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ENTHESES, ENTHESITIS AND ENTHESOPATHY

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- **Enthesitis is the key pathological lesion in the spondyloarthritides and an increased role for the enthesis in the manifestations of osteoarthritis and even rheumatoid arthritis has been recognised in recent times**
- **The recognition of enthesitis at sites such as the Achilles tendon is clinically straightforward in many cases. Imaging modalities, especially MRI, are useful for the assessment of enthesitis at clinically inaccessible sites, including the axial skeleton**
- **Ultrasound studies show a high frequency of subclinical enthesitis in the spondyloarthritides but the extent to which these lesions are significant with respect to disease evolution and prognosis remains uncertain**
- **Enthesitis appears generally to respond well to the anti-TNF therapies but it is contentious as to whether or not the improvement in symptoms and signs is accompanied by a retardation of new bone formation**
- **Disorders of the enthesis are ripe for further clinical, imaging and translational research**

'Enthesitis' is the term used to describe inflammation at tendon, ligament or joint capsule insertions. It thus applies to disease associated with the spondyloarthritides (SpA) including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated SpA. The term 'enthesopathy', however, has a wider meaning and designates all pathological abnormalities of insertions including inflammatory changes and degenerative problems.

ENTHESES

There are two types of enthesis: fibrous and fibrocartilaginous. At the former the fibrous tissue of the tendon or ligament extends all the way up to the bone, but at the latter there is a small plug of fibrocartilage at the attachment site itself.[1] Most entheses of rheumatological significance are fibrocartilaginous. The presence of this tissue at an enthesis stiffens the tendon/ligament and thus helps to create a more gradual change in mechanical properties between soft and hard tissues. In particular, it ensures that any bending of the tendon/ligament fibres during joint movements is spread gently away from the bone – thus dissipating stress concentration. However, tissue specialisations at the enthesis itself are often only part of the adaptations evident at many attachment sites. At many locations there is a whole group of tissue modifications in the immediate vicinity which collectively constitute an 'enthesis organ' (see below). Each component plays a role in the overall task of stress dissipation.

HISTORICAL PERSPECTIVES ON ENTHESITIS

Until the middle of the last century both rheumatoid arthritis and SpA were considered part of the same spectrum of inflammatory disorders. However, the work of Wright in Leeds and pathological studies by Bywaters and Ball, in particular, led to the eventual recognition that enthesitis was an important distinguishing feature between these two categories of disease.[1] Enthesitis was eventually included in the European Spondyloarthropathy Study Group (ESSG) criteria for the classification of SpA. It was also recognised in paediatric inflammatory disease as part of the seronegative enthesopathy and arthritis (SEA) syndrome. The advent of modern imaging modalities, including ultrasound and magnetic resonance imaging (MRI), has transformed our understanding of the clinical significance of enthesitis since clinically unrecognised enthesitis is very commonly found in early SpA when these modalities are used.[2] This review covers recent clinically relevant observations in relationship to the enthesis and observations for imaging and therapy that are relevant to diagnosing and treating enthesitis.

CLINICAL FEATURES OF ENTHESITIS

Enthesitis manifesting as pain, protracted stiffness and prominent swelling of large insertions, including those of the Achilles and patellar tendons, is characteristically seen in ankylosing spondylitis, psoriatic arthritis and reactive arthritis.[3] When such lesions are associated with swelling of joints and/or other extra-articular lesions, clinical recognition of SpA is rendered fairly simple; when they occur as an isolated phenomenon and without a history of infection or psoriasis, diagnostic difficulty can arise. In such cases, patients may be referred to sports medicine or orthopaedic clinics and obtain treatment for alternative conditions such as Haglund's deformity – a mechanically-related condition of the 'enthesis organ' (see below) in the vicinity of the Achilles tendon. These scenarios are all the more likely as radiographic examination may be normal and blood inflammatory markers may not be elevated. Conversely, when imaging of isolated entheseal-based pathologies shows evidence of extensive bone oedema, unnecessary investigations, including bone biopsy, may be undertaken if the primary clinical diagnosis is not recognised.

Enthesitis most frequently presents as pain, stiffness and tenderness of insertions without much swelling. Swelling may, however, be a prominent feature at large insertions in the lower limbs. In addition to being clinically recognised at the Achilles enthesis and patellar tendon insertions, this pattern of disease is well recognised at the plantar fascia, the elbow epicondyles, other insertions about the knees, spinous processes of the vertebrae and at other sites, including the iliac crest. Generally this type of enthesitis is recognised in conjunction with other features of SpA including synovial joint swelling, dactylitis or axial disease (all of which have an entheseal-associated or entheseal-based pathology on imaging).

In the absence of joint swelling, enthesitis may thus be difficult to recognise. Although the SpA are truly inflammatory disorders, the enthesis is a relatively avascular structure and inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), may not be elevated in the presence of entheseal-related pathologies. This is best exemplified in the inflammatory back pain that accompanies ankylosing spondylitis, where undoubted inflammatory activity is not necessarily associated with elevation of inflammatory markers. Therefore it is highly likely that some cases of enthesitis-related disease are being missed, misdiagnosed and not referred to rheumatologists.

WHEN IS ENTHESITIS INFLAMMATORY AND WHEN IS IT MECHANICALLY INDUCED?

Mechanically-related tendinopathy or enthesopathy may occur from injury, including sports-related activity. Imaging studies may confirm the presence of entheseal pathology but the appearances, whether at the annulus or bone-disc interfaces in the spine or the plantar fascia, may be similar in both mechanical and inflammatory disease.[4] In the case of the Achilles tendon, degenerative tendon disease typically occurs 2–6 cm proximal to the enthesis itself, whereas inflammatory disease is based around the insertion and adjacent bone.[5]

It may be that both inflammatory and degenerative enthesopathy share common features. Entheses are sites of high mechanical stressing and with age normal entheses are subject to wear and tear; thus degenerative changes occur at their fibrocartilages that are similar to those seen in osteoarthritic articular cartilage. Imaging of small joints in osteoarthritis and psoriatic arthritis shows that enthesis-related abnormalities are common to both conditions; changes are qualitatively similar in the two but quantitatively greater in the primary inflammatory disorders (Figure 1).[6] In fact, the similarities between mechanical and inflammatory enthesitis have highlighted the possibility that site-specific biomechanical factors may lead to disease initiation in SpA. Such factors include microdamage and repair. It is little wonder that the differentiation between mechanical and inflammatory disease can sometimes be difficult.

HOW CAN IMAGING BE USED TO DIAGNOSE ENTHESITIS?

The choice of imaging modality depends on whether the suspected enthesitis is in the axial or peripheral skeleton. If it is in the former, MRI is the modality of choice. If in the latter, and the suspected site of enthesitis

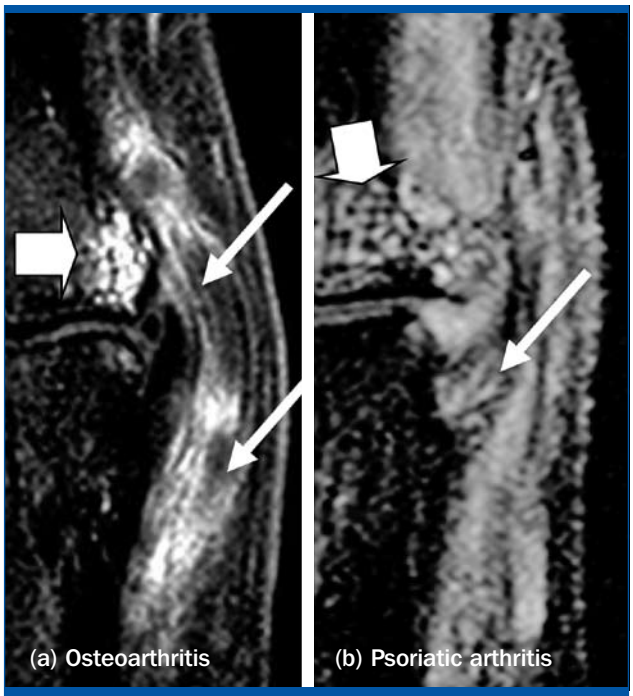

FIGURE 1. Arthritis and enthesitis in osteoarthritis and psoriatic arthritis. This image illustrates similar entheseal changes in inflammatory and degenerative disease. The image on the left (a) shows early osteoarthritis of the distal interphalangeal (DIP) joint and the corresponding image on the right (b) shows the same anatomical territory in psoriatic arthritis. The *thin arrows* show sites of enthesitis in both cases; the *thick arrows* show sites of bone oedema related to enthesitis. Generally, early inflammatory osteoarthritis and early psoriatic arthritis of the DIP joints have a similar anatomical territory of involvement but inflammation is generally more severe in the latter.

is clinically accessible to an ultrasound probe, then ultrasound would be the preferred method. For some synovial joints, including the hip and knee, where the insertions (including those of the cruciate ligaments) may be inaccessible to the probe, MRI is the test of choice.

The features of enthesitis on MRI are twofold. Firstly, perientheseal osteitis at the site of attachment is seen in up to 50% of locations of enthesitis (Figure 2). The other feature is soft tissue oedema at the enthesis and the immediately adjacent area. It has not yet been established whether this osteitis is more common at certain sites and to what degree there may be differences between osteitis lesions in different types of SpA, but its severity is generally greater in HLA-B27 patients. It is important to point out that a normal MRI scan, particularly in the spine, does not exclude enthesitis. This is because (a) bone oedema may be absent in the presence of enthesitis and (b) the enthesis being a relatively avascular structure does not readily accumulate fluid, hence is not well seen on MRI. Furthermore, the spatial resolution of MRI in the spine is quite low. Therefore abnormalities may not be appreciated. This means that in patients with inflammatory back pain the possibility of SpA cannot be excluded on the basis of a normal scan or normal blood investigations. It remains to be determined whether normal MRI scans are associated with less likelihood of future spinal fusion. For the same reason, MRI of synovial joints may not show enthesitis because of an absence of bone oedema at sites of enthesitis; moreover the soft tissue inflammatory changes associated with synovitis may mask enthesitis-related changes.

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.[7] More recently, increasing experience with power Doppler scanning has been also used to assess enthesitis, but this needs further validation. Ultrasound permits good visualisation of accessible insertions, but of course is unable to show the bone oedema changes.

What is becoming increasingly clear is that entheseal involvement may be subclinical. A significant number of patients with psoriasis, but without any musculoskeletal symptoms, have subclinical entheseal abnormalities.[8] It is presently unclear whether these changes indicate true pathology or have prognostic significance.

CLINICAL ASSESSMENT OF ENTHESITIS

The clinical assessment of entheseal pathology is often difficult due to lack of clinically apparent swelling of the structures and clinical inaccessibility of the site. But how do clinical enthesitis scores fare? There are several systems that have been developed for scoring enthesitis and all basically rely on applying pressure over

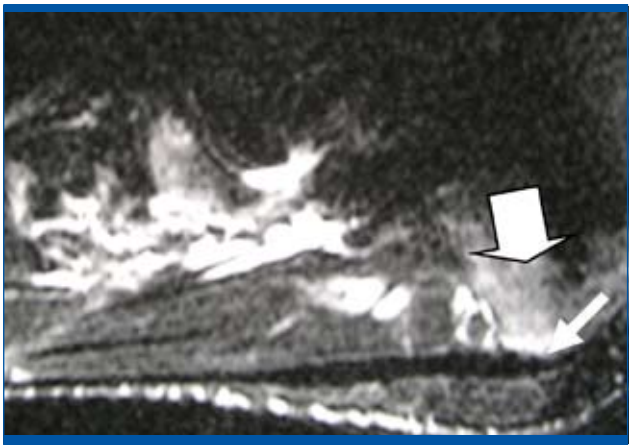

FIGURE 2. MRI of acute plantar fasciitis. This is a fat-suppression MRI scan of acute plantar fasciitis. Note that the enthesis itself looks relatively normal *(thin arrow)*. However, in this case there is diffuse bone marrow oedema adjacent to the insertion *(thick arrow)*. This pattern of oedema in spondyloarthritis has histologically been shown to represent an osteitis. In the heel perientheseal osteitis is present in less than half of cases. Given the low water content of ligaments and tendons there is a need for further refinement in MRI, including improved resolution imaging and new sequences, so the enthesis can be better depicted.

an insertion point to elicit pain. This is taken to be indicative of enthesitis. However, such scoring systems are almost identical to those used for fibromyalgia except that the pressure is applied over different points. Clinical enthesitis scoring systems have thus far proved to be useful surrogate outcomes following anti-TNF therapy, usually showing improvement. However, they have not been assessed as diagnostic tests in early arthritis and their interpretation in osteoarthritis or fibromyalgia has not been resolved since the ultimate gold standard validation of histopathological comparison is not available owing to the difficulty of obtaining entheseal biopsies.

THE LINK BETWEEN NEW BONE FORMATION AND INFLAMMATION AT THE ENTHESIS

In rheumatoid arthritis, joint inflammation is associated with bone loss and this underpins joint damage and disability. Suppression of synovitis prevents bone damage and, ultimately, disability. Conversely, inflammation in ankylosing spondylitis is associated with new bone formation. This new bone forming between two adjoining entheses attached to adjacent vertebrae in the axial skeleton leads to spinal ankylosis which, itself, leads to disability. Thus the relationship between inflammation, new bone formation and disability in ankylosing spondylitis appears to be something of a paradox since inflammation generally has a catabolic effect on bone.

The mechanism of the bone changes at insertions is only now being studied. There is a tendency for new bone formation to occur at normal entheses with age.[9] At the Achilles tendon, bony spurs usually develop at the most distal part of the insertion. In SpA, erosion formation occurs at the proximal part of the enthesis in early disease, but in late disease erosions seem to heal and large spur formation again occurs at the distal part of the attachment site. Therefore, in man, there is an anatomical, biomechanical and temporal uncoupling between the inflammatory phase of disease and new bone formation and it appears that the bone formation follows on from the inflammation and may be a distinct phase. In animal models the uncoupling between inflammation and bone formation is more pronounced but the translational relevance of this observation needs to be defined.[10]

All of this is extremely relevant to clinical practice, especially in terms of SpAs, since it is possible that the suppression of inflammation in ankylosing spondylitis could paradoxically lead to ongoing or even accelerated spinal fusion at the actual site of active enthesitis, something that was predicted several years ago.[11] It remains a possibility that episodes of active inflammation in ankylosing spondylitis inhibit new bone formation and that the effective therapeutic suppression of this could have the unforeseen consequence of new bone formation. This awaits further longitudinal studies of moderate to long durations. In clinical practice patients being treated with anti-TNF agents do not seem to lose spinal mobility, but the currently available short-term follow-up data using radiography suggest that spinal fusion related to entheseal new bone formation may progress in ankylosing spondylitis in spite of biologic treatment.[12] However, most studies of this relationship to date have been of established disease using radiography, which is a relatively insensitive measure. Studies in early disease will determine whether anti-TNF treatment can inhibit new bone formation at insertions. This is important since the prevention of entheseal new bone formation in episodes of inflammatory enthesitis will likely prevent the sequelae.

TREATMENT OF INFLAMMATORY ENTHESITIS

Given that biomechanical factors are likely to play a role in inflammatory enthesitis, reduction of biomechanical stresses by such means as insoles and cushioning should be used where appropriate. Local corticosteroid injections often help if anti-inflammatory agents fail to alleviate pain associated with isolated enthesitis. However, for isolated severe enthesitis with soft tissue swelling, anti-TNF agents have been shown to be effective in case series and in the experience of one of the authors (D McGonagle). However, use of biologic therapies within the UK health service and elsewhere is restricted and there are currently no specific guidelines for the use of these agents for isolated enthesitis. Expert opinion would suggest that the agents should be used if all else fails, as isolated enthesitis can be very debilitating, particularly in the lower limbs. Moreover, since enthesitis is usually self-limiting the problem may eventually settle, so patients may not be committed to indefinite therapy. In the past local radiotherapy has been used with some success, especially with disabling heel enthesitis.[13] Since this can be administered safely as a single dose, bearing in mind the potential side-effects of anti-TNF agents local radiotherapy should still be considered.

Quite often, treatment of enthesitis is simply part of the treatment of an associated polyarthritis where agents including sulfasalazine and methotrexate are used. Robust evidence for the efficacy of these agents in early SpA is lacking. Where mild to moderate enthesitis is recognised in association with more generalised inflammation for which anti-TNF agents are being used, then clinical enthesitis scores and MRI and ultrasound scores all improve.

NEW CONCEPTS IN ENTHESITIS AND SPONDYLOARTHRITIS

Enthesis organs

Enthesitis has historically been considered as a disorder of a focal attachment site; however, entheses together

with adjacent tissues may form mini organs, dubbed 'enthesis organs'.[14] This ensures that the stress dissipation at attachment sites is distributed over a wide area. Perhaps for this reason, the pain with tennis elbow may sometimes be diffuse rather than focally located at the common extensor origin. Rheumatologists need to appreciate that enthesitis-associated pain may be over a greater territory than the insertions themselves. This likely applies to the Achilles tendon enthesis and the retrocalcaneal bursa, as enthesis-related cartilages actually form the walls of the bursa itself. This explains why bursitis may be a prominent feature of Achilles enthesitis.

The enthesis organ concept is shown in Figure 3. It seems likely that the two complementary fibrocartilages adjacent to the enthesis itself derive their nourishment and lubrication from the adjacent synovium. This is identical to the relationship between synovium and articular cartilage. This means that pathology related to the enthesis could trigger synovitis. Indeed, normal entheses are riddled with microdamage in aged subjects; this can be associated with microscopic synovitis, including villus formation and microscopic inflammatory cell infiltration in the immediately adjacent synovium, which is conceptualised in relationship to a synovio-entheseal complex.

The synovio-entheseal complex and synovitis in spondyloarthritis

There is a close anatomical integration between the enthesis and synovium which has recently being termed a 'synovio-entheseal complex'.[15] According to this scenario the enthesis fibrocartilages that occupy a location adjacent to synovium (in joint or bursae or tendons) are dependent on the synovium for lubrication, oxygenation and removal of microdebris. The enthesis insertion being itself fibrocartilagenous is avascular. Therefore derangements in the enthesis would be expected to trigger an inflammatory response in the adjacent vascular synovium.

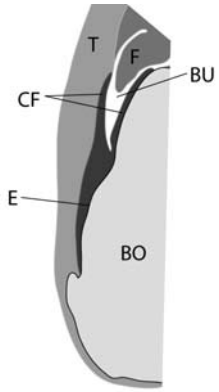

FIGURE 3. A diagrammatic representation of an enthesis organ, modelled on that of the Achilles tendon. It consists of the enthesis itself (E), two complementary fibrocartilages (CF), an intervening bursa (BU) and a pad of synovium-covered protruding fat (F). The complementary fibrocartilages line the deep surface of the tendon (T) and cover the adjacent bone (BO) and protect these surfaces from compression when the foot is dorsiflexed (i.e. the foot is raised so that the toes point upwards). The bursa allows free movement of tendon relative to bone and the fat pad acts as a 'variable plunger' to prevent pressure changes from occurring in the bursa as the foot changes position.

The enthesis may be equally important in osteoarthritis and rheumatoid arthritis

These micro-anatomical considerations may be vital for understanding the importance of the enthesis in synovial joint disease in general. While the role of the enthesis is fully appreciated in SpA, these recent findings point towards novel mechanisms of synovitis and joint damage in osteoarthritis that have previously been unappreciated.[16,17] Normal enthesis fibrocartilage shows age-related changes typical of osteoarthritis, including fissuring, fibrillation and degeneration. It is probably best to use the term 'enthesopathy' to describe the changes in osteoarthritis since these appear to be generally less inflammatory, but it must be pointed out that there are no comparative histological studies to date. Also the role of the enthesis organ in bone erosion formation in rheumatoid arthritis has recently been described.[18] Specifically, early rheumatoid arthritis erosion formation occurs immediately adjacent to the small joint collateral ligament insertions as a result of enthesis-associated compression of bone at these sites.[18]

CONCLUSION

From being a 'second-class citizen' in SpA, the enthesis is now centre stage as a structure responsible for disease in this category of abnormalities. The recognition of the importance of the enthesis has important implications for an improved immunopathological understanding of SpA.[19] The role of the enthesis in other types of arthropathy including osteoarthritis and even in the patterns of joint destruction in rheumatoid arthritis has only recently become appreciated. Although tissue from the enthesis is inaccessible compared to the synovium, it holds great potential for a future better understanding of inflammatory and degenerative disease.[20] Much more work needs to be done pertaining to the clinical evaluation of entheseal-related pathology.

REFERENCES

1. Ball J. Enthesopathy of rheumatoid and ankylosing spondylitis. Ann Rheum Dis 1971;30(3):213-23.

2. McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Emery P. Characteristic magnetic resonance imaging entheseal changes of knee synovitis in spondylarthropathy. Arthritis Rheum 1998;41(4):694-700.

3. Benjamin M, McGonagle D. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. J Anat 2001;199(5):503-26.

4. McGonagle D, Marzo-Ortega H, O'Connor P et al. The role of biomechanical factors and HLA-B27 in magnetic resonance imaging-determined bone changes in plantar fascia enthesopathy. Arthritis Rheum 2002;46(2):489-93.

5. Tan AL, McGonagle D. Imaging of seronegative spondyloarthritis. Best Pract Res Clin Rheumatol 2008;22(6):1045-59.

6. Tan AL, Grainger AJ, Tanner SF, Emery P, McGonagle D. A high-resolution magnetic resonance imaging study of distal interphalangeal joint arthropathy in psoriatic arthritis and osteoarthritis: are they the same? Arthritis Rheum 2006;54(4):1328-33.

7. McGonagle D, Wakefield RJ, Tan AL et al. Distinct topography of erosion and new bone formation in Achilles tendon enthesitis: implications for understanding the link between inflammation and bone formation in spondylarthritis. Arthritis Rheum 2008;58(9):2694-9.

8. Gisondi P, Tinazzi I, El-Dalati G et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. Ann Rheum Dis 2008;67(1):26-30.

9. Benjamin M, Toumi H, Suzuki D, Hayashi K, McGonagle D. Evidence for a distinctive pattern of bone formation in enthesophytes. Ann Rheum Dis 2009;68(6):1003-10.

10. Lories RJ, Derese I, de Bari C, Luyten FP. Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. Arthritis Rheum 2007;56(2):489-97.

11. McGonagle D. Diagnosis and treatment of enthesitis. Rheum Dis Clin North Am 2003;29(3):549-60.

12. Braun J, Baraliakos X. Treatment of ankylosing spondylitis and other spondyloarthritides. Curr Opin Rheumatol 2009;21(4):324-34.

13. Olivieri I, Barozzi L, Padula A. Enthesiopathy: clinical manifestations, imaging and treatment. Baillieres Clin Rheumatol 1998;12(4):665-81.

14. Benjamin M, Moriggl B, Brenner E, Emery P, McGonagle D, Redman S. The 'enthesis organ' concept: why enthesopathies may not present as focal insertional disorders. Arthritis Rheum 2004;50(10):3306-13.

15. McGonagle D, Lories RJ, Tan AL, Benjamin M. The concept of a 'synovio-entheseal complex' and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum 2007;56(8):2482-91.

16. Tan AL, Grainger AJ, Tanner SF et al. High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis. Arthritis Rheum 2005;52(8):2355-65.

17. Benjamin M, McGonagle D. Histopathologic changes at 'synovio-entheseal complexes' suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. Arthritis Rheum 2007;56(11):3601-9.

18. McGonagle D, Tan AL, Muller Dohn U, Ostergaard M, Benjamin M. Microanatomic studies to define predictive factors for the topography of periarticular erosion formation in inflammatory arthritis. Arthritis Rheum 2009;60(4):1042-51.

19. McGonagle D, Stockwin L, Isaacs J, Emery P. An enthesitis based model for the pathogenesis of spondyloarthropathy: additive effects of microbial adjuvant and biomechanical factors at disease sites. J Rheumatol 2001;28(10):2155-9.

20. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. Lancet 1998;352(9134):1137-40.

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