that resemble calcifications) seen in two perpendicular planes on Doppler and/or bony changes including ensophytes, erosions, and irregularities. The causes of enthesopathy are categorized into two, namely, non-inflammatory causes and inflammatory causes. Non-inflammatory causes include trauma, degenerative, autoimmune, genetic, and metabolic. The causes of inflammation areas in seronegative spondyloarthropathy.

1. Introduction

Enthesopathy is defined as abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickening of tendons or ligaments at the site of bone attachment (sometimes containing hyperechoic foci such as calcifications) seen in two perpendicular planes on Doppler and/or bony changes including ensophytes, erosions and irregularities. The causes of enthesopathy are categorized into two, namely, non-inflammatory causes and inflammatory causes. Non-inflammatory causes include trauma, degenerative, autoimmune, genetic and metabolic. The causes of inflammation are as in seronegative spondyloarthropathy.[1,2]

Enthesis is the site of attachment of tendons, ligaments, joint capsules, or fascia to the bone. Enthesis comes from the ancient Greek word "entetikos" which means that which is put in from the outside. In the 19th century, the term was used to denote diseases that were implanted into the body from the outside. In the 20th century, the term enthesis has only been used until recently to refer to a focal insertion abnormality at the site of attachment of tendons, ligaments, fascia, muscles or capsules to the bone. The term enthesopathy was first introduced by La Cava to refer to a traumatic injury to a tendon insertion. Several studies have proposed to extend the concept of insertion not only to the area of attachment of tendons

and ligaments but also to cartilage attachment sites in subchondral bone and all sesamoid and periosteal fibrocartilage. Recently, the European League Against Rheumatism (EULAR) recommended the use of the term " enthesopathy " to denote pathology (including inflammatory and degenerative, metabolic or traumatic changes) and the use of the term " enthesitis " when inflammation occurs. In the rheumatology literature, the term enthesitis almost always refers to the pathological changes that occur in patients with spondyloarthritis.[3]

Enthesopathy is a common feature of spondyloarthropathies (SpA) which is often used to determine diagnostic classification and treatment management. Recognizing enthesopathy is a challenge because of the low sensitivity and specificity of the test. EULAR recommends *magnetic resonance imaging* (MRI) or ultrasonography (USG) to detect enthesopathy. The low availability of MRI limits its use, so ultrasound is often used for the detection of enthesopathy. Ultrasound is an effective examination to detect structural changes such as erosion, bursitis, calcification, thickening, or hypoechogenicity. Enthesopathy is a sign of musculoskeletal stress has been widely used to reconstruct activity levels in human skeletal populations. In general, the few studies that exist focus on the presence of enthesopathy in the upper extremities, which are used in most activities of daily living.[4]

The prevalence of enthesopathy is difficult to assess and quantify given the varied nature, presentation, and etiology of enthesopathy. It has been reported that the prevalence of enthesitis is about 35% in psoriatic arthritis patients. In patients with spondyloarthritis, 10 to 60% of patients have enthesitis [4]. In a study conducted by Santiago *et al* consisting of 60 patients with spondyloarthritis and 30 control groups. This study analyzed the enthesis with ultrasonography to see the signs of enthesopathy. From this study, we found a prevalence of 9.3% for enthesopathy in patients with spondyloarthritis.[5] Another study conducted by Lambert *et al,* covered the prevalence and characteristics of shoulder involvement in *ankylosing spondylitis.* This study included 100 patients with ankylosing spondylitis and 285 controls. From this study, it was found that shoulder enthesopathy occurred in 41.2% of the group of patients with ankylosing spondylitis.[6] Another study conducted by Kamo *et al* explained that the incidence of enthesopathy in spondyloarthritis was 63.6% and 54.1% in patients with trauma, respectively. From this study, it was also found that the risk of enthesopathy increases with age in patients with spondyloarthritis[7].

Traditionally, enthesitis was thought to be a disorder only at the site of insertion, but imaging studies and pathological findings suggest that enthesitis is a diffuse process with effects on adjacent bone and soft tissues. Some of the concepts for the occurrence of enthesitis include a repetitive biomechanical process, which triggers an inflammatory response in the synovium due to microdamage to the enthesis until synovitis occurs. Along with mechanical stress, exogenous bacteria may also play a role in activating the immune response, particularly in individuals with a genetic predisposition encoding the MHC class 1 locus of the HLA-B27 molecule. Recent studies in animals have shown that there is autoimmunity to versican and fibrocartilage proteins and bone morphogenetic protein (BMP) signaling that develops into enthesitis. Currently, the involvement of interleukin-23 (IL-23) in enthesitis is mediated by interleukin-17 (IL-17) and tumor necrosis factor (TNF), as well as interleukin-22 (IL-22)-mediated new bone formation. [8]

Pathophysiological concepts are still under development, disease prevalence is still difficult to determine, diagnosis is difficult, and treatment options are still limited to non-steroidal anti-inflammatory drugs and DMARDs. In recent years, TNF-blocking drugs are beneficial. Further studies on the inhibitory effect on IL-22 and IL-23 also need to be understood. The many obstacles and limitations the authors discuss comprehensively the pathophysiology and management of enthesopathy.

Pathophysiology of enthesopathy

Enthesitis is triggered primarily by the innate immune response. Clinical observations indicate that mechanical stress is a central factor in inducing enthesitis. Enthesitis mainly affects the lower limbs,

which are often subjected to higher mechanical forces than the upper limbs. The exact molecular process by which mechanical stress causes enthesitis remains to be determined. The initial mediator of enthesitis is prostaglandin E2 (PGE2) (Figure 1).[9-13]

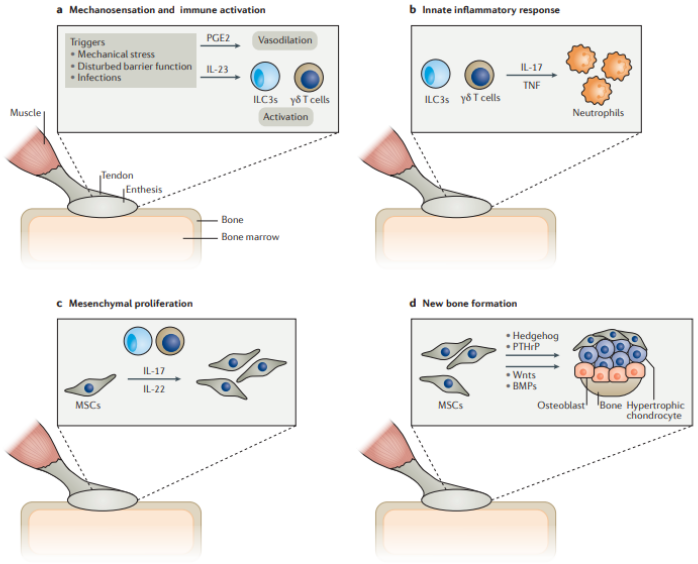

Figure 1. Enthesitis function model[13]

The role of PGE2 in enthesitis is evidenced by its good response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in axial and peripheral enthesitis. Local production of PGE2 may allow a rapid stress response to excessive mechanical loading or other triggers in the enthesis. Local mesenchymal cells express inducible prostaglandin G/H synthase 2 (also known as cyclooxygenase 2), which accounts for the site-specific production of PGE2, which is the main enzymatic product of cyclooxygenase. PGE2 induces vasodilation, which may also widen the transcortical vessels and facilitate the withdrawal of neutrophils from the bone marrow into the enthesis compartment (figure 2) This process explains the development of an inflammatory reaction around the bone marrow (osteitis), which is observed on MRI of patients with PsA and SpA and usually associated with pain. Furthermore, PGE2 stimulates the production of IL-17 by T cells and correlates the initial inflammatory response with activation of the IL-23-IL-17 pathway.[13]

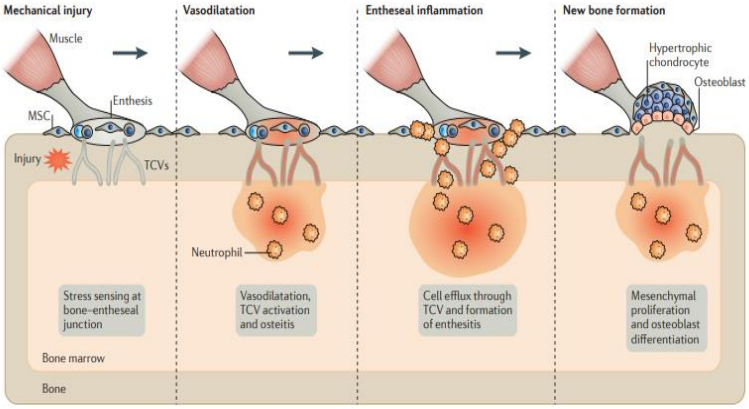

Figure 2. Changes in microanatomy entesitis[13]

Studies in mice suggest that IL-23, a cytokine derived from macrophages and dendritic cells, has a key role in enthesitis. In mouse enthesis, there are T cells that express IL-23R. T cells are known to represent a major cellular source of IL-17 and TNF. Whether other IL-23R-expressing cells populate the enseal site remains to be confirmed.[13]

Some evidence suggests that innate lymphoid cells are of interest in this regard. These cells do not express T cell receptors but share cytokine activation pathways of certain T cell lineages. Innate lymphoid type 3 cells (ILC3), for example, express IL-23R, produce IL-17A and can be found in normal human synthesis. The functional role of these cells in enthesitis, however, remains to be determined. IL-17 production appears to be an important step in enhancing the inflammatory response in the enthesis. IL-17 promotes neutrophil migration and activation, a process also observed in the skin disease psoriasis and links IL-23 and IL-17 activation with the effector phase of inflammation. IL-17 acts as a trigger for enthesitis and induces the production of various cytokines and mediators by mesenchymal cells, which can trigger neutrophil migration and activation. Among these pro-inflammatory cytokine products are a granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6 and IL-8, which are major chemoattractants for neutrophils. Neutrophils are important effector cells in inflammatory enthesis.[12,13]

In enthesitis, neutrophils further enhance the inflammatory response by releasing proteases and reactive oxygen species, which exacerbate the pain response during enthesitis. Very few histopathological studies have been performed on human enthesitis. This study showed that macrophages also infiltrate the enthesis tissue. The state of activation of neutrophils and macrophages is very important in determining the development of enthesitis. Uncontrolled activation of signal transducer and activator of transcription 1 (STAT1) in myeloid cells has also been shown to induce enthesitis by promoting cytokine release. In the absence of protein A20, the negative regulator of STAT1, enthesitis develops spontaneously.[13]

Inflammation of the enthesis is characterized by an overwhelming tissue response (Fig. 1). At the heart of these structural changes is local new bone formation. Although erosion can occur in the context of enthesitis, the effect of inflammation of the enthesis is the addition of new bone, which is often characterized by excessive local apposition of periosteal bone at the enthesopian sites. In the spine, the anterior and posterior parts of the vertebrate body are affected, leading to the formation of syndesmophytes and subsequent spinal ankylosis. At the periphery, enthesis such as the plantar fascia is affected by new bone formation (calcaneal spurs). Furthermore, enthesis in peripheral joints such as the hand joints promotes new bone formation in psoriatic arthritis. Remarkably, the first sign of musculoskeletal involvement in patients with psoriasis is the formation of enthesophytes in the peripheral joints, the role of enthesitis as an early feature of diseases such as psoriatic arthritis and spondyloarthritis.[13]

Mechanically, new bone formation represents a tissue response process that begins after reaching the peak of enthesis inflammation. This process is initiated by local mesenchymal cells, which have the potential to proliferate and differentiate into chondroblasts and osteoblasts and to form cartilage and bone. In some respects, new bone formation enthesis resembles fracture repair, which is characterized by a rapid and vigorous mesenchymal response after the initial inflammatory phase. The molecules linking the inflammatory phase to the tissue response in enthesitis are still unknown but IL-17, IL-22 and PGE2 have been implicated in this process. IL-17, for example, has been shown to effectively activate mesenchymal cells. Furthermore, although epithelial cells are key targets of IL-22, local cells in other enzymes, such as mesenchymal cells, also respond to this cytokine and therefore IL-22 may promote new bone formation. Finally, PGE2 is a strong trigger for osteoblast

differentiation and may therefore link enthesis inflammation with new bone formation.[13]

TNF appears to be the main anti-anabolic inducing Dickkopf-related protein 1 (DKK1) and sclerostin. Both effectively block bone formation. Although there is experimental evidence that the absence of TNF slows fracture repair, the clinical relevance of this observation remains unclear. In contrast to the process of initiation of growth of the ensophyte, the factors required for the differentiation of chondroblasts and osteoblasts are well characterized. Hedgehog protein activates a specific cell population in the enthesis (cells expressing the Hedgehog regulatory transcription factor, GLI1), which is distinct from tendon fibroblasts. These GLI1 cells are essential for forming mineralized fibrocartilage and their activity is controlled by muscle loading. Hence, inhibition of smoothened homologue (SMO), a key component of the Hedgehog signaling pathway, has been shown to block ensophyte formation. Furthermore, parathyroid hormone-associated peptides are also expressed in the enthesis and may support the withdrawal and/or activity of the underlying bone cell population.[13]

Research by Lories *et al*, showed that osteoblast differentiation and new bone formation were facilitated by bone morphogenic protein (BMP) and Wnt protein. Increased expression of BMP and *Wnt* has been associated with excessive new bone formation and bone spur formation. For example, BMP2 is expressed by mesenchymal cells of the enthesis and BMP6 and BMP7 are expressed during later stages of chondrocyte differentiation. Similarly, human and mouse enthesis showed SMAD1–SMD5 activation during inflammation, indicating an active BMP signal. Inhibition of the BMP signaling pathway by *noggin* inhibits new bone formation in the enthesitis-tagged male DBA1 mouse model of enthesitis. Thus, BMP essentially promotes the proliferation of mesenchymal precursors, which are required to form hypertrophic chondrocytes. These cells form the subsequent apposition of new bone by osteoblasts, which form the ensophytes. The protein *Wnt* and its inhibitors, DKK1 and sclerostin, are effector molecules for osteoblast activity and enable the apposition of new bone in the enthesis. The balance between protein *Wnt* and its inhibitors is also important for the amount of new bone formed in the enthesis. For example, blockade of the inhibitor *Wnt* DKK1 is associated with more pronounced differentiation of mesenchymal stem cells into hypertrophic chondrocytes, resulting in bone spur formation in peripheral joints as well as sacroiliac joint ankylosis.[12,13]

Diagnosis of enthesopathy

The history and physical examination of enthesopathy or enthesitis depend on the location of the affected enthesis. Clinically, the only way to assess enthesitis is to assess tenderness at the site of the enthesis. However, the presence of swelling on palpation of the enthesis site indicates inflammation and the absence of pain may rule out an enthesitis or enthesopathy. This is in contrast to synovitis, where swelling and tenderness are important differentiators between inflammation and pain. Swelling is absent in enthesitis except for bone enlargement due to enthesophyte formation. (Table 1).[13]

Various clinical instruments were developed to assess enthesitis. The Spondyloarthritis Research Consortium of Canada (SPARCC) index includes 16 sites of peripheral enthesis relevant to enthesitis such as the Achilles tendon, plantar fascia and femoral trochanter as well as the location of the enthesis in the knee, elbow and shoulder. Other indices such as the Lead enthesitis Index (LEI) were also used but were limited to peripheral enthesitis at six enthesitis sites (Achilles, lateral distal humerus and distal medial femur on each side of the body). Another index is the Maastricht ankylosing spondylitis enthesitis score (MASES), which focuses on axial entheses such as the ribs and iliac crest. To date, these three indices have been widely used in clinical trials assessing the efficacy of DMARDs for enthesitis.[13]

Based on its prevalence, enthesitis occurs in 30-50% of spondyloarthritis patients. This prevalence may be lower than it is. This is caused by the location of the enthesis which is more than the standard clinical examination performed. Entheses are also present in the joints, but the arthralgia that occurs (in patients with spondyloarthritis and psoriatic arthritis) is considered synovitis, thereby reducing data on the prevalence of enthesitis. This concept is supported by MRI findings in spondyloarthritis patients showing the occurrence of enthesitis with arthritis symptoms. In addition to these causes, the application of imaging is still low in patients with spondyloarthritis and psoriatic arthritis so that the prevalence of enthesitis may still be underestimated.[13]

Table 1. Difference between enthesitis and synovitis[13]

Assessment	Enthesitis (Psa and SpA)	Synovitis (RA)
Anatomical location	Extra-articular	Intra-articular
Tissue composition	Fibricartilage	membrane
Triggers Mechanism	+++	+
Etiopathogenesis	Danger Response	Autoimmune
Immune	γδT cell, ILC tipe 3	Tissue-resident macrophages
cells Non-immune	Periosteal and fibrocartilage MSCs	SynovialFibroblast-like synoviocytes
cells Types of activated immune cells	Innate immune cells (neutrophil PMNs)	Mixed
Genetics	MHC Class I genes, IL -23R	MHC class II gene
Clinical symptoms	Pain	Pain, swelling
Preclinical phase	Subclinical enthesitis	Autoantibodies, tenosynovitis
Bone marrow involvement	+++	+
New bone formation	+++	-
Role of PGE2	+++	+
Effects MTX	-	++
Role of IL-17 and IL-23	+++	+
Role of IL-6	-	+++
Role of TNF	+++	+++
Other organ involvement	Intestines, skin	Lung

Imaging features of enthesopathic lesions are delaminated tears, blood vessels, scars on the fibrous area, and erosions and cysts on the fibrocartilage and bone. Due to the presence of delamination and irregular structure of collagen fibers, enthesopathy has blood vessels and granulation tissue. In such cases, histopathological examination revealed collagen fiber damage, scars, degenerative changes (including hypocellular areas, hyalinization, lipid infiltration) as well as rupture and features of the repair process (Figure 3).[15]

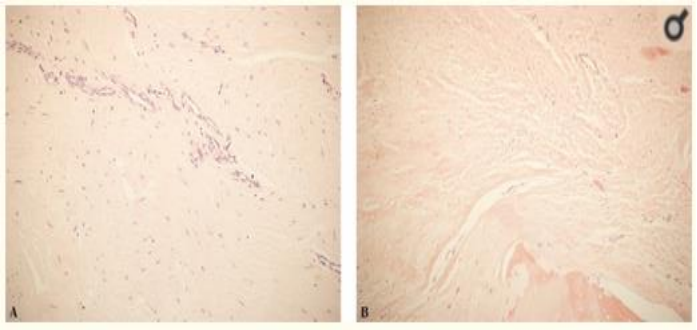

Figure 3. A) Fibrous inflammatory granulation tissue in tendons includes fibrous connective tissue B) Degenerative changes in tendons at the site of attachment to focal necrosis.[15]

In the early phase of enthesopathy, plain radiographs show osteoporosis of the enteeal bone component and soft-tissue thickening. In advanced stages, subchondral sclerosis, ensophytes and erosions may be seen (Figure 4).[16]

MRI can detect enthesitis in spondyloarthritis patients when conventional radiographs are normal. The characteristic features of enthesitis on MRI are inflammatory changes in the soft tissues outside the joint capsule and the presence of perienetic bone marrow edema. On MRI, the fibrous portion of the enthesis is less visible because of the low water content. More specifically, changes in tissue adjacent to an enthesis (e.g. localized in the bursa or adipose tissue). MRI is the only imaging modality that allows the identification of bone marrow edema in the subchondral tissue (Fig. 4.3). MRI also has a limitation, namely that the structures that make up the enthesis have a low signal in conventional MRI. In addition to the above, MRI is also limited by its cost and availability, so ultrasound is the preferred modality for detecting enthesitis [17,18]

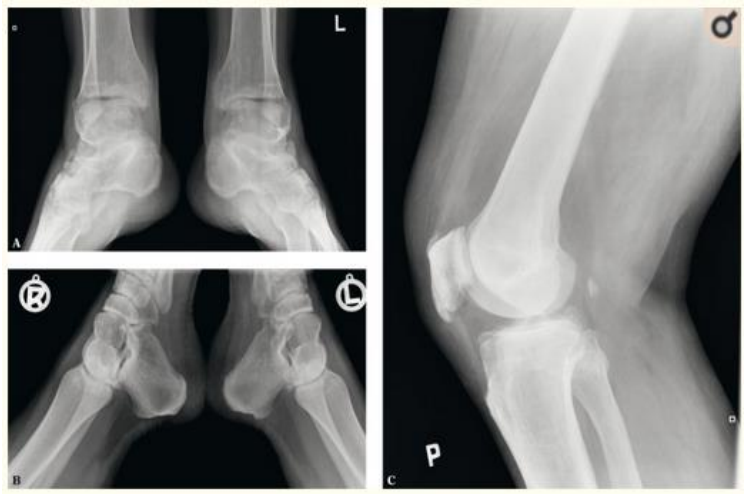

Figure 4. A. mineralized scar (entesophyte or lower spur) on the undersurface of the calcaneal tuberosity of the flexor digitorum brevis enthesis, erosion of the medial malleolus with concomitant ossification reaction; B. erosion of the bony portion of the Achilles tendon enthesis on the left side; C. Mineralized scar on patellar enthesis of quadriceps femoral tendon and patellar ligament[16]

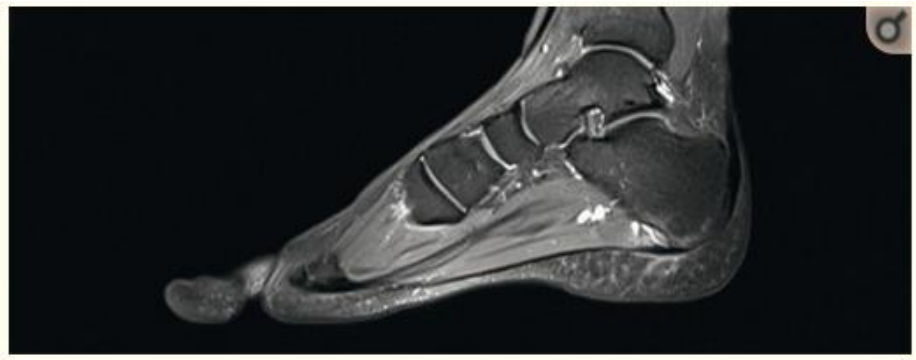

Figure 5. MRI of the foot: bone marrow edema in the plantar area, with thickening of the enthesis and swelling of adjacent fatty tissue.[16]

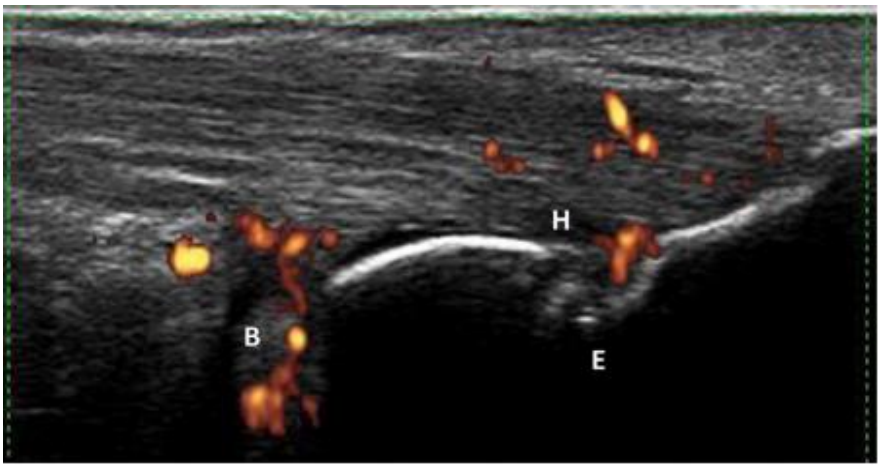

Figure 6. Ultrasound components of enthesitis of the Achilles tendon. (H) hypoechoic, (E) calcaneus erosion, (B) retrocalcaneus bursitis[17]

Ultrasound is the modality of choice in assessing enthesis. Ultrasound is useful in the diagnosis of subclinical enthesitis. In a study of 600 lower extremity enthesitis, 60% of asymptomatic cases found one sign of enthesitis on ultrasound. In a study of 51 spondyloarthritis patients with 24 controls, without MRI examination or using Power Doppler Ultrasounds (PDUS) it was possible to differentiate between spondyloarthritis and controls. D,agostino et al found the presence of cortical bone vascularization detected by PDUS which provided predictive value for the diagnosis of spondyloarthritis with a sensitivity of 76.5% and a specificity of 81.3%. PDUS is a sensitive and reliable technique for detecting increased blood flow in the inflamed area.[8,17]

In addition to PDUS, the ultrasound images that are considered sign of enthesopathy are: reduced echogenicity (due to irregular fibrillar structure), thickening (due to damage to collagen fibers), presence of structural lesions, i.e. multidirectional injury, and scars (ranging from the similar in structure to tendons or ligaments, to ossification, i.e. enthesophytes) and erosion of the bony component of an enthesis and increased vascularity seen on Doppler examination (Figure 6).[8,13,16]

Management of enthesopathy

Several aspects need to be understood before starting the treatment of enthesopathy in spondyloarthritis. The first aspect is to determine whether the disease is inflammatory (associated with spondyloarthritis), or predominantly degenerative (where inflammation can also be a feature). The second aspect to know is primary or secondary enthesopathy. Approaches to the treatment of enthesopathy can lead to remission. Refractory enthesitis, defined as symptoms persisting after 2 years despite adequate treatment, occurs in only a minority of cases with such measures.[17]

First-line therapy

Treatment of enthesitis consists of nonsteroidal anti-inflammatory drugs (NSAIDs). Various NSAIDs are effective in the treatment of spondyloarthritis, including indomethacin, diclofenac, naproxen, piroxicam, meloxicam and cyclooxygenase-2 inhibitors, including celecoxib. In clinical practice, the treatment of enthesitis aims to stop

inflammation and reduce symptoms. Research has shown that enthesitis is more sensitive to NASID than synovitis. This explains the more dominant role of PGE2 in enthesitis than synovitis.[13,17,19]

The effect of NSAIDs on enthesitis is to inhibit the process of vasodilation in transcortical blood vessels and bone marrow, reduce pain, and inhibit the induction of osteoblast formation mediated by PGE2. A study by Poddubbnyy D *et al* in 2012 demonstrated a progression of radiographic features in patients with axial spondyloarthritis with NSAIDs. In addition, a study conducted by Sieper J *et al* in 2016 showed radiographic changes in ankylosing spondylitis patients with diclofenac use for 2 years.[13]

Follow-up therapy

There are conflicting data regarding the use of sulfasalazine or methotrexate. The effectiveness is not satisfactory. With the advent of anti-TNF drugs, the role of surgery for refractory isolated peripheral enthesitis will likely be very limited. Severe peripheral enthesitis responds well to anti-TNF agents.[17]

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDS) methotrexate is effective in treating enthesopathy. In the Tight Control of Psoriatic Arthritis (TICOPA) study, in psoriatic arthritis patients, 25.7% of patients with enthesitis had complete resolution at 12 weeks with methotrexate. In another study comparing methotrexate monotherapy, etanercept monotherapy, and methotrexate and etanercept combination therapy in patients with early psoriatic arthritis, there was complete resolution of enthesitis in 43.1% of patients in the methotrexate monotherapy group. Sulfasalazine was found to be ineffective in reducing the number of enthesitis sites in several studies. No other trials are demonstrating the effectiveness of csDMARDS in treating enthesopathy, therefore it is not recommended.[17]

In contrast, the use of the phosphodiesterase 4 inhibitor apremilast, a targeting synthetic DMARD (tsDMARD) approved for the treatment of psoriatic arthritis, is effective in enthesitis. Apremilast indirectly inhibits the cytokines IL-17A, IL-23, and tumor necrosis factor (TNF) as well as neutrophil migration, thereby interfering with the pathogenesis of enthesitis. In the analysis of studies comparing apremilast with placebo, the percentage of patients with enthesitis who had a complete resolution on apremilast (27.5%) compared with placebo (22.5%) at 24 weeks was not statistically significant.[13,17,19] Long-term research data from the PALACE 1-3 studies show that the percentage of patients who achieved complete resolution of enthesitis (MASES index) increased to 55 and 62.4% at 3 and 5 years, respectively. Similar outcomes were found in psoriatic arthritis patients, with 46.4% of patients taking apremilast achieving a Gladman Enthesitis Index (GEI) of 0 at 16 weeks compared with 33.3% of placebo.[17]

Another oral synthetic DMARD target is tofacitinib, a Janus-kinase (JAK) inhibitor. A combined analysis of the two phase-3 trials, OPAL Broaden and OPAL Beyond, showed a higher proportion of patients treated with tofacitinib achieved resolution at 3 months compared to placebo, as measured by the LEI (36.7%) and SPARCC (36.7%) indices. 29.4%). Further improvement was seen in the 6th month. Filgotonib is another JAK inhibitor studied in psoriatic arthritis. In the EQUATOR trial with psoriatic arthritis patients with enthesitis, more patients receiving filgotinib achieved resolution of enthesitis than placebo. These results are promising and provide a good choice in patients who prefer oral treatment.[13,17,19]

In addition to treatment with DMARDs, the effectiveness of the first approved anti-TNF agents for enthesitis in psoriatic arthritis and ankylosing spondylitis, such as adalimumab and etanercept,

was not specifically assessed. A subsequent trial of ACCLAIM using adalimumab showed a statistically significant improvement in the resolution of enthesitis in the Achilles tendon and plantar fascia at 12 weeks. One randomized controlled trial, which used adalimumab as treatment, showed complete resolution of enthesitis (33%) compared with placebo (19.3%) at 24 weeks. The PRESTA study reported an improved enthesitis improvement outcome in 81.3% of patients with psoriatic arthritis who have treated with etanercept 50 mg weekly. The SEAM study on psoriatic arthritis also reported complete resolution of enthesitis on etanercept monotherapy (52.6%) and combination therapy with methotrexate (47.5%). Infliximab has also been shown to be effective in the IMPACT study.[13]

The newer anti-TNF drugs, certolizumab and golimumab, provide further evidence of the effectiveness of anti-TNF in the treatment of enthesopathy. In the GO-REVEAL study, golimumab 50 mg every 4 weeks reduced the prevalence of active enthesitis (49%) compared with placebo (69%) at 24 weeks. Therefore, it can be concluded that anti-TNF agents are effective for enthesopathy.[18,19]

Stronger evidence is available in drugs that block the Th17 pathway. Ustekinumab, an IL-12/23 p40 inhibitor is effective in treating enthesitis in 47% of psoriatic arthritis patients with the peripheral and axial disease compared with placebo (16%). Significant effectiveness has also been demonstrated in observational studies of peripheral psoriatic arthritis when ustekinumab is used as first-line therapy. A significant reduction in mean LEI (1.2–0.5) was noted at 24 months for all patients treated with ustekinumab. A recent study was also conducted by Cuthbert *et al in* which human spinal T cells have been shown to produce IL-17 independent of IL-23 expression. Guselkumab, an IL-23 p19 inhibitor, has also shown promising results in a phase 3 trial for the treatment of enthesopathy in psoriatic arthritis. Data collected from DISCOVER-1 and DISCOVER-2 showed that administration of guselkumab every 4 and 8 weeks achieved complete resolution of enthesitis in 44.9 and 49.6% of patients, respectively, compared with only 29.4% in the placebo group. [13]

A combined analysis of four phase-3 studies of psoriatic arthritis demonstrated the consistent effectiveness of secukinumab (an IL-17 inhibitor) in achieving complete resolution of enthesitis at doses of 300 mg (53.2%) and 150 mg (44.4%) compared with placebo. (29%). Gladman *et al* researched Ixekizumab, a second higher affinity IL-17A inhibitor, which was shown to be effective for enthesitis in the SPIRIT-P1 and SPIRIT-P2 trials. In an analysis of recently collected data, among psoriatic arthritis patients with pre-existing enthesitis, ixekizumab every 2 and 4 weeks achieved significantly more resolution than placebo at 24 weeks. The third IL-17 inhibitor, brodalumab, was studied in psoriatic arthritis patients presenting with enthesitis for 12 weeks by Mease *et al* in 2014 and no statistically significant reduction was found compared with placebo.[13,17,20]

Overall, all current studies provide strong evidence that IL-17 blocking agents are effective in the treatment of enthesopathy or enthesitis. There are limitations in studies comparing the effectiveness of the two drug classes in enthesopathy. Indirect comparisons between drugs with different mechanisms of action yield contradictory outcomes. A recent meta-analysis assessing the indirect effects of biologic agents versus placebo for enthesopathy demonstrated overlap in the effects of anti-TNF and novel biologic drugs targeting IL-17 and IL-23.[17]

In the relatively small ECLIPSA study, which specifically assessed the resolution of enthesitis with the SPARCC index in psoriatic arthritis patients after 24 weeks, 73.9% of patients with UST and only 41.7% of patients with anti-TNF achieved the primary endpoint. In another study (SPIRIT-H2H),

ixekizumab was found to be superior to adalimumab for complete resolution of enthesitis. This study demonstrated the superiority of ustekinumab and ixekinumab over adalimumab for the skin disease psoriasis. These emerging data suggest that IL-17 and IL-23 inhibitors may be the first choice in psoriatic arthritis patients with enthesitis. However, study Additional comparisons of various cytokine inhibitor agents are needed before definitive recommendations can be made.[17]

2. Conclusion

Enthesis is the site of insertion of tendons and ligaments. Enthesopathy is defined as a pathology affecting the enthesis. Enthesitis is part of enthesopathy, is inflammation of the insertion site of tendons and ligaments in bone. It is associated with diffuse inflammatory disorders such as psoriatic arthritis and spondyloarthritis or non-inflammatory disorders. There are two basic processes that underlie the pathophysiology of enthesopathy, namely the first process of induction and inflammation, the second is the process of tissue proliferation and bone formation. Management of enthesopathy consists of first-line therapy in the form of NSAIDs, and continued therapy with DMARDs, TNF inhibitors and IL-17 and IL-23 inhibitors. Treatments with IL-17 and IL-23 inhibitors is superior to TNF inhibitors in the treatment of enthesitis, but more research is needed to make recommendations.

3. References

1. Sudoł-Szopińska I, Kwiatkowska B, Prochorec-Sobieszek M, Maśliński W. Enthesopathies and enthesitis. Part 1. Etiopathogenesis. *J Ultrason.* 2015; 15(60): 72—84
2. Freemont AJ. Enthesopathies. Current diagnostic pathology. 2002; 8:1—10
3. Falsetti P, Acciai C, Lenzi L, Frediani B. Ultrasound of enthesopathy in rheumatic diseases. Mod Rheumatol. 2009; 19: 103—13
4. Cardoso FA, Henderson CY. Enthesopathy formation in the humerus: Data from known age-at-death and known occupation skeletal collections. Wiley Interscience. 2010; 141(4): 550—60
5. Santiago R, Gutiererrez M, Pena C, Garcia M, Arthuri A, Fillippuci E, et al. Prevalence of Subclinical Enthesopathy in Patients With Spondyloarthropathy: An ultrasound study. J Clin Rheum. 2011; 17: 18—22
6. Lambert RGW, Dhillon SS, Jhangri GS, Sack J, Sack H, Wong B, et al. High prevalence of symptomatic enthesopathy of the shoulder in ankylosing spondylitis : Deltoid origin involvement constitutes a hallmark of disease. American College of Rheumatology. 2004; (51): 681—90
7. Kamo K, Yahiro KI. Incidence and risk factors of calcaneal enthesophytes in spondyloarthritis and trauma patients. Mod Rheumatol. 2016: 1—15
8. Kehl AS, Corr M, Weisman MH. Review: Enthesitis: New Insights Into Pathogenesis, Diagnostic Modalities, and Treatment. Arthritis & Rheumatology. 2015; 68(2): 312—22
9. Claudepierre P, Catherine Voisin M. The entheses : histology, pathology, and pathophysiology. Joint Bone Spine. 2005; 72: 32—37
10. D'Agostino MA. Enthesitis. Best Pract Rest Clin Rheumatol. 2006; 20: 473—86
11. Cormick W. Enthesopathy - a personal perspective on its manifestations,

implications and treatment. Australas J Ultrasound Med. 2010; 13(4): 19–23.
12. Ebstein E, Cuostet B, Behar VM, Forien M, Palazzo E, Dieude P, *et al*. Enthesopathy in rheumatoid arthritis and spondyloarthritis: An ultrasound study. Joint Bone Spine. 2017; 85(5): 557–81
13. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER *et al*. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol. 2017: 731–41
14. Cambré I, Gaublomme D, Burssens A, Jacques P, Schryvers N, De Muynck A, et al. Mechanical strain determines the site-specific localization of inflammation and tissue damage in arthritis. Nat Commun. 2018; (9): 4613
15. McGonagle D, Tan AL. Enthesopathies in Rheumatology 6th ed. Elsevier. 2015; 33(Suppl. 93): S36–39
16. Sudoł-Szopińska I, Kwiatkowska B, Prochorec-Sobieszek M, Pracoń G, Walentowska-Janowicz M, Maśliński W. Enthesopathies and enthesitis. Part 2: Imaging studies. J Ultrason. 2015; 15(61): 196–207.
17. Koppikar S, Eder L. The management of enthesities in clinical practice. Curr Opin Rheumatol. 2020;32(4):380–86
18. Freemont AJ. Enthesopathies. Curr Diagnostic Pathology. 2002; 8:1–10
19. Polacheck A, Li S, Chandran V, Gladman DD. Clinical enthesitis in prospective longitudinal psoriatic arthritis cohort :incidence, prevalence, characteristic, and outcome. Arthritis Care Res. 2017; 69: 1685–91
20. Mease PJ, Smolen JS, Behrens F. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis:24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020; 79:123–31.