Entheseal involvement

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ABSTRACT

Enthesitis is a distinctive pathological feature of spondyloarthritis and may involve synovial joints, fibrocartilaginous joints, syndesmoses and extra-articular entheses. Extrarticular pain may often be present in rheumatoid arthritis patients. This review focuses on peripheral enthesitis which is a clinical hallmark of spondylarthritis, by comparing the same findings in rheumatoid arthritis.

Introduction

Entheses represents the sites of insertion of tendon, ligament, fascia or joint capsule to bone. Recent knowledge regarding the function, anatomy and physiology of the enthesis has led to improve our understanding of entheseal pathology in the course of many inflammatory and non-inflammatory rheumatic diseases. The involvement of enthesis in any pathologic process, whether metabolic, inflammatory, traumatic or degenerative, is referred to as "enthesopathy", while "enthesitis" is restricted to the inflammatory enthesopathy, and it appears to be a cardinal feature of spondylarthritis (SpA) (1, 2). Although Niepel *et al*. first used the term for describing inflammatory symptoms at insertional sites as an important feature of ankylosing spondylitis (AS) (3), enthesitis is a common characteristic feature of all the SpA complex which also include psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD) and the undifferentiated forms (4, 5). Ball firstly suggested in his famous "Heberden oration" that AS and rheumatoid arthritis (RA) differ primarily in the diverse target organs (6). He suggested that inflammation at the enthesis is the distinctive pathological feature of AS (5-8). In contrast, the characteristic feature of RA is a persistent inflammatory synovitis involving mainly the peripheral joints symmetrically (9).

Since this first observation several authors have tried to evaluate whether differences exist between AS and RA in the entheseal involvement (1, 10).
Although axial and peripheral skeletons are a target for both SpA and RA, and any enthesis all over the body can be involved, some insertions seem more important than others for distinguishing between these two inflammatory diseases (10-13).
The purpose of this review is to explore articles looking for enthesitis in RA and AS, to describe the differences in clinical aspects of enthesitis in AS as compared to RA and to discuss the imaging appearance of entheseal involvement in both diseases.

Are entheses involved in RA?

Based on clinical symptoms, extrarticular structures are frequently involved in RA. The throcanter region, heels and hands are reported as the most painful sites (10, 14-16). This involvement seems primarily related to the synovial membrane lining the tendon sheaths and the bursae (10, 17, 18). In the hand, tenosynovitis of both the extensor and the flexor tendon is frequently observed. A trigger finger is often associated with digital sheath tenosynovitis as a consequence of the location of a rheumatoid nodule inside the tendon. Tendon involvement seems to be an early finding of RA (18) and may be predictive for future tendon rupture (19). Actually, persistent hand tenosynovitis may lead to tendon rupture especially of the extensor tendon of the ring and little fingers and of the flexor pollicis longus. In the forefoot, the synovial sheaths of the flexor tendons are usually involved together with the metatarso-phalangeal joints. With regard to the bursae, the most frequently involved include the subacromial, olecranic, ileopsoas, throchanteric, ischial, gastrocnemius, semimembranosus and retrocalcaneal (18).
The involvement of entheses has been the object of several studies performed

since the middle of the last century (6, 10-13, 17, 20-22). The most frequently studied entheses were the heel insertion of the plantar fascia of the Achilles tendons (6, 20, 23-28). In 1954, Bywaters published on 19 patients with RA complaining pain and swelling, or both, in the heel and showing radiological erosions (11). The author emphasized that the frequency of such patients was low, in the order of 2-3%, since in his unselected series of 250 RA patients followed for more than five years only 6 complained of pain in their heels and showed radiological lesions. Two radiological lesions were observed: retrocalcaneal bursitis which eroded the posterosuperior surface of the calcaneus and plantar fasciitis eroding the plantar surface. Patients were classified as suffering from RA but it is not possible to exclude the inclusion of some patients with SpA since 9 patients were female and 10 male, a reversal of the usual sex ratio for RA. Twenty years later, Gerster and co-workers evaluated the frequency of mild and severe talalgia in 100 patients with RA, 35 with AS, 16 with ReA and 70 with generalized osteoarthritis (OA) (10). Talalgia was considered mild when pain was inconsistent on weight bearing, decreased immediately with rest and was provoked by moderate to marked local pressure. It was judged severe when pain occurred on weight bearing, decreased very slowly after prolonged rest and was elicited by slight local pressure. Plantar fasciitis and Achilles enthesitis gave a severe talalgia and were observed mostly in males suffering from AS or ReA. Of the 100 patients with RA, 4 had retrocalcaneal bursitis causing mild pain and 1 plantar fasciitis with severe talalgia. Interestingly, painless subcutaneous rheumatoid nodules were found along the Achilles tendon in 3 patients. The following year, the same authors examined 30 consecutive patients suffering from severe talalgia with the aim to determine the underlying disease (17). Twenty-four out of 30 had SpA (AS, ReA or PsA), 3 nodular tendinitis, 2 RA and 1 chondrocalcinosis. Of the 2 RA patients, 1 had plantar fasciitis and 1 Achilles bursitis during the evolution of a nodular RA. In 1980, Gerster *et al*. examined 150 patients suffering from SpA for plantar fasciitis and Achilles enthesitis and found a frequency of 33% mostly with severe talalgia (22). In contrast, severe talalgia was rare in RA patients being found in only 2 (0.9%) out of 220 with a definite diagnosis observed during the same period. Both patients had plantar fasciitis. Bouysset *et al*. found a frequency of talalgia of 3.7% in 408 rheumatoid feet (28). In 1984, Paolaggi *et al*. systematically examined calcaneal and extra-calcaneal entheses of 48 SpA and 30 RA patients (14). They found a statistically significant difference of clinical and radiographic entheseal involvement between the two groups: 58% of SpA patients had at least one enthesis involved as compared to 6.6% of RA patients ($p<0.0001$). All entheseal findings in RA patients were localised outside the heel. Taken together, these studies suggest that plantar fasciitis and Achilles enthesitis are not frequent features of RA. Nevertheless, retrocalcaneal bursitis is not an uncommon manifestation of RA and usually occurs without severe pain. Spontaneous Achilles tendon rupture has occasionally been observed in patients suffering from RA as a consequence of retrocalcanal bursitis or rheumatoid granulomas within the tendon tissue (29, 30). No case of rupture has been reported in patients with SpA heel enthesitis so far.

Clinical manifestations of enthesitis in AS

Entheses are copious and present ubiquitously, both in the axial and appendicular skeletons, giving reasons for the wide clinical spectrum of enthesitis. Enthesitis can involve (a) synovial joints such as the sacroiliac joints, the zygaphophyseal joints, the hips, and the shoulders; (b) fibrocartilaginous joints such as the pubic symphysis, the intervertebral symphysis, *i.e*. the junction between the intervertebral disk and hyaline cartilage on the vertebral surfaces, and the manubriosternal joint; (c) syndesmoses such as the interosseus sacroiliac ligament filling the irregular posterosuperior space of the sacroiliac joint; and (d) extraarticular entheses (31). From the clinical point of view, extra-articular and extra-vertebral enthesitis are the most important since they constitute the clinical hallmark of SpA.

In primary AS, the frequency of peripheral enthesitis has been found to be between 25% and 58% (10, 32, 33). Sometimes, especially in the juvenile-onset forms, it precedes, in association or not with peripheral arthritis, the symptoms of axial involvement (34, 35). Although any insertion all over the body can be involved, some are more important in clinical practice: the insertion of the plantar fascia on the calcaneal tuberosity; the insertion of the Achilles tendon to the midlevel of the posterior surface of the calcaneus; the attachment of the tendon of quadriceps femori to the base of the patella; the insertions of the ligamentum patellae on the patellar apex and the tubercle of the tibia; the muscle attachments to the greater and lesser throchanters, the iliac crests, the ischial tuberosities and the pubis; the insertions on the humeral lateral and medial epicondyles; the areas of muscular attachment on the external occipital protuberance and lines; the muscle and the ligament insertions of the ribs and vertebral spinous processes (5). Clinically, the entheses of the lower limbs are involved more frequently than those of the upper extremities and heel enthesitis (plantar fasciitis and/or Achilles enthesitis) is the most common (10, 14, 33, 34, 36). The reasons for the preference for the entheses of the lower part of the lower extremities are not known. Probably mechanical factors as well as length, anatomy and physiology of the enthesis may play a role (33, 37). Entheses are subjected to repeated mechanical loading. Recent studies point to an association between mechanical loading and inflammation, calling into question the classic separation between mechanical disorders and inflammatory disease (38, 39). The attachments on the greater and lesser throchanters and on the ischial tuberosities are short and the mechanical load on these entheses and on the adjacent bursae is therefore not marked. In contrast, the patellar ligament, the Achilles tendon, the plantar fascia and the peroneus tertius and brevis are all

long and important bursae are located in close proximity. Tendon movements are more energetic and may cause more tension on the enthesis-bone junction and the adjacent bursae (23, 39).
The involvement of superficial entheses such as those of Achilles tendon, patellar tendon and on the humeral lateral epicondyle often shows a visible soft tissue swelling (40-42). In contrast, the involvement of entheses situated far under the body surface, such as those on the iliac crests, the pubis, the ischial tuberosities and the greater and lesser throchanters, offers only evoked tenderness and palpable swelling. In the latter cases, particularly when the only manifestation is pain, it is necessary to exclude fibromyalgia (43, 44) and to provide evidence of enthesitis with imaging techniques. Histologic proof, the gold standard for the diagnosis, creates significant trouble because of the extreme difficulty in acquiring tissues, even though a study on a small number of patients with plantar fasciitis showed histological changes (44). Entheseal pain can be severe, disabling and continuous, lasting even for several years despite traditional therapy (45-48).
Peripheral enthesitis is under diagnosed. Firstly because it is often confused with sport and overuse pathology (34, 49). In adolescents, enthesitis of the patellar ligament can be mistaken for traction apophysitis, that is to say Osgood-Schlatter disease and Sinding-Larsen disease (50). Secondly some sites of enthesitis, *i.e*. the insertion of patellar ligament, quadriceps tendon and flexor radialis and ulnaris carpi, are so near the joints that their involvement may be attributed to joint synovitis. The opposite may happen, that is to say that joint synovitis may give the impression of the involvement of adjacent entheses. This may happen particularly in hip and knee synovitis (33).
Usually peripheral enthesitis is a source of pain but may also be underestimated or often asymptomatic at the time of clinical examination and only brought to light by imaging methods (51).
Notwithstanding the relevance of enthesitis for diagnostic and therapeutic purposes, no agreement exists on which measure should be used for assessing entheseal involvement (52). Several instruments have been proposed to score clinical enthesitis (52-56). The main objective of these instruments is the responsiveness in the therapeutic follow-up; their value in clinical practice for both diagnostic and therapeutic purposes needs to be evaluated.

Imaging techniques
Understanding of the imaging findings of enthesitis hinges on the knowledge of the relevant joint anatomy (57). Enthesitis has been viewed as focal insertional inflammation. While conventional radiography allows a clear documentation of the later stages of inflammatory changes, MRI and ultrasound, both in grey-scale and power Doppler (PDUS), are sensitive enough to detect early inflammatory lesions.

Conventional radiography: which abnormalities?
Peripheral enthesitis
Historically, the radiographic features of enthesitis have played a pivotal role in defining enthesitis lesions of SpA. These include bone insertion osteopenia, bone cortex irregularity at insertion, erosion, entheseal soft tissue calcification and new bone formation (31, 32). However, entheseal bone changes appear late and are also common in mechanical disorders and in crystal related pathology. Moreover, aging is associated with an increased prevalence of asymptomatic "radiographic enthesopathy" (10, 31, 32). Gerster et al observed that erosions and simple spurs are common features of both RA and AS in their systematic studies of heel enthesitis. However, unlike AS, spurs in RA patients were related to age and particularly frequent in older patients (over 60 years of age) (10). Distinctive findings were the bilateral occurrence of lesions in AS and the different localisation of erosion. In RA, radiographic erosions were seen more frequently on the posterosuperior surface of the calcaneus adjacent to the localisation of inflamed retrocalcaneal bursa. In contrast, in AS erosions were present on the posteroinferior surface of the calcaneus directly related to the tendon insertion. Another observed difference was the absence of plantar erosions in RA. These were only found in AS patients due to plantar fasciitis eroding the plantar surface.
More recently Helliwell *et al*. performed a large international multicenter systematic study with the aim to evaluate the accuracy of radiographic features of enthesitis and to distinguish PsA and AS patients from those with and RA (58). The authors examined the radiographic films of several sites (*i.e*. lumbar and cervical spine, hands, feet, heel, pelvis, shoulder, knee and elbow) and reported significant differences in entheseal erosion and entheseal new bone formation among the groups, mainly due to the higher proportion of these features in AS. However, conventional radiography was unable to discriminate between PsA and RA. They also suggested that entheseal erosion and irregular new bone formation are a distinguishing feature of AS but not of PsA.

Axial involvement
Conventional radiography remains the main imaging modality in clinical practice for diagnosis of axial SpA. New bone formation at enthesis is a fairly characteristic feature, and polyenthesitis causing spinal fusion is diagnostic. The hallmark of AS is radiographic sacroiliitis but several years may elapse between the onset of symptoms and the appearance of radiographic changes (59).
The main site of spinal involvement in RA is the cervical spine. Typical changes are the destruction of the atlantoaxial complex by pannus synovitis with subsequent atlantoaxial subluxation, basilar impression and erosion of the dens axis. In the lower segments of the cervical spine destruction of the apophyseal joints is a distinctive lesion (60).

Ultrasound: which abnormalities?
Over the last few years, ultrasound has proved to be a highly sensitive and non invasive tool, especially in assessing tendon and joint involvement. Lehtinen *et al*. (33) and Balint *et al*. (61) were the first to describe extensively the ultrasound abnormalities of lower limb enthesitis of SpA, revealing the high frequency of asymptomatic ultrasound findings. In grey-scale, the appearance

of enthesitis is characterized by the loss of normal fibrillar echogenicity, an increasing thickness or intralesional focal changes of tendon insertion, calcific deposits at insertion of the tendon and periosteal changes (erosions or new bone formation). These entheseal abnormalities may be associated with abnormalities of the tendon and the adjacent bursae. By using grey-scale ultrasound only, discordant data are published about the capability of ultrasound to differentiate between SpA and other pathologies including RA. Genc *et al*. examined clinically and by grey-scale ultrasound 24 patients with RA, 18 with AS, and 20 healthy controls (62). Five entheseal sites in the lower limbs (Achilles tendon, plantar fascia, quadriceps tendon and patellar ligament insertion on inferior pole of the patella and on tibial tuberosity), and two entheses of the upper limbs (the insertions of biceps brachii and supraspinatus) were evaluated. The frequency of entheseal involvement in RA patients was similar to that of the AS group. Also the ultrasound appearance of RA enthesopathy was similar to that of AS. The most frequently affected entheseal sites in the lower limbs were the base and the apex of the patella and the insertion of Achilles tendon in both groups. The same authors published the absence of responsiveness of grey-scale ultrasound in the follow-up of RA and AS patients under treatment with sulfasalazine for entheseal involvement (63). A major criticism of these studies is that the authors did not distinguish between enthesis involvement and tendon involvement since both were considered as enthesitis. They also evaluated, as sign of enthesitis, tendon thickness, erosion, enthesophytes, which are findings of chronic inflammatory process, and bursitis which is considered the most frequent abnormal finding of the enthesis "region" involvement in RA patients. The same comments are applicable for the lack of responsiveness of ultrasound observed in the second discussed study.

On the contrary, Frediani *et al*. studied the clinical and ultrasound prevalence of quadricipital enthesitis of the tendon of quadriceps femori in PsA and RA (64). They found that enthesitis was more frequent in PsA than in RA patients. In PsA patients entheseal involvement was asymptomatic in half of them. A characteristic feature of PsA enthesitis was the presence of new bone formation.

More recently, power Doppler technology has allowed us to visualize abnormal vascularization and hyperemia of soft tissues in inflammatory articular diseases (65, 66).

In a recent cross-sectional study, D'Agostino *et al*. studied 14 enthesis sites of 164 SpA patients, 34 RA patients and 30 patients with degenerative spinal disease by PDUS (67). The authors showed a high frequency of abnormal peripheral enthesitis among SpA patients in comparison with controls. The landmark of PDUS enthesitis in SpA patients was the presence of abnormal vascularization at enthesis insertion into the cortical bone, which was exclusively detected in SpA patients. In fact, in RA group, vascularisation was exclusively found in the retrocalcaneal bursa confirming previous observations of the primary involvement of this structure in the "rheumatoid enthesitis symptom". The distribution of PDUS enthesitis was uniformly found among SpA patients, irrespectively of the disease phenotype (*i.e*. axial *vs*. peripheral), with a trend towards a more severe PDUS pattern in the peripheral forms (*i.e*. PsA and ReA).

These results have now been confirmed by other studies outlining the capability of PDUS to reveal inflammation of enthesis in SpA patients, and leading to propose several different scoring systems. (68, 69). Despite promising results, the use of PDUS for the diagnosis and the management of SpA has remained less often evaluated than MRI. This discrepancy is probably due to the greater difficulty of assessing vascular blood flow with Doppler in the entheses, than in other tissues, such as the synovium. The latter difference can be explained by a greater abundance of vessels in the inflamed synovium, than in the enthesitis (13, 44). Another reason could be the difficulty to detect "real vascularization", because there are more Doppler artifacts at the entheseal site, due the close proximity of a highly reflecting surface, the cortical bone (70).

A recent study supported the hypothesis that vascularisation seen at enthesis insertion is a landmark of inflammatory enthesitis. Morel *et al*. (71) have explored the normal blood supply of the heel entheses by means of contrast enhanced ultrasound in healthy subjects, before and after an intravenous injection of a contrast agent. They completed the observation performing a histological study of blood supply in cadavers after injection of a red coloured gelatin solution. They showed that the blood supply in cadavers is present around the enthesis and in the bone insertion. However, no evidence of this entheseal vascularization was found with any contrast enhanced imaging technique at the cortical bone insertion of normal heel entheses. Nevertheless, the diagnostic and prognostic value of PDUS remains to be demonstrated in future multi-center studies.

MRI: which abnormalities?

MRI has been shown to be a reliable imaging tool to assess peripheral joint involvement in SpA, and can detect very early changes. The main changes observed are soft tissue oedema, joint effusion, bone erosion, bone marrow oedema and tendon sheath effusion. However, these changes are not universal and cannot be used as a diagnostic test in individual cases yet. The first MRI studies in SpA emphasized the extrasynovial nature of the inflammatory lesions in the synovial joints in SpA (72, 73). McGonagle *et al*. demonstrated by using Fat Sat MRI that the extracapsular inflammatory lesion in synovial joints of SpA is commonly enthesitis, and that the inflammatory process associated with enthesitis may be quite extensive, involving the soft tissues and the bone marrow (73). This aspect has never been observed in RA synovitis. However, the detection of entheseal pathology only by STIR sequences may not be sufficient for visualising mild entheseal disease (74).

MRI pattern of SpA enthesitis is characterized by a diffuse bone oedema adjacent to the enthesis, associated with surrounding soft tissue oedema, and

increasing ligament and bursa signal intensity after intravenous injection of gadolinium contrast (51, 74). Nevertheless, MRI has some limitations in evaluating the entheses. In fact, conventional MRI is limited at certain insertions because of the low spatial resolution and the low water content of entheses. Furthermore, bone oedema is a feature observed also as a nonspecific response to trauma, fracture, infection, neoplastic involvement, osteoarthritis, and inflammatory joint involvement as in RA.

In a study comparing MRI findings of hand and wrist involvement in PsA and RA, Schoellnast *et al*. demonstrated that bone marrow oedema was uniformly observed in both groups, however periosteal contrast enhancement was a characteristic feature of PsA and was not observed in RA (75).

The MRI aspect of patients with mechanical or traumatic enthesopathy addresses the important question whether bone oedema observed in patients with SpA is mainly caused by inflammation or by biomechanical factors (37). The advances in MRI techniques, as the development of high-resolution MRI and of ultrashort echo time MRI sequences, have a promising role to improve the visualisation of entheseal involvement and therefore our understanding of enthesis disease.

Conclusions

The enthesis is increasingly emerging as playing a key role in musculoskeletal disorders (76). This transitional tissue is now the focus of active research. The results can be expected to produce substantial changes in our approach to many rheumatic diseases.

References

1. SLOBODIN G, ROZENBAUM M, BOULMAN N, ROSNER I: Varied presentations of enthesopathy. *Semin Arthritis Rheum* 2007; 37: 119-26.
2. MCGONAGLE D, KHAN MA, MARZO-ORTEGA H, O'CONNOR P, GIBBON W, EMERY P: Enthesitis in spondyloarthropathy. *Curr Opin Rheumatol* 1999; 11: 244-50.
3. NIEPEL G, KOSTKA D, KOPECKY S, MANCA S: Enthesopathy: Piestany; 1966.
4. KHAN MA: Update on spondyloarthropathies. *Ann Intern Med* 2002; 136: 896-907.
5. D'AGOSTINO MA, OLIVIERI I: Enthesitis. *Best Pract Res Clin Rheumatol* 2006; 20: 473-86.
6. BALL J: Enthesopathy of rheumatoid and ankylosing spondylitis. *Ann Rheum Dis* 1971; 30: 213-23.
7. JACOBS JC: Spondyloarthritis and enthesopathy. Current concepts in rheumatology. *Arch Intern Med* 1983; 143: 103-7.
8. OLIVIERI I, SALVARANI C, CANTINI F, CIANCIO G, PADULA A: Ankylosing spondylitis and undifferentiated spondyloarthropathies: a clinical review and description of a disease subset with older age at onset. *Curr Opin Rheumatol* 2001; 13: 280-4.
9. MACGREGOR AJ: Classification criteria for rheumatoid arthritis. *Baillieres Clin Rheumatol* 1995; 9: 287-304.
10. GERSTER JC, VISCHER TL, BENNANI A, FALLET GH: The painful heel. Comparative study in rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, and generalized osteoarthrosis. *Ann Rheum Dis* 1977; 36: 343-8.
11. BYWATERS EG: Heel lesions of rheumatoid arthritis. *Ann Rheum Dis* 1954; 13: 42-51.
12. BYWATERS EG: The early lesions of ankylosing spondylitis. *Ann Rheum Dis* 1969; 28: 330.
13. CANOSO JJ: The premiere enthesis. *J Rheumatol* 1998; 25: 1254-6.
14. PAOLAGGI JB, GOUTET MC, STRUTZ P, SIAUD JR, LE PARC JM, AUQUIER L: [Enthesopathy in inflammatory spondyloarthropathy. Incidence, clinical, radiological and anatomical descriptions. Current status of the question. Apropos of 37 cases] (French). *Rev Rhum Mal Osteoartic* 1984; 51: 457-62.
15. PAOLAGGI JB, LE PARC JM: [nflammatory enthesopathies] (French). *Rev Prat* 1988; 38: 1557-8.
16. PAOLAGGI JB, GOUTET MC, LE PARC JM, SIAUD JR, CHAOUAT D, AUQUIER L: [Enthesopathies in ankylosing spondylitis and seronegative inflammatory rheumatism. 28 cases] (French). *Presse Med* 1983; 12: 2229-32.
17. GERSTER JC, SAUDAN Y, FALLET GH: Talalgia. A review of 30 severe cases. *J Rheumatol* 1978; 5: 210-6.
18. GORDON D, HASTINGS DE: *Clinical features of rheumatoid arthritis*. Edinburgh: Mosby; 2003.
19. WAKEFIELD RJ, O'CONNOR PJ, CONAGHAN PG *et al*.: Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging. *Arthritis Rheum* 2007; 57: 1158-64.
20. BALL J: The enthesopathy of ankylosing spondylitis. *Br J Rheumatol* 1983; 22: 25-8.
21. CANOSO JJ: Bursae, tendons and ligaments. *Clin Rheum Dis* 1981; 7: 189-221.
22. GERSTER JC: Plantar fasciitis and Achilles tendinitis among 150 cases of seronegative spondarthritis. *Rheumatol Rehabil* 1980; 19: 218-22.
23. BENJAMIN M, MCGONAGLE D: The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat* 2001; 199: 503-26.
24. 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: 3306-13.
25. BENJAMIN M, TOUMI H, RALPHS JR, BYDDER G, BEST TM, MILZ S: Where tendons and ligaments meet bone: attachment sites ('entheses') in relation to exercise and/or mechanical load. *J Anat* 2006; 208: 471-90.
26. 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: 1003-10.
27. BENJAMIN M, TOUMI H, SUZUKI D, REDMAN S, EMERY P, MCGONAGLE D: Microdamage and altered vascularity at the enthesis-bone interface provides an anatomic explanation for bone involvement in the HLA-B27-associated spondylarthritides and allied disorders. *Arthritis Rheum* 2007; 56: 224-33.
28. BOUYSSET M, TEBIB J, WEIL G *et al*.: The rheumatoid heel: its relationship to other disorders in the rheumatoid foot. *Clin Rheumatol* 1989; 8: 208-14.
29. RASK MR: Achilles tendon rupture owing to rheumatoid disease. Case report with a nine-year follow-up. *JAMA* 1978; 239: 435-6.
30. MATSUMOTO K, HUKUDA S, NISHIOKA J, ASAJIMA S: Rupture of the Achilles tendon in rheumatoid arthritis with histologic evidence of enthesitis. A case report. *Clin Orthop Relat Res* 1992; 235-40.
31. RESNICK D, NIWAYAMA G: Entheses and enthesopathy. Anatomical, pathological, and radiological correlation. *Radiology* 1983; 146: 1-9.
32. RESNICK D, FEINGOLD ML, CURD J, NIWAYAMA G, GOERGEN TG: Calcaneal abnormalities in articular disorders. Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Reiter syndrome. *Radiology* 1977; 125: 355-66.
33. LEHTINEN A, TAAVITSAINEN M, LEIRISALO-REPO M: Sonographic analysis of enthesopathy in the lower extremities of patients with spondylarthropathy. *Clin Exp Rheumatol* 1994; 12: 143-8.
34. OLIVIERI I, PADULA A, LISANTI ME, BRACCINI G: Longstanding HLA-B27 associated Achilles tendinitis. *Ann Rheum Dis* 1992; 51: 1265.
35. OLIVIERI I, FOTO M, RUJU GP, GEMIGNANI G, GIUSTARINI S, PASERO G: Low frequency of axial involvement in Caucasian pediatric patients with seronegative enthesopathy and arthropathy syndrome after 5 years of disease. *J Rheumatol* 1992; 19: 469-75.
36. LEHTINEN A, PELTOKALLIO P, TAAVITSAINEN M: Sonography of Achilles tendon correlated to operative findings. *Ann Chir Gynaecol* 1994; 83: 322-7.
37. 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: 489-93.
38. MCGONAGLE D, EMERY P: Enthesitis, osteitis, microbes, biomechanics, and immune reactivity in ankylosing spondylitis. *J Rheumatol* 2000; 27: 2302-4.
39. 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: 2155-9.

40. OLIVIERI I, BAROZZI L, PADULA A *et al*.: Retrocalcaneal bursitis in spondyloarthropathy: assessment by ultrasonography and magnetic resonance imaging. *J Rheumatol* 1998; 25: 1352-7.
41. OLIVIERI I, SCARANO E, CIANCIO G, GIASI V, PADULA A: Lateral epicondylitis with marked soft tissue swelling in spondyloarthritis. *Clin Rheumatol* 2004; 23: 275-6.
42. OLIVIERI I, GEMIGNANI G, BINI C, GRASSI L, PASERO G: Diffuse Achilles tendon thickening in juvenile onset seronegative HLA-B27 positive spondyloarthropathy. *J Rheumatol* 1988; 15: 381-2.
43. MCGONAGLE D: Diagnosis and treatment of enthesitis. *Rheum Dis Clin North Am* 2003; 29: 549-60.
44. MCGONAGLE D, MARZO-ORTEGA H, O'CONNOR P *et al*.: Histological assessment of the early enthesitis lesion in spondyloarthropathy. *Ann Rheum Dis* 2002; 61: 534-7.
45. AMOR B, DOUGADOS M, KHAN MA: Management of refractory ankylosing spondylitis and related spondyloarthropathies. *Rheum Dis Clin North Am* 1995; 21: 117-28.
46. D'AGOSTINO MA, BREBAN M, SAID-NAHAL R, DOUGADOS M: Refractory inflammatory heel pain in spondylarthropathy: a significant response to infliximab documented by ultrasound. *Arthritis Rheum* 2002; 46: 840-1.
47. OLIVIERI I, SCARANO E, PADULA A, D'ANGELO S, CANTINI F: Switching tumor necrosis factor alpha inhibitors in HLA-B27-associated severe heel enthesitis. *Arthritis Rheum* 2007; 57: 1572-4.
48. OLIVIERI I, SCARANO E, GIGLIOTTI P, GIASI V, PADULA A: Successful treatment of juvenile-onset HLA-B27-associated severe and refractory heel thesitis with adalimumab documented by magnetic resonance imaging. *Rheumatology* (Oxford) 2006; 45: 1315-7.
49. OLIVIERI I, BARBIERI P, GEMIGNANI G, PASERO G: Isolated juvenile onset HLA-B27 associated peripheral enthesitis. *J Rheumatol* 1990; 17: 567-8.
50. OLIVIERI I, PADULA A, GIASI V, SCARANO E: Enthesitis of spondylarthritis can masquerade as Osgood-Schlatter disease by radiographic findings. *Arthritis Rheum* 2003; 49: 147-8.
51. MAKSYMOWYCH WP: Progress in spondylarthritis. Spondyloarthritis: lessons from imaging. *Arthritis Res Ther* 2009; 11: 222.
52. VAN DER HEIJDE D, CALIN A, DOUGADOS M, KHAN MA, VAN DER LINDEN S, BELLAMY N: Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in Ankylosing Spondylitis. *J Rheumatol* 1999; 26: 951-4.
53. MANDER M, SIMPSON JM, MCLELLAN A, WALKER D, GOODACRE JA, DICK WC: Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987; 46: 197-202.
54. VAN DER HEIJDE D, VAN DER LINDEN S, BELLAMY N, CALIN A, DOUGADOS M, KHAN MA: Which domains should be included in a core set for endpoints in ankylosing spondylitis? Introduction to the ankylosing spondylitis module of OMERACT IV. *J Rheumatol* 1999; 26: 945-7.
55. HEUFT-DORENBOSCH L, SPOORENBERG A, VAN TUBERGEN A *et al*.: Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis* 2003; 62: 127-32.
56. MAKSYMOWYCH WP, MALLON C, MORROW S *et al*.: Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis* 2009; 68: 948-53.
57. MCGONAGLE D, MARZO-ORTEGA H, BENJAMIN M, EMERY P: Report on the Second international Enthesitis Workshop. *Arthritis Rheum* 2003; 48: 896-905.
58. HELLIWELL PS, PORTER G: Sensitivity and specificity of plain radiographic features of peripheral enthesopathy at major sites in psoriatic arthritis. *Skeletal Radiol* 2007; 36: 1061-6.
59. TAN AL, MCGONAGLE D: Imaging of seronegative spondyloarthritis. *Best Pract Res Clin Rheumatol* 2008; 22: 1045-59.
60. OSTERGAARD M, PEDERSEN SJ, DOHN UM: Imaging in rheumatoid arthritis--status and recent advances for magnetic resonance imaging, ultrasonography, computed tomography and conventional radiography. *Best Pract Res Clin Rheumatol* 2008; 22: 1019-44.
61. BALINT PV, KANE D, WILSON H, MCINNES IB, STURROCK RD: Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; 61: 905-10.
62. GENC H, CAKIT BD, TUNCBILEK I, ERDEM HR: Ultrasonographic evaluation of tendons and enthesal sites in rheumatoid arthritis: comparison with ankylosing spondylitis and healthy subjects. *Clin Rheumatol* 2005; 24: 272-7.
63. GENC H, DUYUR CAKIT B, NACIR B, SARACOGLU M, KACAR M, ERDEM HR: The effects of sulfasalazine treatment on enthesal abnormalities of inflammatory rheumatic diseases. *Clin Rheumatol* 2007; 26: 1104-10.
64. FREDIANI B, FALSETTI P, STORRI L *et al*.: Ultrasound and clinical evaluation of quadricipital tendon enthesitis in patients with psoriatic arthritis and rheumatoid arthritis. *Clin Rheumatol* 2002; 21: 294-8.
65. NEWMAN JS, ADLER RS: Power Doppler Sonography: Applications in Musculoskeletal Imaging. *Semin Musculoskelet Radiol* 1998; 2: 331-40.
66. KOSKI JM, SAARAKKALA S, HELLE M, HAKULINEN U, HEIKKINEN JO, HERMUNEN H: Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. *Ann Rheum Dis* 2006; 65: 1590-5.
67. D'AGOSTINO MA, SAID-NAHAL R, HACQUARD-BOUDER C, BRASSEUR JL, DOUGADOS M, BREBAN M: Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003; 48: 523-33.
68. DE MIGUEL E, COBO T, MUNOZ-FERNANDEZ S *et al*.: Validity of enthesis ultrasound assessment in spondylarthropathy. *Ann Rheum Dis* 2009; 68: 169-74.
69. KIRIS A, KAYA A, OZGOCMEN S, KOCAKOC E: Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography. *Skeletal Radiol* 2006; 35: 522-8.
70. BALINT PV, MANDL P, KANE D: "All that glistens is not gold"-- separating artefacts from true Doppler signals in rheumatological ultrasound. *Ann Rheum Dis* 2008; 67: 141-2.
71. MOREL M, BOUTRY N, DEMONDION X, LEGROUX-GEROT I, COTTEN H, COTTEN A: Normal anatomy of the heel entheses: anatomical and ultrasonographic study of their blood supply. *Surg Radiol Anat* 2005; 27: 176-83.
72. MCGONAGLE D, GIBBON W, EMERY P: Classification of inflammatory arthritis by enthesitis. *Lancet* 1998; 352: 1137-40.
73. 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: 694-700.
74. ESHED I, BOLLOW M, MCGONAGLE DG *et al*.: MRI of enthesitis of the appendicular skeleton in spondyloarthritis. *Ann Rheum Dis* 2007; 66: 1553-9.
75. SCHOELLNAST H, DEUTSCHMANN HA, HERMANN J *et al*.: Psoriatic arthritis and rheumatoid arthritis: findings in contrast-enhanced MRI. *AJR Am J Roentgenol* 2006; 187: 351-7.
76. CLAUDEPIERRE P, VOISIN MC: The entheses: histology, pathology, and pathophysiology. *Joint Bone Spine* 2005; 72: 32-7.