

**ASSESSMENT BY DOPPLER ULTRASOUND OF ENTHESEAL  
LESIONS IN SPONDYLOARTHRITIS:  
A LONGITUDINAL STUDY TO DETERMINE STRUCTURAL DAMAGE  
AND DISEASE ACTIVITY LESIONS**

**SANDRA ISABEL SALVADOR FALCÃO**  
Tese para obtenção do grau de Doutor em Medicina  
na Especialidade em Investigação Clínica  
na Faculdade de Ciências Médicas

**Outubro, 2014**

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**Sandra Isabel Salvador Falcão**

**Orientadores: Professor Doutor Jaime da Cunha Branco e**

**Professor Doutor Eugenio de Miguel**

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**Investigação Clínica**

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## ***Identidade***

*Preciso ser um outro  
para ser eu mesmo*

*Sou grão de rocha  
Sou o vento que a desgasta*

*Sou pólen sem insecto*

*Sou areia sustentando  
o sexo das árvores*

*Existo onde me desconheço  
aguardando pelo meu passado  
ansiando a esperança do futuro*

*No mundo que combato morro  
no mundo por que luto nasço*

*Mia Couto, in "Raiz de Orvalho e Outros Poemas"*

*“...for some unexplained reason, ultrasonography applied to disorders of tendons, musculature, soft tissues, and even bones have been largely ignored by many physicians...”*

*Donald Resnick*

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## ABBREVIATIONS

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<b>ASAS</b>	Assessment of SpondyloArthritis international Society
<b>ASDAS</b>	Ankylosing Spondylitis Disease Activity Score
<b>BASDAI</b>	Ankylosing Spondylitis Disease Activity Index
<b>BASFI</b>	Bath Ankylosing Spondylitis Functional Index
<b>BASRI</b>	Bath Ankylosing Spondylitis Radiology Index
<b>BMI</b>	Body Mass Index
<b>BMP</b>	Bone Morphogenetic Proteins
<b>CASPAR</b>	CIASsification criteria for Psoriatic Arthritis
<b>CRP</b>	C-reactive protein
<b>DAS</b>	Disease Activity Score
<b>DKK-1</b>	Dickkopf-related protein 1
<b>DISH</b>	Diffuse Idiopathic Skeletal Hyperostosis
<b>ERAP1</b>	Endoplasmic reticulum aminopeptidase 1
<b>ESR</b>	Erythrocyte sedimentation rate
<b>ESSG</b>	European Spondylarthropathy Study Group
<b>ESU</b>	Early Spondyloarthritis Unit
<b>FOP</b>	Fibrodysplasia Ossificans Progressiva
<b>GUESS</b>	Glasgow Ultrasound Enthesitis Scoring System
<b>HLA</b>	Human leucocyte antigen
<b>IBD</b>	Inflammatory bowel disease
<b>IL</b>	Interleukin
<b>IL23R</b>	Interleukin-23 receptor
<b>MASEI</b>	Madrid Sonography Enthesitis Index
<b>MASES</b>	Maastricht Ankylosing Spondylitis Enthesitis Score
<b>MEI</b>	Mander Enthesis Index
<b>MRI</b>	Magnetic resonance imaging
<b>OMERACT</b>	Outcome Measures in Rheumatology Clinical Trials
<b>PG</b>	Proteoglycan-rich matrix
<b>PGE2</b>	Prostaglandin E2

<b>PsA</b>	Psoriatic Arthritis
<b>RA</b>	Rheumatoid Arthritis
<b>SEI</b>	Sonographic enthesitic index
<b>SpA</b>	Spondyloarthritis
<b>TNF</b>	Tumor necrosis factor
<b>VAS</b>	Visual analogic scale
<b>WNT</b>	Wingless type like signaling

## SUMMARY

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Enthesitis is the hallmark of spondyloarthritis (SpA), and is observed in all subtypes. Wide information on SpA abnormalities, including synovitis, tendinitis and enthesitis, can be efficiently perceived by Doppler ultrasound. Furthermore, several studies on imaging of enthesitis showed that imaging techniques are better than clinical examination to detect enthesitis alterations; and vascularized enthesitis detected by Doppler ultrasound appears to be a valuable diagnostic tool to confirm SpA diagnosis. However, data published until now concerning enthesal elementary alterations that characterize SpA enthesitis (enthesitis inflammatory activity) or enthesopathy (permanent structural changes) reflect rather the authors' empiric opinion than a methodological validation process. In this sense it seems crucial to identify elementary enthesal lesions associated with activity or damage, in order to improve monitoring and treatment response in SpA patients. The development of better assessment tools is today a challenge and a need in SpA.

The first study of this thesis focused on the analysis of the reliability of inter-lector and inter-ultrasonography equipment of Madrid sonography enthesitis index (MASEI). Fundamental data for the remaining unrolling project validity.

In the second and third studies we concerned about two enthesal elemental lesions: erosions and bursa. In literature erosions represent a permanent structural damage, being useful for monitoring joint injury, disease activity and therapeutic response in many rheumatic diseases; and to date, this concept has been mostly applied in rheumatoid arthritis (RA). Unquestionably, erosion is a tissue-related damage and a structural change. However, the hypothesis that we decided to test was if erosions represent a permanent structural change that can only grow and worsen over time, as occurs in RA, or a transitory alteration. A longitudinal study of early SpA patients was undertaken, and the Achilles enthesitis was used as a model. Our results strongly suggested that previously detected erosions could disappear during the course of the disease, being consistent with the dynamic behavior of erosion over time. Based on these striking results it seems reasonable to suggest that the new-bone formation

process in SpA could be associated with the resolution of cortical enthesal erosion over time. These results could also be in agreement with the apparent failure of anti-tumor necrosis factor (TNF) therapies to control bone proliferation in SpA; and with the relation of TNF- $\alpha$ , Dickkopf-related protein 1 (Dkk-1) and the regulatory molecule of the Wnt signaling pathway in the bone proliferation in SpA. In the same model, we then proceeded to study the enthesal bursa. Interestingly, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) enthesopathy definition does not include bursa as an elementary enthesal lesion. Nonetheless, bursa was included in 46% of the enthesal studies in a recently systematic literature review, being in agreement with the concept of “synovio-enthesal complex” that includes the link between enthesitis and osteitis in SpA. It has been clarified in recent data that there is not only a close functional integration of the enthesal with the neighboring bone, but also a connection between enthesitis and synovitis. Therefore, we tried to assess the prevalence and relevance of the bursa-synovial lesion in SpA. Our findings showed a significant increase of Achilles bursa presence and thickness in SpA patients compared to controls (healthy/mechanical controls and RA controls). These results raise awareness to the need to improve the enthesopathy ultrasonographic definition.

In the final work of this thesis, we have explored new perspectives, not previously reported, about construct validity of enthesal ultrasound as a possible activity outcome in SpA. We performed a longitudinal Achilles enthesal ultrasound study in patients with early SpA. Achilles ultrasound examinations were performed at baseline, six- and twelve-month time periods and compared with clinical outcome measures collected at basal visit. Our results showed that basal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are higher in patients with Doppler signal in enthesal, and even that higher basal ESR, CRP and Ankylosing Spondylitis Disease Activity Score (ASDAS) predicted a higher Doppler signal (an ultrasound alteration accepted as representative of inflammation) six months later. Patients with very high disease activity assessed by ASDAS (>3.5) at baseline had significantly higher Achilles total ultrasound score verified at the same time; and ASDAS <1.3 predicted no Doppler signal at six and twelve months. This seems to represent a connection between classical biomarkers and clinical outcomes associated with SpA activity and Doppler signal, not only at the same

time, but also for the following months. Remarkably, patients with inactive disease (ASDAS < 1.3) at baseline had no Doppler signal at six and twelve months. These findings reinforce the potential use of ultrasound related techniques for disease progression assessment and prognosis purposes. Intriguingly, Ankylosing Spondylitis Disease Activity Index (BASDAI) didn't show significant differences between different cut-offs concerning ultrasound lesions or Doppler signal, while verified with ASDAS. These results seem to indicate that ASDAS reflects better than BASDAI what happens in the enthesis.

The work herein discussed clearly shows the potential utility of ultrasound in enthesitis assessment in SpA patients, and can be important for the development of ultrasound activity and structural damage scores for diagnosis and monitoring purposes. Therefore, local promotion of this technique constitutes a medical intervention that is worth being tested in SpA patients for diagnosis, monitoring and prognosis purposes.

## INTRODUCTION

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### **“Once upon a time in Rheumatology land...”**

Ultrasonography is a well-known and widely used method within several medical specialties, such as cardiology and gynecology, but not in rheumatology. Possibly this is related with the clinical expertise of senior rheumatologists – accustomed to “old methods”, not feeling any interest in this revolutionary technique – and the relatively slow learning process of this imaging method. Initial developments in the field were led by radiologists. In the '70s, ultrasound B-scanning was used in the differentiation of Baker's cyst and thrombophlebitis, and in a relatively short period of time was considered the technique of choice for the detection and assessment of popliteal cysts.<sup>1,2</sup> In the early '80s Tiliakos and colleagues<sup>3</sup> used ultrasound to identify tophaceous versus rheumatoid nodules, and Aisen and colleagues<sup>4</sup> provided new insights about ultrasound use for measuring the articular cartilage thickness in humans, as well as to detect changes in its surface and internal characteristics. During that decade several studies were published supporting the role of ultrasound in the detection of soft tissues changes, enlargement of joint cavity, effusion and synovial reaction; and in measuring disease activity in RA.<sup>5-8</sup> This research was mainly focused on large joints because the low frequency transducers that were available at that time did not allow a careful assessment of small joints. Even so, these data strongly contributed to the progress of knowledge and to promote a widespread interest in ultrasound. In 1988 De Flaviis and colleagues<sup>9</sup> published the first description of ultrasound detection of bone erosion in rheumatoid arthritis. In the '90s, the dramatic improvement of spatial resolution, due to the new generation high frequency probes, opened up new possibilities for the exploration of otherwise undetectable anatomical details. Ultrasound research during this period was enhanced by the growing use of color Doppler and power Doppler and by the first prototypes of three dimension ultrasound. In 1993, Martinoli and colleagues elegantly demonstrated that the internal network of fine parallel and linear echoes that characterizes tendinous echotexture is caused by specular reflections at the interface between collagen bundles and endotendineum septa.<sup>10</sup> In the same year, Grassi and colleagues published the first

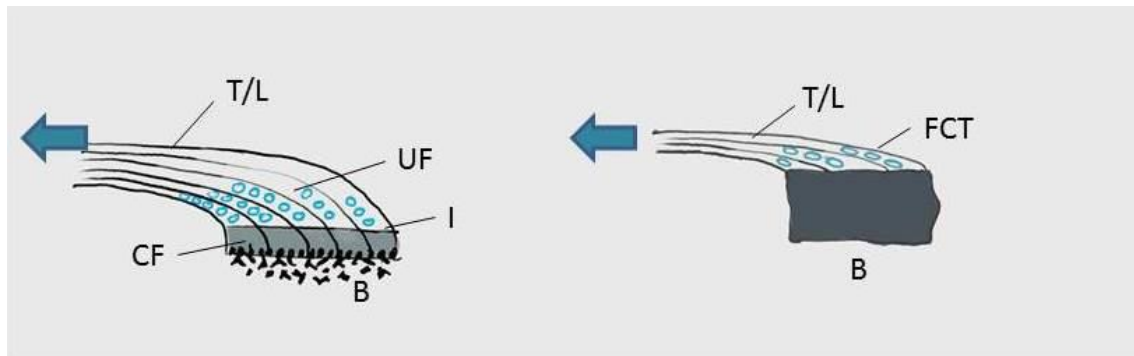
study of the metacarpophalangeal joints in patients with RA with a 13 MHz probe.<sup>11</sup> Ultrasound was able to detect a wide spectrum of abnormalities including joint cavity widening, effusion, synovial thickening, bone erosions, loss of definition of the metacarpal articular cartilage, widening of the flexor tendon sheath, irregularities of flexor and extensor tendons and tendon rupture. In the following year, Lehtinen and colleagues clearly demonstrated the potential of ultrasound to provide morphological information of entheses, which is unobtainable by a clinical assessment of patients with SpA.<sup>12</sup> Ultrasound demonstrated its pivotal role in giving more detailed information about the causes of pain at the insertions of tendons; being described a wide range of sonographic changes, such as edema at the insertion of the tendon, bursitis, focal intra-tendinous changes and periosteal changes. The late '90s and early '2000s were characterized by a constant increase of ultrasound studies focused on its application in several clinical conditions, such as diagnosis of monoarticular symptoms, psoriatic arthritis, seronegative spondyloarthritis, juvenile rheumatoid arthritis, polymyalgia rheumatic, osteoarthritis, crystal deposition diseases, enthesitis, preoperative evaluation of tendons, intra-articular steroid injections, synovial biopsy and therapy monitoring. Ultrasound was also compared with other well-known imaging techniques. Wakefield and colleagues in 2000 verified that ultrasound was capable to detect more erosions than conventional radiography, especially in early RA;<sup>13</sup> Szkudlarek and colleagues showed that power Doppler ultrasound is a reliable technique for assessing inflammatory activity in metacarpophalangeal joints of patients with rheumatoid arthritis, using dynamic magnetic resonance imaging (MRI) as the standard;<sup>14</sup> and Terslev and colleagues published that estimates of synovial inflammatory activity by Doppler ultrasound and post-contrast magnetic resonance were comparable.<sup>15</sup> Ultrasound has also demonstrated its value in therapy monitoring. In 2002, Hau and colleagues verified that ultrasound was able to detect a decrease in synovial vascularization of small fingers joints in RA patients one month after treatment with TNF blocker,<sup>16</sup> while Terslev and colleagues described a significant decrease in synovial vascularization after intra-articular treatment with glucocorticosteroids in patients with RA.<sup>17</sup> Power Doppler ultrasound with an echo contrast agent has also proven to be a useful tool in distinguishing between inflammatory and non-inflammatory pannus.<sup>18</sup> Several papers have reported that ultrasound is more sensitive than clinical



examination in the detection of enthesal abnormalities of lower limbs in SpA,<sup>19</sup> and synovitis in RA.<sup>20</sup> In the field of guided procedures ultrasound also represented an enormous progress concerning intra-lesional injections.<sup>21</sup> The constant progress in ultrasound technology allowed amazing improvements in its images, and in the quality of relevant information that can be achieved. Thus, it is not surprising that ultrasound has revealed the potential to make a clinically substantial impact in the assessment of the extra-articular involvement of rheumatic diseases (salivary glands, skin, lung, and blood vessels).<sup>22-26</sup> Despite the growing evidence of the clinical value of ultrasound in daily practice, the dissemination of this imaging technique is still limited. It is predictable that ultrasound has a long way to go, but it will certainly be more relevant in the near future.

### **Enthesis: “The synovial-entheseal complex”**

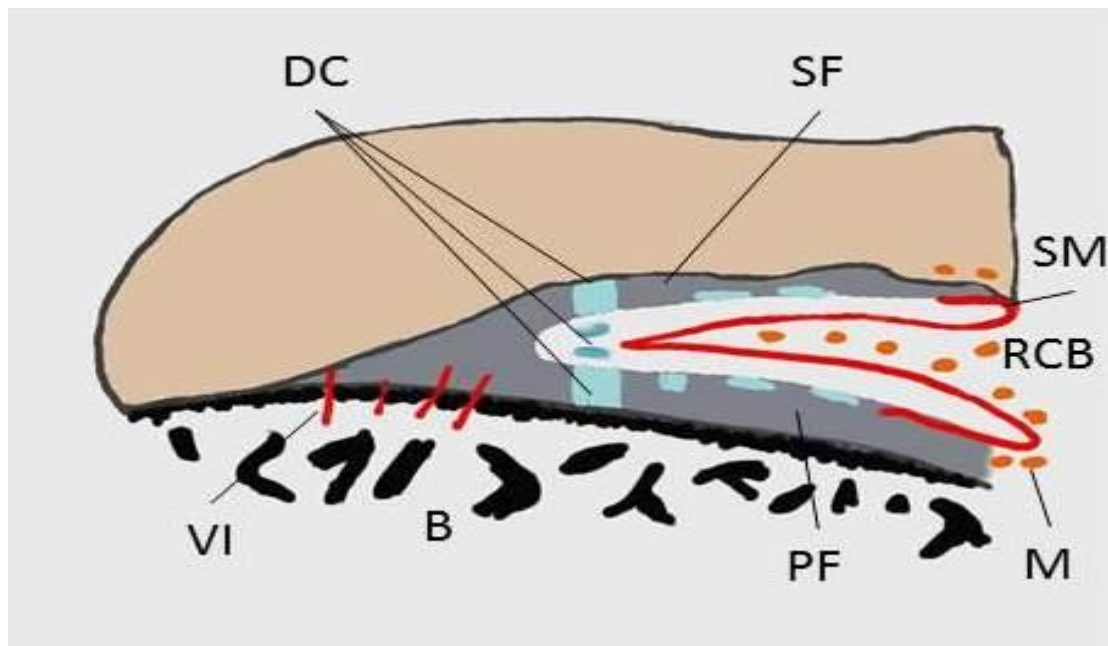
The conceptual understanding of entheses has changed in recent years, with new developments coming from the integration of anatomical, histological and imaging data.<sup>27</sup> The term entheses was firstly defined as the site of attachment of tendon, ligament, joint capsule or fascia to bone, with the functions of anchorage and stress dissipation.<sup>28</sup> Nowadays it has become clear that entheses is often more than a focal attachment, and can form part of an elaborate “entheses organ” or “synovial-entheseal complex” that may include functional integration with a synovial membrane.<sup>29</sup> Furthermore, there are two types of entheses, one purely fibrous and the other containing fibrocartilage in the insertional zone (Figure 1).



**Figure 1.** Diagrammatic representation of the two types of enthesis: fibrocartilaginous and fibrous. Fibrocartilaginous (left) insertions are usually close to an articular margin where tendons or ligaments (T/L) are “bent” by tensional forces (in the direction of the arrow) during joint movement. This creates a shearing force at the bone junction, which is resisted by the irregularity of the interface (I) lying between the zone of calcified fibrocartilage (CF) and the bone (B). The change in “insertional angle” of the T/L that occurs with joint movement also creates compressional forces that are most prominent in the deeper part of the enthesis. These are resisted by the zone of uncalcified fibrocartilage (UF), which gradually dissipates the bending of the collagen fibers away from the bone, with the proteoglycan-rich matrix promoting compression tolerance. The thickness of the UF zone can vary with changing stress levels as a functional adaptation to load. In contrast to a fibrocartilaginous enthesis, a tendon or ligament with a purely fibrous enthesis (right) (e.g., one attaching to the shaft of a long bone) has no cartilage matrix and its collagen fibers attach to the bone at an oblique angle. It consists purely of dense fibrous connective tissue (FCT), and the characteristic cell type is the fibroblast.

Adapted from McGonagle D, Marzo-Ortega H, Benjamin M, Emery P. Report on the Second international Enthesitis Workshop. *Arthritis Rheum* 2003;48:896-905.

The fibrocartilage of enthesis has a pivotal role in balking shear and compressive mechanical stress. This is best explained at the Achilles tendon, where the components of the enthesis organ consist of the enthesis itself, together with periosteal (fibrocartilage covering the surface of the bone, immediately adjacent to the osteotendinous junction) and sesamoid fibrocartilages (on the anterior surface of the tendon), the retrocalcaneal bursa, and the tip of Kager’s fat pad (Figure 2).



**Figure 2.** Diagrammatic representation of the synovio-entheseal complex, using the Achilles tendon enthesis organ to illustrate the concept.

The synovial membrane (SM), which is intimately related to the enthesis itself, lines much of the retrocalcaneal bursa (RCB), except in the region where the sesamoid fibrocartilage (SF) in the deep part of the tendon presses against the periosteal fibrocartilage (PF) covering the superior tuberosity. Macrophages (M) are an integral part of the synovium, and their anatomic proximity to fibrocartilage adjacent to insertions could contribute to an inflammatory response in relation to degenerative changes (DC) in the walls of the bursa or at the enthesis itself. Although a young healthy enthesis is probably avascular, blood vessel invasion (VI) of the enthesis is common in older individuals. The blood vessels may come from the underlying bone at sites of focal absence of the subchondral bone plate, as depicted, or they may invade from tissue on the surface of the tendon, including synovium.

Adapted from 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;56:2482-91.

Together, these structures help to dissipate load over a wide area. Thus, although there is no neighboring synovial joint lined by articular cartilage at this location, the enthesis is still intimately related with the synovial membrane that covers the tip of the protruding fat pad. In addition, it should also be remembered that the enthesis organ is also present at numerous other sites in a close anatomic relationship to synovial joints, and can play a non-negligible role in pathophysiology damage process in inflammatory arthritis. For instance, traditional defined concepts, such as the "bare area" and "cartilage-pannus junction"<sup>30</sup> may be neither essential nor necessary for the erosive process in RA. Histologic studies have demonstrated that periarticular erosion formation in RA has a propensity to occur adjacent to ligaments in which bone microdamage is common,<sup>31,32</sup> suggesting that inflammation drives the inherent propensity for damage to occur at characteristically predisposed sites.

Given the extent and complexity of entheses, it is likely that the presence of synovium and synovial fluid in the retrocalcaneal bursa and bursae, associated with other attachment sites, reflect a physiologic role identical to that in synovial joints. Type A and type B bursae synoviocytes are likely to be involved in maintaining the rheological properties of synovial fluid, lubricating and nourishing periosteal and sesamoid fibrocartilages.<sup>27</sup> Although “synovio-entheseal complex” seems to be advantageous in health, the very fact that a tissue prone to microdamage is closely related with synovium means that, in fact, the “synovio-entheseal complex” is an enabling immunologic environment and may be a region that is particularly prone to inflammation.

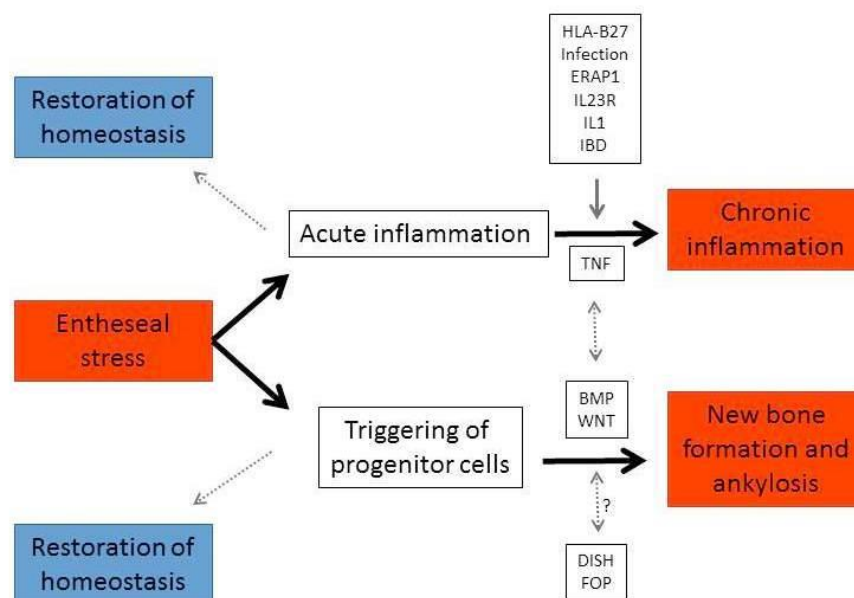
### **Spondyloarthritis: the enthesal disease**

Spondyloarthritis describes a group of interrelated rheumatic conditions comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis/spondylitis with inflammatory bowel disease (IBD) and reactive arthritis. One of the major clinical problems is, and always has been, the search for proof of sacroiliitis in patients who present with the typical clinical picture of AS and normal X-ray films of sacroiliac joints. These patients were classified for years as having undifferentiated SpA or diagnosed with an alternative rheumatic disorder or even a non-rheumatic condition, such as mechanical back pain. The observation that many patients with inflammatory back pain but without sacroiliitis on X-ray films represent the earliest phase of AS and will develop radiographic changes diagnostic for AS within a period of time, usually measured in years, has created a platform for the development of the new disease concept.<sup>33</sup> It has been demonstrated that the presence of HLA-B27 and/or MRI findings of active sacroiliac joints inflammation in these patients could, with a significant degree of accuracy, help to predict which patients will subsequently develop the classical picture of AS.<sup>34</sup> This led to the development of the concept of pre-radiographic AS, which, together with classical AS, formed the basis for the new entity of axial SpA.<sup>35</sup> Other SpA with predominant spinal involvement, such as related to psoriasis or inflammatory bowel disease, and sharing many clinical and imaging

features with AS can also be classified in the group of axial SpA. Therefore, it has been suggested that patients with SpA should be distinguished according to their clinical presentation as patients with predominantly axial SpA or with predominantly peripheral SpA.<sup>36,37</sup> These new concepts not only unifies patients with a similar disease pattern (an entity that shares clinical, pathological and genetic characteristics), permitting advanced research, but also provides the opportunity for earlier diagnosis and better management of patients with pre-radiographic AS and AS-like psoriatic and inflammatory bowel disease-related arthritis.

The main pathological feature in SpA is the chronic inflammatory involvement of the enthesis and the adjacent bone,<sup>38</sup> which may sometimes be present several years as an isolated clinical manifestation.<sup>39</sup> As previously described, the typical clinical articular affection are the sacroiliac joints and spinal inflammation, as well as peripheral arthritis and enthesitis, often with a nonsymmetrical distribution. Although features of joint destruction can be dramatic, in particular in some forms of PsA, skeletal damage in SpA is only partially due to the loss of articular cartilage and bone erosion. In contrast, new cartilage and bone formation, presenting as ankylosing enthesopathy and leading to bony spurs, syndesmophytes, enthesophytes and eventually joint or spine ankylosis, are hallmark signs of this disease. However, the relationship between enthesitis, new-bone formation and bone erosion in SpA remains poorly understood. The introduction of targeted therapies, in particular anti-TNF drugs, has met unprecedented success in the treatment of signs and symptoms of SpA. Some studies reported the histological and immunohistochemical features of the bone adjacent to enthesal sites and the actual point of enthesal contact with the bone, where fibrocartilage is abundant, particularly in the early stages of SpA. In early and established SpA, human studies showed that the predominant infiltrating cell at the enthesal fibrocartilage is the macrophages,<sup>40</sup> while in the underlying bone is lymphocytic infiltration.<sup>41</sup> These facts are in accordance with two pathophysiologic processes well recognized in SpA: the importance of innate immunity where the macrophages have a crucial role, and that autoimmunity in SpA might be primarily directed against a bone antigen.<sup>40,42</sup> As macrophages are the main source of TNF, it is not surprising the apparent good response of enthesitis to biologic blockade with anti-

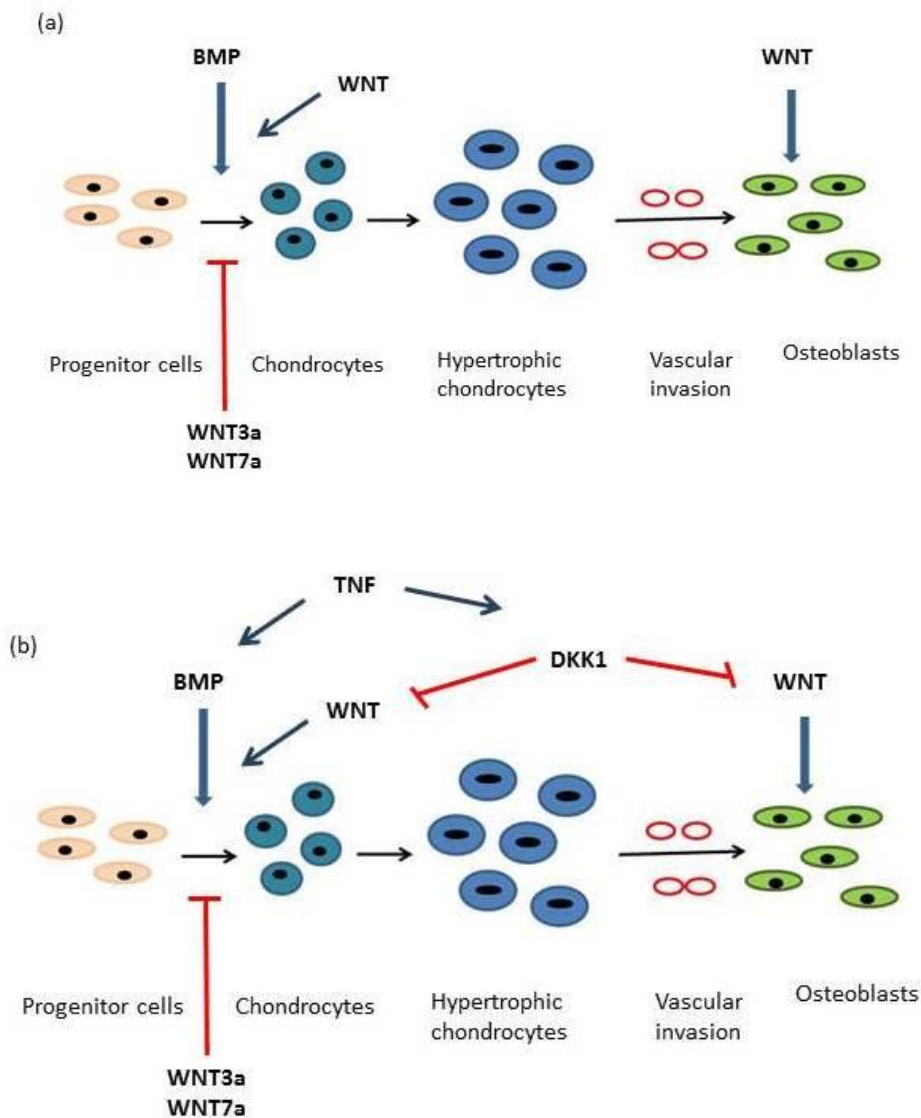
TNF.<sup>43</sup> Nonetheless, current radiographic relatively short follow-up data suggest that these drugs do not affect the process of ankylosis.<sup>44-46</sup> This apparent lack of structural effect is in sharp contrast to what is seen in the erosive destruction of joints in RA.<sup>47</sup> Intriguingly, continuous treatment with nonsteroidal anti-inflammatory drugs, as compared with on-demand treatment, does appear to influence ankylosis in AS.<sup>48</sup> It seems that prostaglandin E2 (PGE2) inhibition may act differently than TNF blockade, and PGE2 modulation has shown to delay new bone formation in AS. However, one can remain doubtful whether this effect of PGE2 inhibition truly proves the link between inflammation and new bone formation, as PGE2 is an important mediator for osteoblast differentiation and function, and inhibition of new bone formation may merely reflect the anti-anabolic effect of PGE2 inhibition, rather than its anti-inflammatory effect.<sup>49</sup> Nevertheless, the pathophysiological SpA process can be seen as a complex slow waltz between pro-inflammatory molecules and new tissue formation, with restoration of tissue integrity or tissue remodeling as a final outcome.<sup>50</sup> It seems that the development of SpA is dependent on a multi-step process that leads to chronic or recurrent inflammation, but also to the triggering of new tissue formation, completely or partially independent of inflammation (Figure 3).<sup>51</sup>



**Figure 3.** A view on the relationship between inflammation and ankylosis in SpA. The primary event is considered “enteseal stress”. Biomechanical factors and microdamage are likely to play roles in this. Enteseal stress leads to triggering of an acute inflammatory reaction and of progenitor cells. In most instances, the acute events go unnoticed and homeostasis is restored. Under specific circumstances, the acute events can turn into a chronic situation in which inflammation and/or

ankylosis are prominent. Different pathways regulate chronic inflammation and new tissue formation, but these pathways are likely to influence each other. Genetic factors are likely to steer chronic inflammation and new tissue formation. For the latter aspects, clues may be found in other bone-forming diseases. ERAP1, endoplasmic reticulum aminopeptidase 1; IBD, inflammatory bowel disease; IL23R, interleukin-23 receptor; BMP, bone morphogenetic proteins; WNT, wingless type like signaling; DISH, diffuse idiopathic skeletal hyperostosis; FOP, fibrodysplasia ossificans progressiva.

The degree to which inflammation and the new bone formation are linked remains conjectural, but data from MRI studies of spinal inflammation support the concept of such coupling; however, these studies also suggest a role for the involvement of non-inflammatory pathways, such as those involving bone morphogenetic proteins (BMPs), wingless type like signaling (Wnt) proteins and dickkopf – related protein 1 (DKK-1), in the formation of new bone (Figure 4).



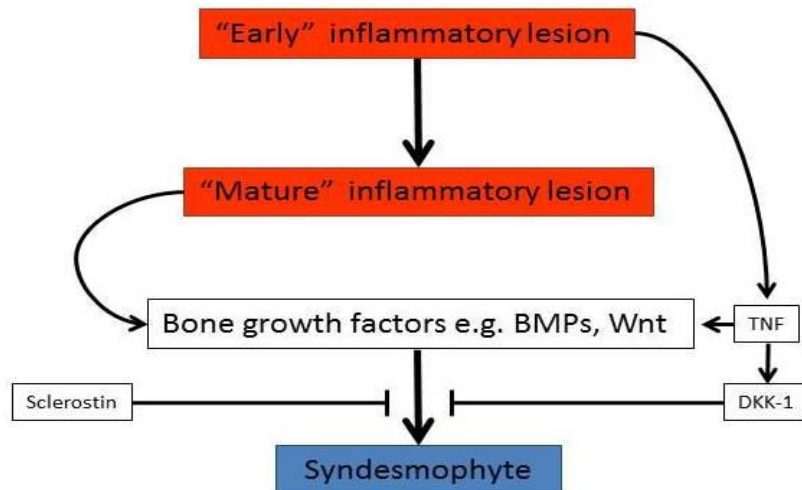
**Figure 4.** Roles of BMPs and WNTs in endochondral bone formation.

(a) Physiological endochondral bone formation is stimulated by BMPs. WNT signaling plays a supportive role in relation to BMPs. However, some WNTs have a negative effect on early chondrocyte differentiation. (b) In the presence of inflammation, TNF may stimulate BMP signaling but also the expression of DKK1, which acts a WNT antagonist. The balance between TNF, BMP and WNT signaling may determine the onset and progression of ankylosis. DKK, dickkopf.

Adapted from Lories RJ, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. *Arthritis Res Ther.* 2009;11:221.

The “TNF brake” hypothesis was proposed to explain the sequence of events of new syndesmophytes formation in an established inflammatory lesion (Figure 5).<sup>52</sup>





**Figure 5.** The “TNF brake” hypothesis.

In well-established (mature) inflammatory lesions, repair pathways leading to new bone formation activated through BMPs, Wnts and other signaling proteins are held in check by inhibitors, such as sclerostin and DKK-1; DKK-1 is up regulated by TNF. Although pro-inflammatory cytokines such as TNF “trigger” the expression of BMP, TNF also up regulates DKK-1; resolution of inflammation by anti-TNF therapy and the associated reduction in DKK-1 would thereby allow new bone formation to proceed.

This hypothesis was put forward to explain the observation that new syndesmophytes are more likely to develop at sites where inflammation has been resolved (low TNF, low DKK-1, high Wnt) as opposed to sites of persistent inflammation (high TNF, high DKK-1, low Wnt). In a more detailed elaboration of the hypothesis, it was proposed that early inflammatory lesions are resolved without sequelae, such as new bone, if effective therapy is instituted and inflammation resolves prior to activation of bone formation pathways by triggers such as TNF.<sup>53</sup> While complex inflammatory lesions, and the majority having fat lesions, can also be resolved following anti-TNF therapy, they are associated with the development of new syndesmophytes. Fat lesions, both established and newly evolving, are also associated with new bone formation. These data support a window-of-opportunity concept of disease modification for anti-inflammatory therapy in SpA, especially if it is used early in the disease course; and a model of new bone formation that is dependent on the activation of inflammatory pathways followed by tissue metaplasia that includes fat.

The extent of inflammatory involvement in SpA has been changed in the last years. Currently, the relationship between enthesitis and osteitis is well known. They are particularly characteristics of SpA, but they can also be a feature of degenerative and mechanically enthesopathy. For example, in SpA associated plantar fasciitis, the HLA B27 gene appears to determine the extent and severity of the condition, but not the susceptibility to osteitis; and 50% of patients with plantar fasciitis have an associated osteitis, as determined by MRI.<sup>54</sup> It is reasonable to consider that osteitis is a feature of mechanically induced enthesopathy, suggesting common mechanisms of osteitis in SpA and mechanically induced disease. Furthermore, osteitis adjacent to functional entheses (i.e., where there is contact, but no attachment to bone) has been reported in SpA and mechanically related foot and ankle pain, where MRI studies demonstrated bone edema in wraparound regions of tendons.<sup>55,56</sup> Like true insertions, these sites are also prone to adjacent periostitis. These observations have important implications for understanding pathogenesis of SpA, because they reinforce the role of mechanical stress (shear and compression) as a distinct etiopathogenic factor inducing bone abnormalities.

Bony spurs are other well recognized lesions in SpA. Although, they also can be a feature in degenerative, metabolic enthesopathies (e.g., acromegaly), they are widespread in DISH, in athletes, and occur in healthy individuals not necessarily as indication of disease.<sup>57</sup> Enthesophytes appear as irregular outgrowths of varying size that extend from the bone into the tendon or ligament and often develop in parallel with osteophytes at the periphery of articular cartilage.<sup>58</sup> Studies at Achilles tendon level have demonstrated that bony spurs can developed without the need for preceding microtears or any inflammatory reaction, and they are formed mainly by endochondral<sup>59</sup> ossification of entheses. Bony spur formation appears to be initiated by vascular invasion into the tendon from the underlying bone marrow. The capillaries migrate along the rows of fibrocartilage cells that have developed by metaplasia from tendon fibroblasts. Each fibrocartilage cell within a row dies in turn, becomes reabsorbed, and thus creates space for the invading capillary. Bone is subsequently deposited along the walls of the tunnels and a spur is formed.<sup>60</sup> Thus, the potential for bony spur development continues beyond the growing period, and bone grows into

the tendons and not vice versa. However, this does not normally happen while the avascularity of the enthesis fibrocartilage is maintained. Increased loading of tendon is likely to lead to increased fibrocartilage formation and, simultaneously, to trigger osteoblast activity at enthesis and bony spur formation.<sup>61</sup>

A number of known factors may contribute to structural damage and chronicity in SpA. The cytokines such as TNF play a pivotal role, but other factors should not be neglected, such as structural properties of HLA-B27; activation of the immune system by the presence of inflammatory bowel disease or infection; polymorphisms in cytokines and cytokine processing molecules, that lead to either more severe inflammation or delayed clearance of inflammation; biomechanical factors that lead to stress responses or microdamage in the enthesis; and specific genetic factors, not yet identified and different from those that determine disease susceptibility.

### **Ultrasound of enthesis – enthesopathy and enthesitis features and scores**

The term "enthesopathy" is usually used to designate enthesal lesions related to any pathology, including degenerative changes; while the concept of "enthesitis" is used when enthesal inflammation is prevalent, both occurring in the course of SpA.

The prevalence of enthesitis in SpA is not easy to determine. Firstly, related to the expected subclinical enthesis involvement in SpA; and secondly connected with the apparent lack of diagnostic accuracy of the clinical examination, related to the absence of enthesis visible signs of inflammation. Nonetheless, there are three validated scores to clinically assess enthesitis in patients with AS: Mander enthesis index (MEI),<sup>62</sup> Maastricht Ankylosing Spondylitis enthesitis score (MASSES)<sup>63</sup> and Major,<sup>64</sup> and two validated indices for PsA (Gladman<sup>65</sup> and Leeds<sup>66</sup>). The MEI was published in 1987 and evaluates 66 entheses. The high number of entheses to be accessed per patient, and a graduation score system established according to the intensity of pain by each enthesis pressure, makes it particularly difficult to apply in clinical practice.<sup>62</sup> Subsequently the

index MASES was published, as a simplification of the previous index, that explores 13 entheses concerning the presence or absence of pain (I and VII costochondral joints, V lumbar spinous process, Achilles tendon, anterior and superior iliac spine, iliac crest). The Major index includes 12 entheses assessments: iliac crests, trochanters, medial and lateral epicondyles, Achilles and plantar fascia. The Gladman index assesses 8 entheses: rotator cuff, anterior tuberosity of the tibia, Achilles and plantar fascia; and the Leeds index includes 6 entheses in the evaluation: Achilles, medial femoral condyle and lateral epicondyle. The exploration is done by exerting sustained pressure with the fingertips on the entheses (sufficient to blanch the finger nail of the examiner - approximately 4 Kg), which makes you lose objectivity while considering the pain threshold, as it is not the same for each patient.

The OMERACT defines enthesopathy as an “abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in 2 perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity”.<sup>67</sup>

This definition has the advantage of focusing on the main characteristic of enthesal abnormalities, but has the great limitation of not clearly defining the difference between enthesopathy and enthesitis. Despite previous data concerning the usefulness of ultrasound in the evaluation of entheses in the course of SpA, it seems that the most affected peripheral entheses are located in the lower limbs<sup>38</sup> and the combination of grey-scale with power Doppler increases diagnostic accuracy for SpA.<sup>68</sup>

In recent years, numerous scoring systems have been developed with great heterogeneity regarding sites, abnormalities included and evaluation with power Doppler (Table 1). Also, the prevalence of enthesitis in SpA is variable depending on enthesal site and diagnostic ultrasound criteria (see Table 1).

**Table 1.** Principal scores of enthesis ultrasound examination in spondyloarthritis patients

Score	B mode parameters and settings	Doppler parameters and setting	Description of sites of vascularization	Sites	Percentage of abnormal entheses on ultrasound in spondyloarthritis	Scoring system
Balint 2002 Glasgow ultrasound enthesitis scoring system (GUESS) <sup>19</sup>	Thickness, bursitis, enthesophytes and erosions 7-15 MHz	NA	NA	Quadriceps tendon entheses, proximal and distal patellar ligament, Achilles tendon, plantar aponeurosis	56% (22% on clinical examination) – no controls	GUESS score (0 to 36): each item score one point, total possible score on both lower limbs is 36. Quadriceps tendon thickness $\geq 6.1$ mm, patellar ligament thickness (proximal, distal) $\geq 4$ mm, Achilles tendon thickness $\geq 5.29$ mm, plantar aponeurosis thickness $\geq 4.4$ mm Sub score: soft tissue score (thickness and bursitis) and bone score (erosions and enthesophytes)
D'Agostino 2003 <sup>68</sup>	Thickness, bursitis, calcification or periosteal changes, hypoechogenicity 13 MHz	Binary (0 or 1) PRF 0.75KHz, gain 50-53 DB (constant temperature of the room)	Cortical bone insertion, body of the tendon, bursa, junction tendon/entheses	Bilaterally: great trochanter, pubis, quadriceps tendon entheses, patellar tendon (proximal insertion), Achilles tendon, plantar aponeurosis, tibialis anterior tendon insertion, medial and lateral epicondyles	38% (14% on clinical examination) versus 10% for mechanical back pain and 14% for rheumatoid arthritis patients	stage 1: Vascularization at the cortical junction without abnormal findings in Grey-scale stage 2a: Vascularization associated with swelling and/or decreased echogenicity at the cortical junction in Grey-scale stage 3a: Same as stage 2a, plus erosions of cortical bone and/or calcification of entheses, and optional surrounding bursitis stage 2b: Abnormal findings in B mode as in stage 2a, but without vascularization stage 3b: Abnormal findings in B mode as in stage 3a, but without vascularization
Kiris 2006 <sup>69</sup>	Bursitis, calcification, hypoechogenicity, cortical reactive changes (cortical reabsorptive changes,	Semi-quantitative (0-3) and a final sum of each tendon examined PRF 0.5-1 KHz,	Tendon/entheses: no precision concerning the exact location of vascularization	I and VII costochondral joints, V lumbar spinous process, Achilles tendon, anterior and superior iliac spine, iliac crest	44.8% (51.5% on clinical examination) – no controls	Cumulative power Doppler score: grade 0: no flow signal grade 1: mild flow signal refers to the presence of separate dot signals or short linear signals grade 2: moderate flow signal refers to the presence of clearly

	new bone formation, cortical irregularity) 7-14 MHz	gain 50-55, low wall filter (constant temperature of the room)				discernible vascularity with either many small vessels or several long vessels with or without visible branching though involving less than half of the enthesis grade 3: severe flow signal refers to the presence of vessels involving more than half of the enthesis
Alcalde 2007 Sonographic enthesitic index (SEI) <sup>70</sup>	Thickness/loss of thickness, bursitis, hypoechogenicity, peritendinous edema, calcifications, tendon tears, erosions 7.5 MHz	NA	NA	Quadriceps tendon enthesis, proximal and distal patellar ligament, Achilles tendon, plantar aponeurosis	25% ( 8% on clinical examination) versus 0% healthy controls matched for age	SEI = the total sum of SEI-A (acute injury) and SEI-C (chronic injury). Maximum SEI scoring is 76 points SEI-A (0 to 36): each variable is scored as 0 (absence) or 1 (presence): thickening of tendon/aponeurosis, hypoechogenicity of tendon/aponeurosis, peritendinous/periaponeurotic edema, bursitis (where applicable) SEI-C (0 to 40): each variable is scored as 0 (absence) or 1 (presence): tendon tear, loss of thickness, tendon calcification, bone erosion
De Miguel 2009 Madrid sonography enthesitis index (MASEI) <sup>71</sup>	Thickness, bursitis, structure/hypoechogenicity, calcification, erosions 7-12 MHz	Binary (0 or 3) PRF 0.4 KHz, gain 20 dB, low wall filter	Enthesis, tendon, bursitis	Quadriceps tendon enthesis, proximal and distal patellar ligament, Achilles tendon, plantar aponeurosis, distal brachial triceps tendon	NA	MASEI score (0 to 136 on both sides): Calcifications were scored on a semi-quantitative score of 0 to 3 Doppler and erosions were scored as 0 or 3 points Scores for tendon structure, tendon thickness and bursa were either 0 or 1. Calcifications were examined at the area of the enthesis insertion, and scored as 0 if absent, or 1 if a small calcification or ossification with an irregularity of enthesis cortical bone profile was seen. Calcifications were given a score of 2 if there was clear presence of enthesophytes or if medium sized calcifications or ossification were observed. Lastly, they were classified as a 3 if large calcifications or ossifications were present. To simplify things, ossifications and enthesophytes at the enthesis were also included as calcifications.

D'Agostino 2009 <sup>72</sup>	Thickness and/or hypoechoogenicity, calcifications and/or enthesophytes, erosions 13MHz	Binary (0-1) and semi-quantitative (0-3) PRF 0.5 KHz, gain 113 dB, medium wall filter	Enthesis insertion into the cortical bone	Quadriceps tendon entheses, proximal patellar ligament, Achilles tendon, plantar aponeurosis, lateral epicondyle	NA	Grey-scale: hypoechoogenicity/thickness: 0 to 1, Calcification/enthesophyte: 0 to 1, erosion: 0 to 1 Doppler : (0 to 3): 0: no signal, 1: minimal (1 spot), 2: moderate (2 spot), 3: severe (> = 3 spots) or Doppler scored as 0 to 1 (absent/present)
Fillippucci 2009 <sup>73</sup>	Tendon hypoechoogenicity and thickening, enthesal hypoechoogenicity, bursal effusion, calcifications (tendon, entheses), enthesophytes, erosions and bone irregularities 6-18 MHz	Binary (0-1) and semi- quantitative (0-2) PRF 0.75 KHz, low wall filter	Enthesis, tendon, bursitis	Achilles tendon	NA	Soft tissue inflammation (seven items): tendon hypoechoogenicity, Tendon thickening, Enthesal hypoechoogenicity, Bursal effusion, PDS signal at tendon level, PDS signal at enthesal level, PDS signal at bursal level Tissue damage (five items): Intratendinous calcifications, Enthesal calcifications, Enthesophytes, Bone erosions, Bone Irregularities (the last not used to calculate total score) (1) a total score for soft tissue inflammation, which resulted from the sum of the scores assigned to the 7 US findings indicative of soft tissue inflammation, ranging from 0 to 7 with presence/absence data and from 0 to 14 with semiquantitative scores (from 0 to 2: 0:none; 1 mild-moderate; 2:severe); (2) a total score for tissue damage, which resulted from the sum of the scores assigned to the 4 US findings indicative of tissue damage, ranging from 0 to 4 with presence/ absence data and from 0 to 8 with semiquantitative scores. Scoring system: 0: none, 1: mild-moderate, 2: severe Tendon thickness: 0:<5.3mm, 1: between 5.3 and 6.3mm, 2:>6.3mm Bursal size: 0:<2mm, 1:between 2 and 4mm, 2:>4mm Bone erosions: 0: no bone erosion, 1: between 0.1 and 2mm, 2:>2mm

The majority of the authors explored entheses of the lower limbs. The position of the examined entheses, especially for lower limbs, is available in most of the studies. Authors predominantly used 90° flexion of the feet during examination of Achilles tendon and plantar fascia, in a neutral position, and 30° to 70° flexion of the knee during examination of the patella ligament and the quadriceps tendon.

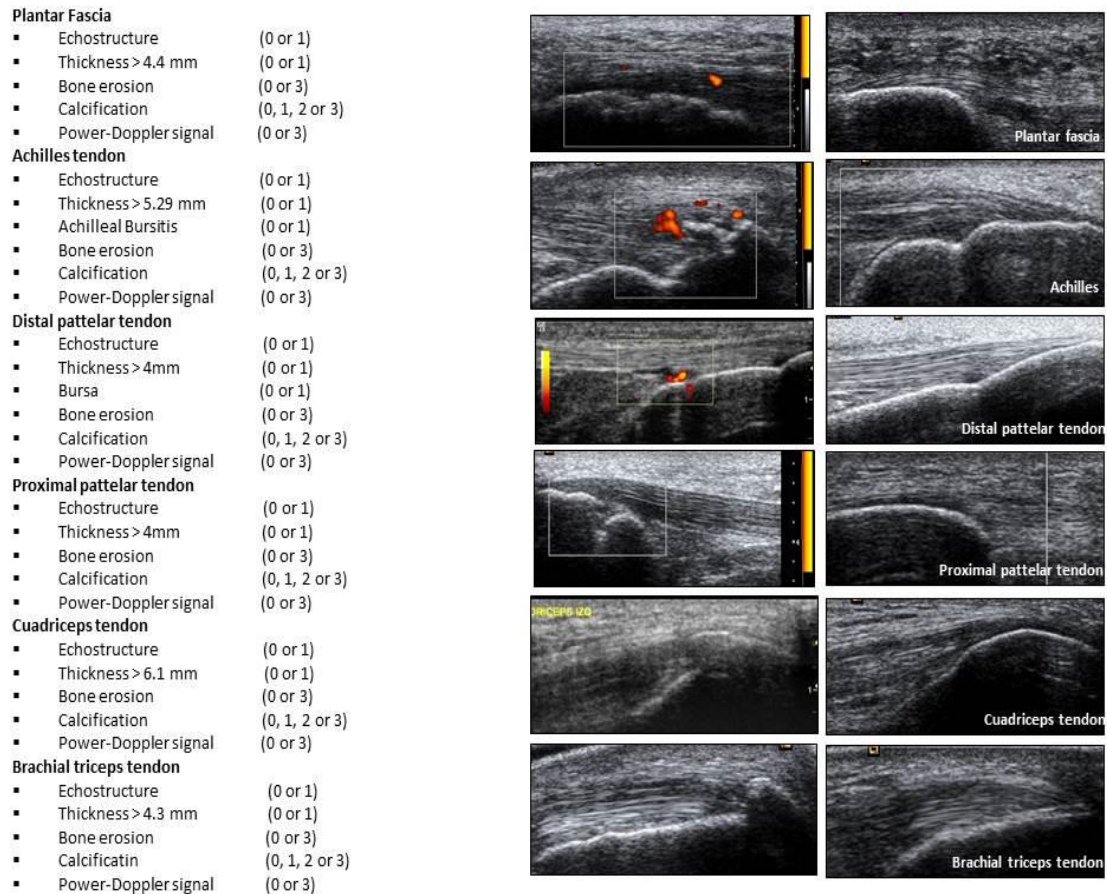
The first score created in 2002 by Balint and colleagues<sup>19</sup> is actually the most employed in studies, probably due to its fast and easy use. The GUESS score (0–36) analyses enthesopathy of lower limbs (quadriceps, proximal and distal patellar, Achilles and plantar fascia entheses) only in B-mode, assessing the thickness of entheses and the presence or absence of bony erosion, enthesophytes and bursitis. In particular, the thickness was measured at the maximum point proximal to the bony insertion and was defined on the basis of the normal range,<sup>74-77</sup> and hypoechogenicity, in contrast to the OMERACT definition,<sup>67</sup> was excluded because it was considered a subjective sign of enthesitis. This score also has some limitations. First of all, Balint did not employ a control group and defined the abnormalities based only on normal ultrasound features and dimensions of the examined structures published in previous studies.<sup>74-77</sup> Secondly, the score was validated only with an intra-reader evaluation (images stored and re-scored by the same operator) and not by intra- or inter-observer reliability. Thirdly, GUESS did not include power Doppler evaluation, which is considered to be a hallmark of enthesitis in SpA.<sup>68</sup> However, the GUESS was subsequently employed and validated by comparison with healthy controls, matched for body mass index (BMI), age, sex and cardiovascular factors, and with inter-observer evaluations, in other cases with good reliability.<sup>78-80</sup> Differently from Balint,<sup>19</sup> the classifications of D'Agostino and colleagues<sup>68</sup> and Alcalde and colleagues<sup>70</sup> have included calcification in the B-mode abnormalities, but not enthesophytes. Subsequently, D'Agostino and colleagues<sup>72</sup> included calcification and enthesophyte in B-mode evaluation. Calcification was defined as a hyperechoic spot with or without acoustic shadow in the area of the entheses insertion, and enthesophyte as an ossification with irregularities of entheses cortical bone aspect. Although, particularly in this study, a consensus was reached for scoring calcification and enthesophyte together as a unique lesion, owing to the difficulty of differentiating small enthesophytes from calcifications. A comparable



consensus was reached for scoring increased thickness and hypoechogenicity of enthesis insertion as a unique feature, arguing that both are signs of acute inflammation. Meanwhile, De Miguel and colleagues<sup>71</sup> and Filippucci and colleagues<sup>73</sup> used judgment in their scores. A semi-quantitative score was used regarding the calcification dimension, but it is not clear or well defined how to distinguish between the different sizes. Additionally, while Balint<sup>19</sup> separated abnormalities into soft tissue (thickness and bursitis) and bone (enthesophytes and erosions), Filippucci<sup>73</sup> grouped the enthesal lesions in soft tissue inflammation (tendon hypoechogenicity, enthesal hypoechogenicity, bursal effusion, power Doppler signal at tendon level, at enthesal level and at bursal level) or tissue damage (intratendineous calcifications, enthesal calcifications, enthesophytes, bone erosions and bone irregularities), and Sonographic Enthesitic Index (SEI)<sup>70</sup> described acute (thickening, hypoechogenicity, edema of surrounding structures and bursitis) versus chronic (tear, loss of thickness, calcification and erosions) alterations. In the same study, Alcalde<sup>70</sup> demonstrated that edema, tears and loss of thickness do not have great frequency or relevance in SpA and are probably difficult to define because they are not well described and quantified in other studies. Similarly to GUESS, SEI do not include power Doppler evaluation, with the limitations that may come. The first score including power Doppler was proposed by D'Agostino.<sup>68</sup> This score presents some difficulties in application because there are too many sites evaluated. It is not clear if the mix of abnormalities with B-mode and power Doppler is only descriptive, or if there is a rationale for classification linked to different degrees of severity. In this study the intra- and inter-observer variability was excellent but it was calculated on the final score (not for a single defect), and it was not validated in subsequent studies. Furthermore, power Doppler was considered only as a binary system (present/absent). The power Doppler signal (similar to B-mode lesions such as thickness or bursitis) might be important for follow-up purposes, together with other clinical and serological indices, to guide the choice of drugs and to monitor the efficacy of treatments. For this reason, semi-quantitative systems of power Doppler scoring were proposed.<sup>69,72,73</sup> Kiris and colleagues<sup>69</sup> made a descriptive and topographic classification (presence of separate linear signals - grade 1; discernible vessels involving less than half enthesis - grade 2; and vessels involving more than half enthesis - grade 3), followed by D'Agostino and colleagues<sup>72</sup> with a simplified version, describing only

the number of power Doppler spots (one - score 1; two - score 2; and  $\geq 3$  signals - score 3). The most attractive part of these methods is to evaluate a total power Doppler score, calculated by summing the flow signal grades on entheses, which might be particularly useful for future clinical trials.

The systematic ultrasound exploration of MASEI is represented in Figure 6.



**Figure 6.** Madrid sonography enthesitis index.

Despite these promising results, the use of power Doppler for the management of SpA has remained less frequent than other innovative imaging techniques such as MRI. This discrepancy is probably due to the perception that ultrasound remains an unreliable imaging technique. The operator dependence on ultrasound performance, artefacts of power Doppler on image acquisition, the optimization of power Doppler dependence on the type of used device and on settings are some of the given reasons for this fact.

The validity of enthesis ultrasound involves various aspects, not always clearly defined in the studies. The discrepancies in methods, the lack of comparison with a gold standard, such as biopsy, or the lack of evaluation of a real prognostic value of enthesal lesions detected by ultrasound makes it difficult to compare several studies efficiently (see table 2).

**Table 2.** Validity aspects of enthesis ultrasound studies

Study	Face validity	Content validity	Concurrent validity	Predictive validity	Construct validity	Reliability	Sensitivity to change	Diagnostic value
Balint 2002 (GUESS) <sup>19</sup>	-	+ erosions, enthesophytes, bursitis, thickness	-	-	-	-	-	- (no controls)
D'Agostino 2003 <sup>68</sup>	-	++ (GUESS, +calcifications,+PD,- enthesophytes)	-	-	+	Intra and inter	-	+ (RA and mechanical back pain)
Kiris 2006 <sup>69</sup>	-	++ (GUESS, +calcifications, +PD)	-	-	+	Intra	-	- (no controls)
Alcalde 2007 (SEI) <sup>70</sup>	-	+++ (GUESS, +edema,+tendon tear,+loss of thickness)	-	-	-	Inter	-	- (no controls)
De Miguel 2009 (MASEI) <sup>71</sup>	-	++ (GUESS,+calcifications,+PD,+,- enthesophytes)	+	+	-	Inter	-	+ (healthy controls)
D'Agostino 2009 <sup>72</sup>	-	++ (GUESS,+calcifications,+PD,-bursitis)	-	-	-	Intra and inter	-	- (no controls)
Fillippucci 2009 <sup>73</sup>	-	++ (GUESS,+calcifications,+PD,+tendon)	-	-	-	Intra and inter	-	- (no controls)
Aydin 2010 <sup>81</sup>	-	+ (Achilles tendon and entheses thickness and hypoechogenicity, PD tendon, entheses and bursa )	+	-	+	Intra*	+	- (no controls)
Naredo 2010 <sup>82</sup>	-	++ (entheses hypoechogenicity and/or thickness, calcifications, bone erosion and/or enthesophyte, bursitis, intraentheses and perientheses (tendon body and/or bursa) PD signal Lateral and medial elbow epicondyle, quadriceps, proximal and distal patellar tendon, Achilles tendon, plantar fascia	+	(no correlation established)	+	Intra	+	- (no controls)

De Miguel 2011 <sup>83</sup>	-	++ (GUESS,+calcifications,+PD,+,- enthesophytes) MASEI	+	+	-	-	-	+	(inflammatory and non-inflammatory controls <sup>#</sup> )
D'Agostino 2011 <sup>84</sup>	-	++ (GUESS,+calcifications,+PD,-bursitis) Quadriceps tendon enthesis, proximal patellar ligament, Achilles tendon, plantar aponeurosis, lateral and medial epicondyle, gluteus medius tendon	+	+	-	-	-	+	(no controls)

\* The inter-observer agreement for US evaluation of the Achilles tendon was tested in a previous study.

<sup>#</sup> Non-inflammatory controls: healthy persons, non-inflammatory lumbar pain and posterior uveitis unrelated to SpA; inflammatory controls: patients from ESPERANZA project that did not meet SpA diagnostic criteria.

Face = credibility for measuring what it is supposed to; content = comprehensiveness of all aspects of the attribute to be measured; concurrent = degree to which a measure reflects a gold standard applied at the same time; predictive = degree to which a measure predicts a future gold standard outcome; construct = consistency with theoretical concepts; reliability = intra- and inter-observer variation to allow reliable detection of this change; sensitivity to change = variation of the measure over time (e.g., follow-up after treatment); diagnostic value = ability to distinguish between different diseases.

GUESS = Glasgow Ultrasound Enthesitis Scoring System; MASEI = Madrid Sonographic Enthesis Index; PD = Power Doppler; SEI = Sonographic Enthesitic Index; RA = rheumatoid arthritis

The capability of ultrasound to evaluate enthesitis earlier and better than radiography is well demonstrated but, until now, there only have been a few studies that have compared ultrasound with more sensitive imaging techniques, such as MRI<sup>63,85</sup> and scintigraphy,<sup>86</sup> but did not clearly investigate the correlation between B-mode and power Doppler findings.

The enthesis ultrasound sensitivity to change has been evaluated in SpA patients treated with anti-TNF drugs. These studies have the limitation for a relative short period of follow-up, but they showed a reduction of B-mode and power Doppler enthesis abnormalities, such as morphologic abnormalities (tendon hypoechogenicity and/or thickening), power Doppler signal, and bursitis.<sup>81,82</sup>

On the other hand, the diagnostic value of ultrasound (ability to distinguish between different diseases) was verified not only by D'Agostino and colleagues,<sup>68</sup> who compared SpA to rheumatoid arthritis and mechanical back pain, but also by De Miguel and colleagues (MASEI total score  $\geq 18$  points was the best cut-off point for differentiation between cases and controls (healthy persons), and demonstrated a sensitivity, specificity, positive and negative likelihood ratios of 83.3%, 82.8%, 4.8%, and 0.2%, respectively, for the diagnosis of SpA regardless of the presence of other clinical manifestations).<sup>71</sup> Similar results have been established by the same authors in early SpA. In a cross sectional, blinded and controlled study with 113 early SpA patients De Miguel and colleagues achieved for a MASEI total score  $\geq 20$  points a likelihood ratio of 5.3, with a specificity of 89.47% and a sensitivity of 55.75% for SpA diagnosis.<sup>83</sup> Additionally, in a two years prospective cohort study with 118 early SpA patients D'Agostino and colleagues<sup>84</sup> demonstrated that the power Doppler ultrasound detection of at least one vascularized enthesis provided good predictive value for diagnosing SpA (sensitivity 76.5%, specificity 81.3%, positive likelihood ratio 4.1, OR 14.1;  $p < 0.0001$ ).

As described, the various published ultrasound studies for SpA enthesal assessment, meet both permanent structural damage and non-permanent enthesal injuries related with inflammatory disease activity. This fact is in agreement with the increasing knowledge about enthesal ultrasound study in SpA. However, for its use in daily

practice, a profound understanding on the behavior of enthesal structural alterations should be developed. The OMERACT enthesopathy definition includes the main lesions of the enthesis at bone and enthesis tendon insertion identified by ultrasonography, and it is now widely cited and accepted in the ultrasound community. Nevertheless, this definition does not comprehend bursitis as an elementary lesion, or the distinction between injuries related with enthesal structural damage or inflammatory activity.

Until now published data concerning these enthesal alterations reflect rather the authors' empiric opinion than a methodological validation process. Progress in this study area is one of the main objectives of a reduced number of ultrasound investigation teams; and I am integrated in one of these groups.

## DETAIL DESCRIPTION

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In 2006, the integration into a research group in a reference center for inflammatory rheumatic diseases - Rheumatology Department of Hospital Universitario La Paz in Madrid - not only provided me with additional training in the field of musculoskeletal ultrasound, but also my involvement with a research group in SpA, headed by Prof. Eugenio de Miguel. Since then, and in partnership with this research group, several studies have been developed in the musculoskeletal ultrasound area and have been used to assess inflammatory rheumatic diseases.<sup>87-98</sup>

The integration into the research group occurred slowly and progressively in a two steps pathway. Firstly, a structured learning process in what concerns structural lesions in SpA and systematic enthesal exploration was developed; and secondly, the validation process to guarantee the entrance in this research team was preceded by head to head reliability studies with other members of the investigation group.<sup>99</sup>

Since 2006 longitudinal studies have been developed with more than five years of follow-up of SpA patients; and several papers have been published.<sup>71,83,100-107</sup> The developed database has been used for different analysis. Clinical, analytical, radiographic and 2D and 3D ultrasound data are integral part of the records.

The patient sample was selected from individuals attending the Early Spondyloarthritis Unit (ESU), as part of the ESPERANZA program, a nation-wide health management program designed to provide excellence in care for early SpA, promoted by the Rheumatology Spanish Foundation. The referral criteria included: 1) age below 45; 2) symptom duration between three and 24 months; and 3) at least one of the following: a) inflammatory low back pain, defined as at least two of the following: insidious onset, morning stiffness for more than 30 minutes, or clear improvement of the symptoms with physical activity but not relieved by rest; b) asymmetric arthritis, preferably of the lower limbs; or c) low back pain or arthralgia and at least one of the following: psoriasis, inflammatory bowel disease, anterior uveitis, family history of spondylitis, psoriasis, radiographic sacroiliitis or HLA-B27+ status. Patients will be classified as SpA according to accepted classification criteria, as follows: 1) ankylosing



spondylitis if they fulfilled the modified New York criteria; 2) psoriatic arthritis if they fulfilled the classification criteria for psoriatic arthritis (CASPAR) criteria; 3) SpA without definitive radiographic sacroiliitis (at least bilateral grade II or unilateral grade III) and undifferentiated SpA if the European Spondylarthropathy Study Group (ESSG) preliminary criteria for classification of SpA were fulfilled without any other specific diagnostic criteria; 4) reactive arthritis if the patient fulfilled ESSG criteria or had arthritis, confirmed by a rheumatologist, with recent evidence of related infection; 5) arthritis-associated inflammatory bowel disease if IBD was present in a patient with the New York criteria or ESSG criteria; and 6) anterior uveitis if it had been diagnosed by an ophthalmologist. The diagnosis of IBD required typical histological findings of Crohn's disease or ulcerative colitis. Exclusion criteria included previous history of ankle surgery, peripheral neuropathy, or corticosteroid injection within the previous 6 weeks in the Achilles tendon. All patients completed the Spanish version of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Radiology Index (BASRI). Peripheral joint count, enthesal clinical evaluation and analytical data were also registered on the same day of the visit. The subjects have been followed-up in a regular scheme with systematic clinical, analytical and imaging records. The controls were non SpA inflammatory patients and asymptomatic subjects, without any known medical history of inflammatory or mechanical musculoskeletal disease. They were selected among hospital workers and friends of patients, all of whom volunteered to participate after receiving an explanation of the procedure.

The ultrasound protocol was performed using a Logiq 9 (General Electric Medical Systems, Milwaukee, WI) equipped with a linear probe at 9-14 MHz and a broadband high-frequency (8-15 MHz) volumetric probe. Focus was positioned at the level of the region of interest; grey-scale frequency was 15 MHz; Doppler settings were standardized with a pulse repetition frequency of 400 Hz, wall filter of 48Hz and color-mode frequency of 7.5 MHz. The color gain was 36-45 (increased to the highest value not generating Doppler signals under the bony cortex). The sonographer was blinded to patients' clinical or therapeutic data and subjects were advised to withhold these

data from the ultrasound examiner. All acquired images were stored in a digital format to be subsequently analyzed.

The study of entheses was conducted according to local regulations and the Declaration of Helsinki, and local approval was obtained from the ethical committee and institutional review board of Hospital Universitario La Paz - Madrid. All patients and controls signed an informed consent.

Nowadays, the development of new technologies that enable the recording of images in digital format, and their further analysis after acquisition, allowed not only reliability studies, but also established long distance working partnerships. This was the followed methodology for 2D and 3D data processing and analysis.

Data collected in this project is expected to contribute for a better understanding of the behavior of enthesal damage in SpA, identifying new assessment tools for diagnosis and follow-up purposes, and hopefully providing physician with improved tools for assessing disease prognosis and response to treatment.

## AIMS

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The main objective of this work is to improve the knowledge of SpA enthesal lesions. Namely, understand the behavior of enthesal erosion and the importance of the enthesal bursa that could be involved in futures scores of structural damage or disease activity; analyze the validity of enthesal ultrasound in the quantification of SpA disease activity and to contribute for enthesitis ultrasound definition, using the Achilles tendon as a model.

Our specific objectives are:

- I. To evaluate if Doppler ultrasound is a reliable method to assess enthesal structural lesions in SpA in a well-trained observer;
- II. To know whether erosion in SpA represents a persistent structural damage that can be used for structural damage ultrasound scores, or as a non-permanent lesion that should be included in future ultrasound disease activity scores;
- III. To assess the prevalence and the relevance of the bursa-synovial lesions in SpA;
- IV. To determine the predictive value of enthesal ultrasound lesions in SpA, and its relationship with other well-established SpA activity or structural damage outcome measures.

## RESULTS

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In agreement with the Decreto-Lei 388/70, art. 8º, the results presented and discussed in this thesis were published in the following scientific peer-reviewed journals:

- I. **Falcão S**, De Miguel E, Castillo C, Branco JC, Martín-Mola E. Doppler ultrasound – a valid and reliable tool to assess spondyloarthritis. *Acta Reumatol Port* 2012;37(3):212-7.
- II. **de Miguel E\***, **Falcao S\***, Castillo C, Plasencia C, García M, Branco JC, Martín-Mola E. Enthesis erosion in spondyloarthritis is not a persistent structural lesion. *Ann Rheum Dis* 2011;70:2008-10.  
(\*de Miguel E and Falcao S contributed equally for this work)
- III. **Falcao S**, de Miguel E, Castillo-Gallego C, Peiteado D, Branco J, Martín Mola E. Achilles enthesitis ultrasound: the importance of the bursa in spondyloarthritis. *Clin Exp Rheumatol* 2013;3:422-7.
- IV. **Falcao S**, Castillo-Gallego C, Peiteado D, Branco J, Martín Mola E, de Miguel E. Can we use enthesitis ultrasound as an outcome measure of disease activity in Spondyloarthritis? A study at Achilles level. *Rheumatology* 2014;doi:10.1093/rheumatology/keu399.

## PART I

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### **Doppler ultrasound – a valid and reliable tool to assess spondyloarthritis**

## Doppler ultrasound – a valid and reliable tool to assess spondyloarthritis

Sandra Falcão<sup>\*</sup>, Eugenio De Miguel<sup>†</sup>, Concepción Castillo<sup>†</sup>, Jaime C Branco<sup>†</sup>, Emilio Martín-Mola<sup>†</sup>

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### ABSTRACT

Enthesitis is the hallmark of spondyloarthritis and is observed in all subtypes. Namely, a wide information on spondyloarthritis abnormalities, including synovitis, bursitis, tendinitis, enthesitis and cortical bone abnormalities (erosions and enthesophytes), can be efficiently perceived by ultrasound power Doppler. Furthermore, several studies on imaging of enthesitis showed that imaging techniques are better than clinical examination to detect pathology at asymptomatic enthesitis. Vascularized enthesitis detected by ultrasound power Doppler appears to be a valuable diagnostic tool to confirm spondyloarthritis diagnosis. This article focuses on the validity and reliability of ultrasound enthesitis assessment in the management of spondyloarthritis patients.

**Keywords:** Ultrasound; Power Doppler; Enthesitis; Spondyloarthritis

### BACKGROUND

There is an increasing interest among rheumatologists for using ultrasonography (US) as an investigation and management tool for musculoskeletal disorders<sup>1</sup>. This imaging modality has not only a number of advantages, such as low cost, good accessibility, and ability to dynamic real-time assessment of multiple joints in relatively short period of time, but also the ability to detect and monitor bone and joint soft tissue inflammation and its structural sequelae<sup>2</sup>. A growing body of evidence in many rheumatic conditions, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), suggests that US is a high sensitive and non-invasive tool in the

detection and monitoring of early synovitis, bone erosions, tenosynovitis and enthesitis<sup>3-5</sup>. The early detection of inflammatory joint pathologies would ideally allow clinicians to initiate relevant therapies in order to prevent destruction of bone and joint soft tissue, and, subsequently, improve morbidity and long-term outcome.

Spondyloarthritis (SpA) is a group of disorders that are characterized by inflammatory involvement of the enthesitis and the adjacent bone<sup>6</sup>. Enthesitis is regarded as the primary lesion and is observed in all SpA subtypes, and may sometimes be present several years as an isolated clinical manifestation<sup>6,8</sup>. Encouraging data suggest that US enthesitis scores could be used as a valid tool for SpA assessment<sup>9,10</sup>.

Chronic inflammatory low back pain and radiographic changes involving the sacroiliac joints are key diagnostic features for AS according to the modified New York (MNY) criteria established in 1984<sup>11</sup>. Although the MNY criteria have been widely used in both clinical and research settings the absence of both radiographic sacroiliitis and impaired spinal mobility at early stages of the disease have contributed to a long delay (5-10 years) in AS diagnosis in many patients<sup>12</sup>. Recently the Assessment of SpondyloArthritis International Society (ASAS) developed new classification criteria for axial SpA that demonstrated much better specificity compared to the European Spondylarthropathy Study Group (ESSG) criteria modified for Magnetic Resonance Image (MRI) (sensitivity 85.1%, specificity 65.1%) and slightly superior to the modified Amor criteria (sensitivity 82.9%, specificity 77.5%)<sup>13</sup>. Nevertheless the sensitivity of ASAS classification criteria for peripheral SpA was slightly worse compared to the registered for axial SpA ASAS criteria (77.8% versus 82.9%)<sup>14</sup>. Despite these encouraging data, several studies on imaging of enthesitis showed that imaging techniques, such as MRI or US are superior to clinical examination, and frequently pathology at asymptomatic enthesitis might only be detected by imaging te-

<sup>\*</sup>Rheumatology, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal

<sup>††</sup>La Paz University Hospital, Rheumatology Unit, Madrid, Spain

chniques<sup>15</sup>. Furthermore, it has been suggested that US might be superior to MRI for detecting early signs of enthesopathy<sup>16,17</sup>.

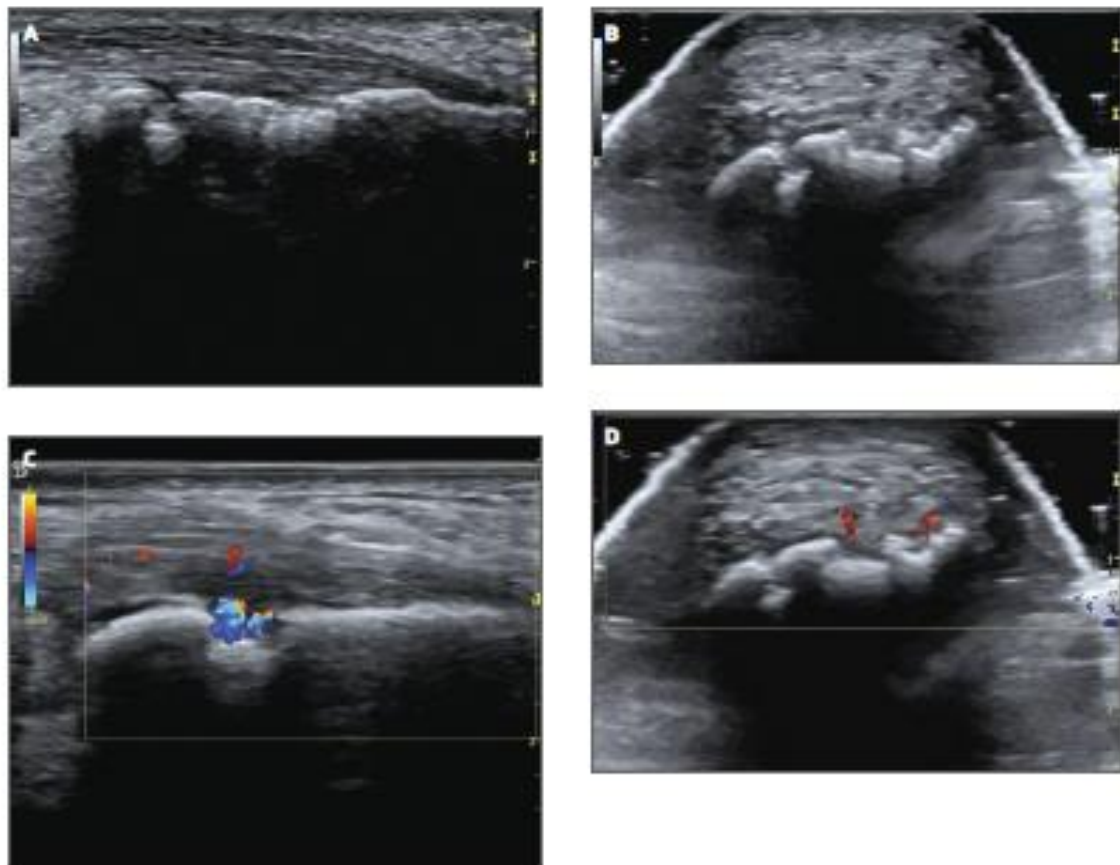
Despite the promising results about US examination of the enthesis in SpA, further research should be prompt to assess its specific role in diagnosis and follow up of disease course. This article focuses on the validity and reliability of US enthesitis assessment in the management of SpA patients.

#### VALIDITY OF ULTRASOUND ENTHESITIS ASSESSMENT IN SPONDYLOARTHRITIS

US provide a widely information on SpA abnormalities, including synovitis, bursitis, tendinosis, enthesi-

tis and cortical bone abnormalities (erosions and enthesophytes).

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) defines enthesopathy as an “abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in 2 perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity” (Figure 1)<sup>18</sup>. Although grey-scale US depict enthesis structural damage, it seems that the combination with power Doppler increases diagnostic accuracy for SpA. The first description was made by D’Agostino and colleagues who demonstrated that US, in grey-scale combined with power Doppler, allowed



**FIGURE 1.** Ultrasonographic images of Achilles enthesopathy: (A) Longitudinal view: thickening, loss of fibrillar pattern, bone proliferation and erosions. (B) Transversal view: loss of fibrillar pattern and erosions. (C) Longitudinal view: thickening, loss of fibrillar pattern, bursa, erosions and Doppler signal. (D) Transversal view: loss of fibrillar pattern, erosions and Doppler signal



the detection of abnormal vascularization at entheses insertion into cortical bone profile in the majority of SpA patients, but not in mechanical back pain or RA patients. This study included 164 SpA patients and 64 controls (thirty four with mechanical back pain and thirty with RA). Abnormal US findings consistent with at least one enthesitis were observed in 98% and 52% of SpA and control patients, respectively. US enthesitis was most commonly distributed in the distal portion of the lower limbs, irrespective of SpA subtype and of skeletal distribution of clinical symptoms, and none of abnormal entheses in control patients showed vascularization, compared with 81% of entheses in SpA patients<sup>8</sup>. More recently, the same author reported in a prospective single-center cohort study with 118 patients that power Doppler US detection of at least one vascularized entheses provided good predictive value for diagnosing SpA (sensitivity 76.5%, specificity 81.3%, positive likelihood ratio 4.1, OR 14.1,  $p < 0.0001$ )<sup>19</sup>.

In recent years, several US scores for entheses SpA structural damage assessment have been developed. Balint and colleagues developed the GUESS (Glasgow Ultrasound Enthesitis Scoring System). In this index an enthesitis score is formulated from the detection of bursitis, structure thickness, bony erosion, and enthesophyte (bony spur) on US examination of both lower limbs at five entheses sites (superior pole and inferior pole of patella, tibial tuberosity, Achilles tendon, and plantar aponeurosis). The authors concluded that US is better than clinical examination in the detection of enthesitis in patients with SpA<sup>20</sup>. Alcalde and colleagues have tested an index (Sonographic Enthesal Index - SEI) that evaluates five entheses regions from both lower limbs. Hypoechoogenicity, increased tendon thickness, peritendinous oedema and bursitis were considered as signs of acute injury (SEI-A); and insertional bone erosions, intratendinous calcifications, decreased thickness and tears as chronic lesions (SEI-C). Each variable was scored in absent (0) or present (1) and total SEI was the sum of SEI-A and SEI-C (maximum 76 points). SEI correlated with lower Shober's test, but not with other SpA activity or severity parameters<sup>10</sup>. These studies represent the landmark of US entheses attempt for structural damage assessment, but they did not include power Doppler signal on US lesion evaluation. Based on previous data, power Doppler signal is highly sensitive for detection of small vessels<sup>21</sup>, is significantly correlated with clinical examination<sup>22</sup>, and enables the distinction between inflam-

matory enthesitis and entheses lesions of purely mechanical origin<sup>8</sup>. In this regard, de Miguel and colleagues elaborated a 136-point US-based scoring, examining elemental structural damage, including power Doppler signal, in twelve entheses areas: proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps and brachial triceps tendon. Enthesis thickness, structure, calcifications/cortical bone proliferation, erosions, bursa, and power Doppler were scored in cortical bone profile, tendon, and bursa of 25 SpA patients and 29 healthy controls. After logistic regression analysis of the core of three of the elementary lesions were overestimated: calcifications (0-3), Doppler (0 or 3) and erosion (0 or 3); while scoring tendon thickness, structure and bursa were classified as 0 or 1 (absence/presence). The established US score of  $\geq 18$  was the best cut-off point for differentiation between cases and controls; and demonstrated a sensitivity, specificity, positive and negative likelihood ratios of 83.3%, 82.8%, 4.8%, and 0.2%, respectively, for the diagnosis of SpA regardless of the presence of other clinical manifestations<sup>9</sup>. Kiris and colleagues evaluated the relationship between power Doppler US SpA entheses assessment and the Maastricht Ankylosing Spondylitis Enthesis Index. This study illustrated some important points that should be considered. Firstly, clinical examination of entheses seemed to be sensitive, except for Achilles tendon assessment where the US power Doppler was significantly more accurate. Secondly, clinical and sonographic results were discordant for three regions of the thirteen explored entheses (first costochondral joint, seventh costochondral joint and iliac crest) where tenderness of entheses occurred without ultrasonographically proven enthesitis. Results were probably related with the chosen US acoustic window. Thirdly, in agreement with other data, pain or tenderness of entheses is related to local increased vascularity easily detected by power Doppler, and thus the value of a uniform system for grading enthesitis should be properly adapted to assess its role in diagnosis and follow up of disease course<sup>22</sup>.

Recent data suggest that power Doppler US can also be efficiently used in diagnosis of early SpA<sup>19,23</sup>. Using the Madrid sonography enthesitis index (MASEI) as a model de Miguel and colleagues developed a cross-sectional, blinded and controlled study including 113 early SpA patients. A cut-off point of MASEI  $\geq 18$  achieved a positive likelihood ratio of 4.26, sensitivity and specificity of 87.26% and 84.21%, respective-



ly, for SpA diagnosis. Furthermore, it seems that entheses are early affected in SpA, and the incidence of involvement is higher in men and independent of SpA subtypes, HLA-B27 status or presentation pattern (axial, peripheral or mixed forms)<sup>23</sup>.

The therapeutic follow up of structural damage represents another potential goal for power Doppler US use in SpA. The introduction of targeting therapies, in particular tumor necrosis factor (TNF)-alpha blocking drugs, has seen unprecedented success in the treatment of signs and symptoms of SpA<sup>24</sup>, but current radiographic follow up data suggest that these drugs do not affect the bone proliferation process<sup>25</sup>. This apparent lack of structural stopping effect is in sharp contrast to what is seen for the erosive joint destruction in RA and represents a differential finding in SpA<sup>26</sup>. Although evidence supports the apparent inefficacy of anti-TNF drugs on bone formation in SpA pathophysiologic process, it seems that other enthesal abnormalities detected by US, such as morphologic abnormalities (tendon hypoechoogenicity and/or thickening), power Doppler signal, and bursitis are responsive to these drugs<sup>27</sup>. Underlying the relevance of knowledge on enthesal pathophysiologic events in SpA; and supporting the challenge of introduce the US entheses study in SpA to improve the objective knowledge about disease activity, structural permanent damage, and its relation with present and future disease assessment tools.

#### RELIABILITY OF ULTRASOUND ENTHESITIS ASSESSMENT IN SPONDYLOARTHRITIS

It is a consensual fact that one of the major disadvantages of musculoskeletal US is operator dependency. The images generated are mainly qualitative and agreement as to be reached by different observers as to the presence or absence of pathological signs of disease. If quantitative measurements are required, then intra- and inter-observer errors become more important. Few studies have evaluated the overall reliability of US in rheumatology, most of them have been accomplished in RA patients or regarded joint examination<sup>28-31</sup>. Despite promising results, prior to the implementation of US as a valid method for detecting and monitoring the disease process in SpA patients, reliability assessment is crucial.

Previous reports have already studied the intra and inter-observer reliability in US enthesal study, using

a pragmatic methodology concerning the interpretation of static images<sup>8,9,20,22</sup>. More recent data have been published, with valid results on acquisition and interpretation of images using patients<sup>8,10,32</sup>.

Furthermore, moderate to excellent intra and inter-observer agreements were found, not only for most of the US elementary lesions indicative of enthesopathy<sup>32,33</sup>, but also for the conventional two-dimension and three-dimensional assessments of enthesal sonographic lesions<sup>33</sup>. Filippucci and colleagues obtained weighted kappa values estimating the inter and intra-observer agreements for soft tissue inflammation of 0.696 and 0.816, respectively and for tissue damage of 0.711 and 0.901, respectively. The levels of agreement were estimated using a dichotomous (presence/absence) and a semi-quantitative score system for assessment of Achilles tendon enthesopathy. The elementary Achilles enthesal US findings that characterized soft tissue inflammation were tendon hypoechoogenicity, tendon thickening, enthesal hypoechoogenicity, bursal effusion and power Doppler signal at tendon, enthesal or bursal level. Therefore lesions such as intratendinous or enthesal calcifications, enthesophytes, bone erosions or bone irregularities were considered as tissue damage. This study revealed a relatively poor agreement concerning two elementary lesions: bone irregularity and enthesal hypoechoogenicity, with inter-observer unweight kappa values of 0.2 and 0.49, respectively. Reasons such as the affection of tendon hypoechoogenicity by anisotropy or the difficulty to reach a consensus about which bone irregularities represent a pathologic state were pointed by the authors for the relatively low Kappa values obtained<sup>33</sup>. This study illustrated an important point: lower levels of agreement generally are in the context of inter-observer image acquisition rather than intra-reader agreement level, which is generally more demanding and examiner-dependent.

Moreover, when evaluated the level of agreement between 2D and 3D of Achilles entheses erosions two different authors achieved excellent kappa values of 0.85 and 0.86<sup>34,35</sup>.

However, to improve the reliability of US to assess enthesitis in SpA more data are needed concerning evaluation of inter-machine reliability<sup>36</sup>. In this regard we studied prospectively one hundred and ninety-two entheses of nine SpA patients with two US equipments: Acuson-Antares Siemens (Medical Systems equipment) with a lineal 5-13 MHz probe (equipment 1; 9 patients 108 entheses) and LOGIQ9 (GE Healthcare)

**TABLE I. AGREEMENT BETWEEN READER 1 AND 2 MASEI SCORING USING A LOGIC9 AND AN ACUSON-ANTARES SIEMENS**

	Interpretation of Static Images	
	(ICC)	(95%CI; p)
Inter-reader / US equipment 1 (n=9)	0.97	0.90-0.99; p<0.0001
Inter-reader / US equipment 2 (n=7)	0.93	0.87-0.98; p<0.0001

**TABLE II. AGREEMENT BETWEEN EQUIPMENT 1 AND 2 OF MASEI SCORING PERFORMED BY READER 1 AND 2**

	Interpretation of Static Images	
	(ICC)	(95%CI; p)
Inter-equipment - reader 1 (n=7)	0.77	0.20-0.93; p<0.01
Inter-equipment - reader 2 (n=7)	0.87	0.33-0.97; p<0.0001

with a lineal 9-14 MHz probe (equipment 2; 7 patients 84 entheses). The following enthesal sites were examined bilaterally in longitudinal and transversal plane: proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps, and brachial triceps tendons. The obtained images were punctuated according MASEI score by two sonographers with different levels of experience in US (an expert US rheumatologist familiarized with MASEI score and a rheumatologist with training on US). Prior to the study consensus rules about entheses scanning, the definition about abnormal findings, and the MASEI score system were achieved. The lectures were blinded to clinical data and carried out independently. Inter-reader, and inter-US equipment reliability were assessed according to the two-way, mixed-effect model (absolute agreement) and single-measure intraclass correlation coefficients (ICCs). A Kappa value less than 0.20 was considered poor, between 0.41 and 0.60 moderate, between 0.61 and 0.80 good, and between 0.81 and 1 excellent<sup>20</sup>. They were determined by SPSS (version 10.5), and values of p<0.05 were considered significant. The inter-reader and inter-equipment agreements are reported in Table I and Table II, respectively. With regard to the inter-equipment reliability good to excellent results were achieved.

To the best of our knowledge, this was the first study to investigate the inter-equipment reliability for assessing enthesitis in SpA. The low variability achieved could reflect the importance of specific training, and consensus rules that took place prior the study. The two sonographers had different levels of experience in performing MASEI scoring system, but they routinely search for morphologic and elementary lesions used in this score system in their daily practice. Such aspect would possibly make easier the improvement of skills that they

were already very familiar with, and lowered the variability of a technique that includes several possible sources of discrepancy between sonographers, such as definition, detection, and scoring of lesions, and data acquisition. In this sense a standardized model for teaching sonographers with different levels of experience achieves an effective learning on entheses US<sup>21</sup>.

In summary, US seem to be a valid and reliable tool, even inter-equipment, to assess enthesitis in SpA. Nevertheless, its ultimate utility in the core set of SpA diagnostic criteria and disease monitoring remains to be determined, and prior clinical application, learning and strict consensus guidelines are highly warranted.

**CORRESPONDENCE TO**

Sandra Falcao  
Hospital Egas Moniz, Centro Hospitalar de Lisboa  
Occidental E.P.E.  
Rheumatology Department  
Rua da Junqueira nº126  
1200 Lisbon, Portugal  
E-mail: sfalcao70@gmail.com

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## PART II

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**Enthesis erosion in spondyloarthritis is not a persistent structural lesion**

## Concise report

## Enthesis erosion in spondyloarthritis is not a persistent structural lesion

Eugenio de Miguel,<sup>1</sup> Sandra Falcao,<sup>2</sup> Concepción Castillo,<sup>1</sup> Chamaida Plasencia,<sup>1</sup> Miriam García,<sup>1</sup> Jaime C Branco,<sup>2</sup> Emilio Martín-Mola<sup>1</sup>

► Additional data are published online only. To view the full paper please visit the journal online (<http://ard.bmj.com>)

<sup>1</sup>Rheumatology, La Paz University Hospital, Madrid, Spain

<sup>2</sup>Rheumatology, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal

## Correspondence to

Dr Eugenio de Miguel, Rheumatology Unit, La Paz University Hospital, Pº de la Castellana 261, 28046 Madrid, Spain; [eugenio.demiguel@gmail.com](mailto:eugenio.demiguel@gmail.com)

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## ABSTRACT

**Objective** To evaluate the ability of ultrasound (US) to detect the presence and change of Achilles erosions in spondyloarthritis (SpA).

**Methods** A blind prospective two-dimensional (2D) and three-dimensional (3D) US study of Achilles entheses erosions in early SpA was undertaken. US examinations were performed at baseline and at 6 and 12 months of follow-up. Clinical outcomes measures were collected.

**Results** Bilateral Achilles entheses of 68 patients (35 women) were investigated. The mean Bath Ankylosing Spondylitis Disease Activity Index and C reactive protein (CRP) levels were  $4.58 \pm 2.05$  and  $5.97 \pm 9.91$  mg/l, respectively. The  $\kappa$  values for intrareader agreement for 2D and 3D images were 0.84 and 0.85 for two readers. 2D US visualised 10 erosions (7.4%) and 3D US visualised 13 erosions (9.6%) in 10 patients (14.7%). At 6 and 12 months of follow-up, 25% and 50% of basal erosions had disappeared, respectively and, of the new erosions that appeared at 6 months, 40% had disappeared 6 months later. A statistically significant association between erosion and CRP levels, enthesal Doppler signals and the number of tender and swollen joints was found.

**Conclusions** US examination of Achilles erosions is reliable and sensitive to change. An association was found between Achilles erosions and objective activity-based measurements of SpA outcomes.

## BACKGROUND

Spondyloarthritis (SpA) is characterised by the inflammatory involvement of the entheses.<sup>1–4</sup> In the last few years, several studies have provided relevant data on the advantages and validity of using ultrasound (US) to study entheses in SpA.<sup>4–9</sup>

The Outcome Measures in Rheumatology Clinical Trials includes erosion in the definition of enthesopathy.<sup>10</sup> Systematic studies of entheses by US in patients with SpA have demonstrated erosions and some of their characteristics.<sup>7–9, 11</sup>

The usefulness of assessing erosions in longitudinal studies to monitor joint injury, disease activity and therapeutic responses in many rheumatic diseases is well-known and has mostly been applied in rheumatoid arthritis (RA).<sup>12–15</sup> However, information concerning the entheses is sparse. It is therefore important to emphasise that RA erosions and SpA entheses erosions probably represent a different aetiological disease-response mechanism.

The aims of this study were to evaluate the persistence, increase or resolution of erosion of the Achilles entheses in SpA and to survey the reliability

of two-dimensional (2D) US and the concurrent validity of Achilles entheses erosion in the light of other SpA outcomes measures.

## METHODS

## Patients

Sixty-eight consecutive non-selected patients with early-stage SpA were included. Previously published referral criteria were used.<sup>14, 15</sup> All patients were characterised using the Spanish version of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and measurements employing the Bath Ankylosing Spondylitis Radiology Index (BASRI) and a peripheral joint count were also completed on the day of the visit (see additional data in online supplement).

## US scanning protocol

Blind prospective 2D and three-dimensional (3D) US examinations of Achilles entheses erosions were performed using a Logiq 9 device (General Electric Medical Systems, Milwaukee, Wisconsin, USA) equipped with a linear probe at 9–14 MHz and a broadband high-frequency 8–15 MHz volumetric probe. During the scanning session, US was first performed in the B mode using a longitudinal and transverse scanning technique, moving from medial to lateral and proximal to distal at the level of the entheses to detect morphological changes and abnormal vascularisation by application of the Doppler technique immediately afterwards. Following the 2D US examination, 3D datasets were obtained by placing the volumetric probe over the area of interest. All images were stored in a digital format after the initial visit and at the 6- and 12-month follow-up visits (see additional data in online supplement).

In this study we considered erosion as a cortical breakage with step-down of >1 mm in depth and width in both the longitudinal and transverse axes. The measurement of end erosion was classified using a dichotomous scale (presence/absence) and was determined from the mean value of three consecutive measurements of the maximal diameter obtained in the longitudinal and transverse axes. The presence or absence of a Doppler signal in the tendon entheses or bursa was also recorded.

All 2D and 3D US images were analysed in a blind and independent manner by two readers. The presence of erosion on the 3D revision volume was used as a 'gold standard' (see online supplement).



**Statistical analysis**

For inter-reader reliability, the  $\kappa$  coefficient for categorical variables was used; *p* values <0.05 using the  $\chi^2$  test were considered to be significant.

**RESULTS****Demographic data**

Sixty-eight patients (35 women) with early SpA and 136 Achilles tendon entheses were examined. The mean±SD age of the patients was 32±7 years (range 18–45) and the mean disease evolution time was 10 months (range 3–23). Forty-two per cent of the patients with SpA were HLA-B27-positive and 31% had heel pain at the initial visit. The mean±SD BASDAI, Bath Ankylosing Spondylitis Functional Index and BASRI spine measurements were 4.58±2.05 (range 0–8), 2.27±1.92 (range 0–7.4) and 0.65±0.75 (range 0–3), respectively. The mean erythrocyte sedimentation rate was 10.83±11.83 mm/h (range 1–53.1) and the mean C reactive protein (CRP) measurement was 5.97±9.91 mg/l (range 0–51). At baseline all patients were being treated with non-steroidal anti-inflammatory drugs and eight patients started treatment with classic disease-modifying antirheumatic drugs (sulfasalazine or methotrexate) during the follow-up period.

**US data**

In the 136 basal Achilles entheses studied, 2D US visualised 10 erosions (7.4%) and 3D US visualised 13 erosions (9.6%) in 10 patients (14.7%). Using 3D US evaluation as the gold standard, the sensitivity of 2D US for the detection of an erosion was 76.92% and the specificity was 100%. All 10 erosions seen by 2D US were also confirmed by 3D US, and 123 Achilles entheses were reported to be without erosions by both 2D and 3D US.

Statistically significant differences between the clinical and laboratory-based measurements of basal data in the SpA patients and the presence or absence of Achilles entheses erosions are shown in table 1.

Figure 1 shows the results from the 55 patients who completed the 12-month follow-up visit. The flowchart demonstrates the dynamic structural behaviour of entheses erosion in patients with SpA over time; 25% and 50% of basal erosions had disappeared at 6 and 12 months of follow-up, respectively, and 40% of the new erosions that appeared after 6 months of follow-up had disappeared 6 months later.

The  $\kappa$  inter-reader variability in 2D and 3D US of Achilles entheses erosions was 0.85 and 0.84. The  $\kappa$  intra-reader variability

between 2D and 3D images was 0.84 for reader 1 and 0.85 for reader 2 (figure 2).

**DISCUSSION**

To the best of our knowledge, this is the first study to investigate the sensitivity to change of US-based techniques in assessing Achilles entheses erosions. Previous reports have classified erosions as tissue damage-related or chronic lesions.<sup>5–7</sup> However, our preliminary data strongly suggest that previously detected erosions could disappear during the course of SpA, indicating that these erosions are not persistent structural changes as is the case in RA.

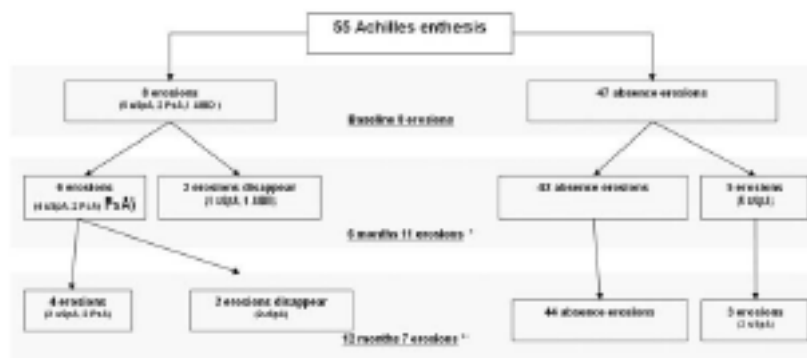
We were concerned about the reliability of the data we obtained. Several previous studies have indicated moderate to good interobserver agreement for 2D US acquisition and excellent intrareader agreement for 2D and 3D US studies of entheses erosion.<sup>7–16</sup> These data are also confirmed by our results.

We were also concerned that we might have had a false negative or positive in the basal or subsequent US examination. One limitation of the current study is that we used 3D US as a gold standard although the accepted standard is x-ray CT. However, because CT uses radiation, it is not easily included in longitudinal studies. We therefore prospectively recorded 3D images. By re-examining stored volumes of 3D entheses images we confirmed

**Table 1** Associations between clinical and laboratory-based measurements of basal data of patients with spondyloarthritis and the presence or absence of Achilles entheses erosions as assessed by three-dimensional ultrasound

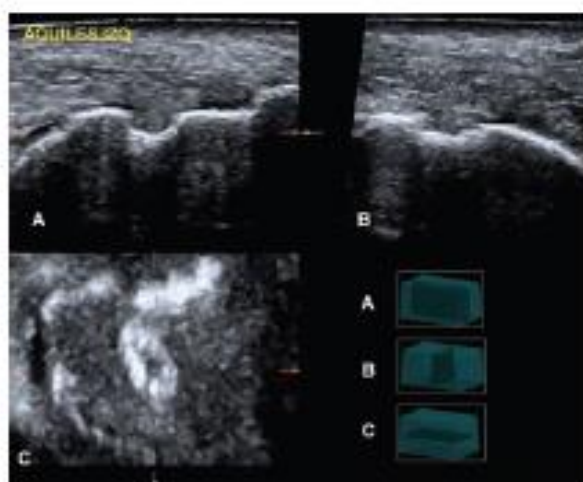
	Erosion		p Value
	Absence (mean±SD)	Presence (mean±SD)	
CRP (mg/l)	5.23±7.08	16.2±21.94	0.05
ESR (mm/h)	10.31±11.25	15.8±20.86	0.36
BASDAI	4.56±2.08	4.2±2.43	0.72
BASFI	2.15±1.88	2.7±2.69	0.55
BASRI spine	0.59±0.74	1±0.93	0.28
Heel pain	0.29±0.45	0.4±0.55	0.62
Tender joints	0.2±0.5	1.6±3.04	0.01
Swollen joints	0.2±0.5	1.6±3.04	0.01
Achilles Doppler signal	0±0	0.4±0.5	0.001

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASRI, Bath Ankylosing Spondylitis Radiology Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.



**Figure 1** Longitudinal 12-month evolution of ultrasound study of Achilles entheses erosion (n=55).

## Concise report



**Figure 2** Achilles erosion three-dimensional view: (A) longitudinal view; (B) transverse view; (C) coronal view. Confluence of image in three dimensions.

the results obtained. It is likely that 3D US is not as accurate as CT, but it seems to be reliable and to improve operator variability.<sup>17</sup>

A striking finding in the current study was the frequency of erosion disappearance. It seems reasonable to suggest that the formation of new bone in SpA could be associated with erosion resolution. Consistent with these findings, previous results on spinal MRI in SpA showed that new syndesmophytes developed from inflammatory lesions in spinal vertebral corners into fat infiltration or erosions and progressed to bone sclerosis and syndesmophyte formation.<sup>18</sup> This result could also be in agreement with the apparent failure of anti-tumour necrosis factor (anti-TNF) therapies to control bone proliferation in SpA and with the relationship between TNF $\alpha$ , Dkk-1 and the Wnt pathway in bone proliferation in SpA.<sup>19,20</sup>

The third finding, not previously reported, is the significant association between erosion and objective activity outcomes in SpA such as peripheral joint involvement (swollen and tender counts), biochemical inflammatory markers (CRP) and the presence of an enthesitis Doppler signal.

In conclusion, our results strongly support the view that Achilles tendon enthesitis erosion in SpA is not always a persistent structural lesion, is reliable and has a significant association with other objective disease activity outcomes measures.

**Funding** This study was supported by an unrestricted grant from the Spanish Rheumatology Foundation and Pizar (ESPERANZA programme).

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** This study was conducted according to local regulations and the Declaration of Helsinki, and local approval was obtained from the ethical committee and institutional review board of the Hospital Universitario La Paz, Madrid, Spain.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## PART III

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### **Achilles enthesis ultrasound: the importance of the bursa in spondyloarthritis**



## Achilles enthesis ultrasound: the importance of the bursa in spondyloarthritis

S. Falcao<sup>1</sup>, E. de Miguel<sup>2</sup>, C. Castillo-Gallego<sup>2</sup>, D. Peiteado<sup>2</sup>, J. Branco<sup>1</sup>,  
E. Martín Mola<sup>2</sup>

<sup>1</sup>Rheumatology Department, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal; <sup>2</sup>La Paz University Hospital, Rheumatology Department, Madrid, Spain.

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### Abstract

#### Objectives

*This paper aims to assess the prevalence and relevance of the bursa-synovial lesion in spondyloarthritis (SpA).*

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#### Methods

*A transversal blind and controlled two-dimensional (2D) and three-dimensional (3D) ultrasound (US) study of Achilles enthesis bursa in early SpA was undertaken. Clinical outcome measures were collected.*

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#### Results

*Bilateral Achilles enthesis of 66 early SpA patients (34 women) and 46 control patients (23 asymptomatic healthy subjects and 23 rheumatoid arthritis [RA] patients) were analysed. Mean BASDAI, BASFI and BASRI-spline were 4.55±2.08, 2.16±1.95 and 0.65±0.77, respectively. Mean erythrocyte sedimentation rate (ESR) was 10.93±12.35 mm/h and C-reactive protein (CRP) was 6.46±10.09 mg/l. The κ-values for intra-reader agreement for 2D and 3D images and bursa measurement were 0.82 and 0.98, respectively. Bursas were visualised in 89/132 SpA entheses (67.4%) vs. 27/46 entheses (58.7%) of healthy controls ( $p<0.01$ ), and 10/46 entheses (21.7%) of RA controls ( $p<0.01$ ). When the thicknesses of the bursas were analysed, the SpA group had a mean of 1.52±1.47 mm versus 0.76±0.76 mm in the healthy control group ( $p<0.0001$ ), and 0.38±0.62 mm in the RA control group ( $p<0.0001$ ). A positive likelihood ratio of 4.6 with a cut-off point of bursa >2 was found. No Doppler signal was detected in controls, but 6.6% of SpA Achilles entheses had Doppler bursitis. Heel pain was more frequent when bursa was present ( $p<0.05$ ). When Doppler was present, male predominance, HLA B27 positive, heel pain, and higher number of swollen joints, CRP levels, disease activity by the patient and BASDAI questions 2 and 3 achieved statistical significance ( $p<0.01$ ).*

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#### Conclusion

*The presence of bursa and Doppler signal at retrocalcaneal bursa level could have a relevant contribution to differentiate SpA patients, and were correlated with clinical outcomes of SpA disease activity.*

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#### Key words

spondyloarthritis, ultrasonography, power Doppler, enthesis

Sandra Falcao, MD  
 Eugenio de Miguel, MD, PhD  
 Concepción Castillo-Gallego, MD  
 Diana Peiteado, MD  
 Jaime Branco, MD, PhD  
 Emilio Martín Mola, MD, PhD  
 Please address correspondence to:  
 Sandra Falcao, MD,  
 Rheumatology Unit,  
 Hospital Egas Moniz,  
 Rua da Janqueira 126,  
 1349-016 Lisbon, Portugal.  
 E-mail: sfalcao76@gmail.com

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## Introduction

Enthesitis is a distinctive feature of spondyloarthritis (SpA) (1). The central importance of the enthesitis in understanding SpA pathophysiology has reemerged in the last decade relating structural enthesal damage with inflammation, regional microanatomy and biomechanics, and its correlation with enthesal new bone formation, and erosion (2-5). Considering the cardinal role of enthesitis inflammation on SpA and the striking finding that clinical examination lacks sensitivity and specificity, as has been demonstrated by several studies comparing clinical evaluations with new imaging techniques such as ultrasound (US) (6-8), it is fundamental to study and define the elemental lesions that build the concept of enthesitis.

Over the last few years US has proved to be a high sensitive and non-invasive tool in the study of enthesitis. Furthermore, US elemental lesions included in enthesitis pathology have been described (9, 10) and consensus about definitions initiated.

The importance of enthesitis in SpA is growing, since the new Assessment of the SpondyloArthritis Society (ASAS) classification criteria for peripheral SpA includes enthesitis as one of the three entry criteria (the other two being arthritis and dactylitis) (11). It is also included in the EULAR recommendation for psoriatic arthritis management (12), which recommends anti-TNF therapy for patients with active enthesitis and/or dactylitis and insufficient response to non-steroidal anti-inflammatory drugs or local steroid injections.

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) define enthesopathy as "abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in 2 perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity" (13). This definition includes the principal lesions of the enthesitis at bone and enthesitis tendon insertion identified by ultrasonography, and it is now widely

cited and accepted in the US community. On the other hand, there are multiple studies that added the bursa to the elementary enthesal lesions considered in the OMERACT enthesopathy definition (6-8, 14-16). In fact, bursa was included in 46% of enthesitis studies in a recently systematic literature review (9). This is in agreement with the concept of "synovio-enthesal complex", which includes the link between enthesitis and osteitis in SpA. It has been clarified in recent studies that demonstrate not only a close functional integration of the enthesitis with neighbouring bone, but also the connection between enthesitis and synovitis that occurs (4, 5, 17-19).

Today, the debate is open and the relevance of bursa in previous publications remains sparse, likely because bursa seems to be a non-specific SpA enthesal lesion, and is often mistaken for sport and overuse pathology (20). Therefore, new insights about the understanding of the bursa in the pathogenic process in SpA could be relevant in the development of: a) US definitions, we have OMERACT enthesopathy definition but we are waiting for enthesitis definition, and b) US disease scores with diagnostic purpose or to assess disease activity or damage, and to monitor patients' response to drugs.

The aim of the present study was to use two-dimensional (2D), in grey scale and Doppler, and three-dimensional (3D) US to assess the prevalence and relevance of the bursa-synovial lesion in SpA, using as model the Achilles enthesitis.

## Patients and methods

A blind and controlled Achilles enthesitis bursitis US study was performed on early-stage SpA patients. The study was conducted according to local regulations and the Declaration of Helsinki, and the ethical committee and IRB of our hospital granted approval to the study.

## Patients

The patient sample was selected consecutively from individuals attending the Early Spondyloarthritis Unit, as part of the ESPERANZA programme, a nation-wide health management programme designed to provide excellence

*Funding:* this study was supported by an unrestricted grant from the Spanish Rheumatology Foundation and Pfizer (ESPERANZA programme).

*Competing interests:* none declared.

in care for early Spondyloarthritis promoted by the Rheumatology Spanish Foundation (21). The referral criteria included: 1) age below 45, 2) symptoms duration between 3 and 24 months, and 3) at least one of the following: a) inflammatory low back pain, defined as at least two among insidious onset, morning stiffness for more than 30 minutes, or clear improvement of the symptoms with physical activity, but not relieved by rest, b) asymmetric arthritis, preferably of the lower limbs, or c) low back pain or arthralgia and at least one among psoriasis, inflammatory bowel disease, anterior uveitis, family history of spondylitis, psoriasis, radiographic sacroiliitis or HLA-B27+ status. The last sixty-six consecutive SpA patients were included. Patients were classified as SpA according to accepted classification criteria, as follows: 1) ankylosing spondylitis (AS), if they fulfilled the modified New York criteria (22), 2) psoriatic arthritis (PsA), if they fulfilled the CASPAR criteria (23), 3) non-radiological SpA, if ASAS criteria for classification of SpA were fulfilled without definitive radiographic sacroiliitis (11, 24), 4) reactive arthritis (ReA), if the patient fulfilled ESSG criteria or had arthritis, confirmed by a rheumatologist, with recent evidence of related infection, and 5) arthritis-associated inflammatory bowel disease (AIBD), if IBD was present in a patient with the New York criteria or ASAS SpA criteria. The diagnosis of IBD required typical histological findings of Crohn's disease or ulcerative colitis. Exclusion criteria included previous history of ankle surgery, peripheral neuropathy, or corticosteroid injection within the previous 6 weeks at Achilles tendon. All patients completed the Spanish version of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI); Bath Ankylosing Spondylitis Radiology Index (BASRI) and peripheral joint count were also registered on the same day of the visit.

#### Controls

Forty-six sex-matched controls (92 Achilles entheses) were included. Half of the controls were patients who ful-

filled the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 revised criteria for rheumatoid arthritis (RA) (25), but who did not have advanced deformities of the hand, and another half were asymptomatic healthy subjects. Healthy people were selected among hospital workers and friends of patients, all of whom volunteered to participate after receiving an explanation of the procedure.

#### Ultrasound scanning protocol

Ultrasonography was performed by an experienced rheumatologist, using a Logiq 9 (General Electric Medical Systems, Milwaukee, WI, USA) equipped with a linear probe at 9–14 MHz and a broadband high-frequency (8–15 MHz) volumetric probe. Focus was positioned at the level of the region of interest; Doppler settings were standardised with a pulse repetition frequency of 400 Hz, wall filter of 48Hz and colour-mode frequency of 7.5 MHz. The colour gain was 36–45 (increased to the highest value not generating Doppler signals under the bony cortex) (26). Colour box was positioned at the level of the Achilles tendon enthesis, enlarging the box to upper part of the image. The sonographer was blinded to patients' clinical or therapeutic data; and subjects were advised to withhold these data with the US examiner. The patients were asked to take a prone position with the feet hanging out the examination table in neutral position for examination of the Achilles tendon. In all cases, bilateral examination was carried out after having previously applied gel to the skin to provide an acoustic interface; particular attention was paid on not applying probe pressure on the anatomical structures under examination (27). The same protocol was used for both 2D and 3D examinations.

#### 2D US and 3D examination

During the same scanning session, US was firstly performed in B-mode modality using a longitudinal and transverse scanning technique to detect morphological changes and immediately afterwards by using Doppler technique to

access abnormal vascularisation (28). Immediately after the 2D US exploration, the acquisition of 3D data sets was obtained placing the volumetric probe over the area of interest. All acquired images were stored in digital format.

#### Methods of US image interpretation

Presence of retrocalcaneal bursa was defined by a grey-scale US aiming at detecting bursal enlargement. The maximal diameter obtained on longitudinal and transversal scan was collected (29). The measurement end of bursa was classified in a dichotomous scale (presence/absence) and a continuous quantitative scale. The presence or absence of Doppler signal in the cortical bone profile or bursal area was also recorded (Fig. 1). To improve reliability and accuracy a quantitative measurement was determined in the storage 3D volumes of 53 consecutive SpA patients and 23 healthy controls, the average of three consecutive measurements of the maximal thickness obtained in longitudinal and transverse axes was scored.

#### Statistical analysis

Mean  $\pm$  standard deviation was used to describe the demographic characteristics of patients and ultrasonographic features. To compare quantitative and qualitative variables of clinical, biochemical and ultrasound data, the independent sample *t*-test and the chi-squared test were used, respectively. The reliability analysis was performed using the kappa correlation coefficient for qualitative presence of bursa, and intraclass-correlation coefficient (ICC) for bursa thickness measurement. ROC curves were used to calculate sensitivity and specificity in the different cut-off points. *p*-values of less than 0.05 were considered to be statistically significant. All data analyses were performed with SPSS version 11.5 software (SPSS, Chicago, IL, USA).

## Results

#### Demographic data

One hundred and thirty-two Achilles tendon entheses of 66 early SpA patients (34 female, 32 male) were studied. Mean age was 32.5 $\pm$ 7.66 (range 18–45) years. Mean disease evolution



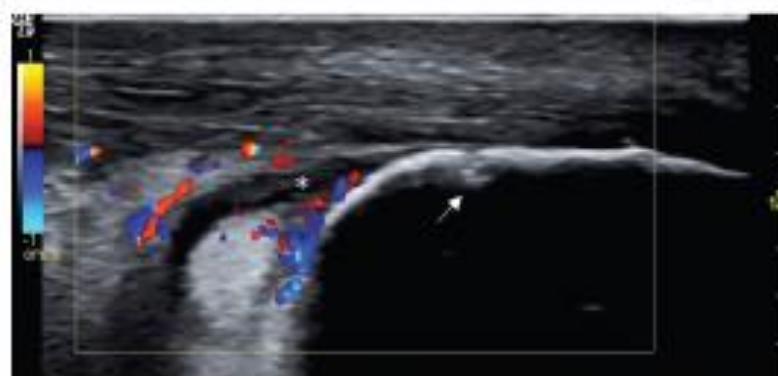


Fig. 1. Ultrasonographic appearance of enthesal Achilles insertion. Bursal enlargement with Doppler signal (\*), and erosion (arrow) in a longitudinal view.

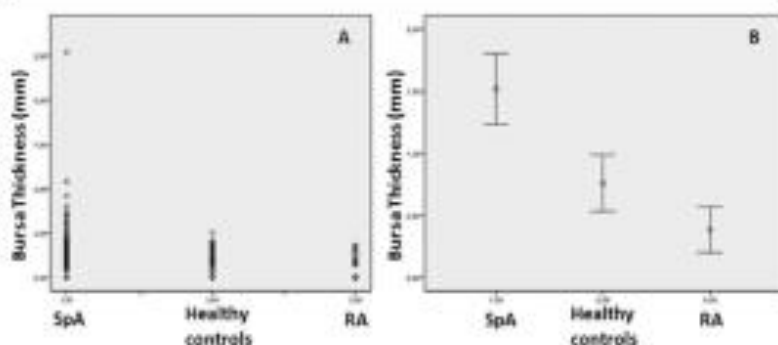


Fig. 2. Ultrasound bursa measure in spondylarthrititis (SpA) and controls. A. Scattergram dots distribution in SpA, healthy controls and rheumatoid arthritis (RA) control group. B. Mean and 95%CI of bursa thickness in SpA, healthy controls and RA controls.

time was 10 months (range 3–23). The sample included three cases of AS, ten cases of PsA, two cases of AIBD, three cases of ReA and forty eight cases fulfilled the non-radiological ASAS SpA classification criteria. Forty-five percent of SpA patients were HLA-B27 positive; and thirty-one percent had heel pain. Mean (range) BASDAI, BASFI and BASRI-spine were  $4.55 \pm 2.08$  (0–8.8),  $2.16 \pm 1.95$  (0–7.4) and  $0.65 \pm 0.77$  (0–3), respectively. Mean erythrocyte sedimentation rate (ESR) was  $10.93 \pm 12.35$  mm/h (range 1–53) and C-reactive protein (CRP) was  $6.46 \pm 10.09$  mg/l (range 0–51). At baseline all patients were being treated with anti-inflammatory drugs, and eight began classic disease-modifying anti-rheumatic drugs (DMARD): sulfasalazine or methotrexate. Forty-six sex-matched controls were included. Mean DAS 28 (disease activity score) in RA control group was  $2.78 \pm 1.5$ .

#### Ultrasound results

**Reliability.** Unweighted kappa value for the dichotomous evaluation of intra-reader 2D-3D images was 0.82. The intra-reader ICC agreement in 2D-3D quantitative measurements of US Achilles entheses bursa was 0.98 (95%CI 0.97–0.99;  $p < 0.0001$ ).

**Validity.** Bursas were visualised in 89/132 SpA entheses (67.4%) versus 27/46 entheses (58.7%) of healthy controls ( $p < 0.01$ ), and 10/46 entheses (21.7%) of RA controls ( $p < 0.01$ ). When the thicknesses of the bursas were analysed, the SpA group had a mean thickness of  $1.52 \pm 1.47$  mm versus  $0.76 \pm 0.76$  mm in the healthy control group ( $p < 0.0001$ ), and  $0.38 \pm 0.62$  mm in the RA control group ( $p < 0.0001$ ). SpA patients show a tendency to have more and higher bursas than control population. The ROC curve analysis showed 60.4% sensitivity and 68.5% specificity

when bursa was  $>1$  mm, and 34% sensitivity and 87% specificity when bursa was  $>1.5$  mm. A cut-off of bursa  $>2$  mm showed a low sensitivity of 19.8% with a specificity of 97.8% in front of the overall group, and a sensitivity of 19.8% and a specificity of 95.7% with a positive likelihood ratio of 4.6 in front of healthy controls. Figure 2 shows ultrasound bursa measurements in Achilles entheses of control groups and SpA patients. No Doppler signal was detected in any bursa of control patients, but 6.6% of SpA Achilles entheses had Doppler bursitis.

The correlation between bursas  $>2$ mm and quantitative measures are shown in Table I. Other qualitative variables as HLA B27, sex, heel pain, showed as bursa  $>2$  were more frequent in men ( $p < 0.01$ ). Heel pain was more frequent when bursa was present ( $p < 0.05$ ), and mean bursa thickness was  $1.96 \pm 1.24$  mm in SpA patients with heel pain compared with  $1.31 \pm 0.62$  mm in SpA patients without heel pain ( $p < 0.05$ ). When Doppler was present, male predominance, HLA B27 and heel pain achieved statistical significance ( $p < 0.01$ ).

#### Discussion

The purpose of this study was to determine whether the US recognition of bursa affection on entheses could be relevant as elemental lesion in the concept of enthesal damage and enthesitis definition in SpA. While the link between enthesitis and osteitis in SpA has been clarified in recent studies that demonstrate a close functional integration of the entheses with the neighbouring bone (3), the connection between enthesitis and bursal-synovitis remains a subject of debate (4). OMERACT's enthesopathy definition does not include bursa affection as previously mentioned in the introduction. The quality of diagnostic tests used for the care of patients is not judged only by their analytical characteristics, but mainly for their ability to distinguish between alternative states of health. For the bursa US to be used in routine medical practice, this diagnostic test must reduce uncertainty towards a specific diagnosis and contributes to accurate therapeutic decision making.

**Table 1.** Correlation between bursa thickness and Doppler presence in bursa with demographic, clinical, laboratory and other ultrasound characteristics of SpA patients.

	Bursa >2mm		p-value	Doppler bursa		p-value
	No	Yes		No	Yes	
MASEI	19.5	25.4	NS	21.3	40.5	0.01
Erosion	1.1	2.7	<0.05	1.7	7.5	0.01
Doppler	4.1	4.5	NS	4.5	12	0.05
Bursa	1.1	2.7	<0.01	2	1.5	NS
Thickness	0.8	0.7	NS	0.7	3	0.05
Structure	2.9	2.9	NS	3.1	5.5	0.01
Bone proliferation	9.4	11.8	NS	9.8	13.5	NS
Age	33.6	32.9	NS	33.3	30.0	NS
MASES	1.3	0.7	NS	1.25	2	NS
NSJ	0.2	1.6	<0.05	0.16	3.5	<0.01
ESR	14.4	7.6	NS	13.1	7.0	NS
CRP	6.5	4.4	NS	6.3	27.0	0.01
BASRI spine	0.7	0.6	NS	0.8	0.5	NS
Disease activity (patient)	2.8	3.7	NS	2.8	5.0	0.01
VAS (patient)	5.1	4.2	NS	4.9	6.5	0.01
BASDAI	4.8	3.9	NS	4.7	5.1	NS
BASFI	2.2	1.6	NS	2.2	3.5	NS
ASQoL	6.8	5.4	NS	6.6	10.0	NS
BASDAI 2	5.5	4.2	NS	5.6	2	0.01
BASDAI 3	3.4	3.7	NS	3.3	7.5	0.01
BASDAI 6	4.4	4.6	NS	4.6	5	NS

MASEI: Madrid Sonography Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; NSJ: number of swollen joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASRI: Bath Ankylosing Spondylitis Radiology Index; VAS: visual analogic scale for pain; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 2: question 2 (How would you describe the overall level of AS neck, back or hip pain you have had?); BASDAI 3: question 3 (How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?); BASDAI 6: question 6 (How long does your morning stiffness last from the time you wake up?); BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; NS: non-significant.

Our study tries to assess the prevalence and relevance of the bursa-synovial lesion in SpA using the Achilles enthesitis as a model. In this sense, similar to previous data, our findings demonstrate that retrocalcaneal bursa can be detectable by US in normal subjects (20, 30). However, this study shows a significant increase of Achilles bursa presence and thickness in SpA patients compared to controls (healthy/mechanical controls and RA controls). Furthermore, when bursa's thickness was measured, our results showed an increase in SpA patients with statistical significant differences. A cut-off point of bursa  $\geq 2$ mm had a positive likelihood ratio of 4.6 in front of healthy/mechanical subjects. A likelihood ratio between 2 and 5 generates small, but sometimes important changes in probability. A striking finding is the relatively low prevalence and thickness of bursa in RA control group (21.7% in RA control group versus

58.7% in healthy controls;  $p < 0.01$ ). This control population was composed by RA patients all treated with disease modifying anti-rheumatic drugs without advanced deformities, and low disease activity. Another possible explanation could be bursa presence of mechanical origin in healthy control population related with overuse. In agreement with what has been shown by other authors, the presence of Doppler signal seems to have a high significance in the correct classification of SpA patients (6, 14, 31, 32). Table 1 summarises interesting results about Doppler signal in the bursa. In our study Doppler signal is associated with other clinical measures accepted for assessment of SpA disease activity (C-reactive protein, heel pain, patient VAS for pain and global disease activity evaluation, number of swollen joints and BASDAI 3), but not with axial question of BASDAI, it even had a negative association

with spine pain (BASDAI 2). The association with the number of swollen joints, BASDAI 3 and C-reactive protein is in agreement with the idea that bursal-synovial specific factors could trigger innate immune responses and may be pivotal players in the phenotypic expression of SpA, as suggested by the synovio-entheseal complex concept proposed by McGonagle *et al.* (4, 17, 18). In this sense, and supporting the idea of the importance of the participation of the synovial bursal tissue in enthesitis damage, previous reported data have demonstrated that erosions typically occur in the bursal proximal portion of the enthesitis in SpA patients, possibly establishing a link between these lesions (5, 33). Additionally, a longitudinal study of patients treated with TNF-alpha blocking agents demonstrated that the only elemental lesions that achieved a significant reduction after the treatment were entheseal hypoechogenicity and/or thickening, bursa and Doppler signal (34, 35). This reinforces the possible importance of the introduction of these elementary lesions in future scoring systems for activity, damage, or follow-up purposes. A limitation of the present study was the low number of patients and controls weakening the statistical power of our results. Another limitation is the low sensitivity of bursa in grey scale, which reduces the value of bursa in enthesitis US examination, but this is not different from other elemental lesions included in enthesopathy definition such as thickness that had less contribution (31). Probably no one lesion, as bursa presence, but the combination of entheseal lesions improve the knowledge of the SpA enthesitis pathological process. The Doppler presence seems to have a high diagnostic value for SpA, but has the limitation of its low prevalence. One possible explanation for the low prevalence of Doppler signal could be related with the low vascularisation flow of the enthesitis. Even in other published data by expert groups a similar low prevalence of Doppler signal was found. (31, 34, 35). In this sense, it is remarkable that the analysis of Doppler presence taking into account clinical variables achieved statistical significance.



### Conclusion

In conclusion, our results showed that US findings at retrocalcaneal bursa level have low sensitivity, but could have an important contribution in differentiating patients with SpA, and probably to assess the disease as supported by correlations with clinical outcomes of disease activity. The inclusion of bursa in future new consensus definition of enthesitis should be evaluated.

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## PART IV

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**Can we use enthesitis ultrasound as an outcome measure of disease activity in Spondyloarthritis? A study at the Achilles level.**

## Concise report

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## Can we use enthesis ultrasound as an outcome measure of disease activity in spondyloarthritis? A study at the Achilles level

Sandra Falcao<sup>1</sup>, Concepción Castillo-Gallego<sup>2</sup>, Diana Peiteado<sup>2</sup>, Jaime Branco<sup>1</sup>, Emilio Martín Mola<sup>2</sup> and Eugenio de Miguel<sup>2</sup>

### Abstract

**Objective.** The aim of this study was to evaluate the construct validity of enthesis US in the assessment of disease activity in SpA.

**Methods.** A longitudinal Achilles enthesis US study in patients with early SpA was undertaken. Achilles US examinations were performed at baseline, 6 and 12 months and compared with clinical outcome measures collected at the baseline visit.

**Results.** Bilateral Achilles enthesis of 146 early SpA patients (68 women) were analysed. Basal mean BASFI, BASRI-spine, BASDAI and Ankylosing Spondylitis Disease Activity Score (ASDAS) were 2.44 (s.d. 2.05, range 0–8), 0.67 (s.d. 0.74, range 0–3), 4.60 (s.d. 2.07, range 0–9.5) and 2.51 (s.d. 1.16, range 0–5), respectively. The mean ESR was 15.0 mm/h (s.d. 16.99, range 0–109) and the mean CRP was 8.67 mg/l (s.d. 16.98, range 1–90). At baseline, the Achilles Doppler signal and US structure alteration were significantly associated with higher CRP and ESR levels. Patients who had very high disease activity at baseline, as assessed by the ASDAS (>3.5), had a significantly higher Achilles total US score at baseline ( $P=0.04$ ), and ASDAS <1.3 predicted no Doppler signal at 6 and 12 months. Overall, the Achilles total US score was significantly higher in patients with higher levels of CRP (baseline  $P=0.04$ , 6 months  $P=0.006$ , 12 months  $P=0.003$ ) and ESR (baseline  $P=0.02$ , 6 months  $P=0.04$ , 12 months  $P=0.005$ ) at baseline. The Doppler signal at the baseline visit predicted a higher total US score at 6 and 12 months.

**Conclusion.** Doppler US has significant associations with other commonly accepted disease activity measures, such as ESR, CRP and ASDAS, and seems to be an objective outcome measure for enthesitis.

**Key words:** spondyloarthritis, ultrasonography, disease activity.

### Introduction

SpA is a group of disorders characterized by inflammatory involvement of the enthesis and the adjacent bone, and enthesitis is regarded as the primary lesion in all SpA subtypes [1, 2]. The importance of enthesitis has increased in recent years as a result of its inclusion in the recently developed Assessment of SpondyloArthritis International

Society (ASAS) classification criteria for axial and peripheral SpA [3–5], as well as in the most recent European League Against Rheumatism recommendations for the management of PsA [6]. One of the major problems in daily practice is the diagnosis and monitoring of enthesitis, which is consistent with the lack of sensitivity and reliability reported in the previous literature [7]. It has been suggested that imaging techniques are superior to clinical examination for this purpose, and even US might be superior to MRI for detecting early signs of enthesopathy [8]. Furthermore, US is currently considered a powerful tool for identifying enthesal affection, capable of improving diagnostic accuracy in SpA [9–11]. The OMERACT enthesopathy definition [12] encompasses a wide range of lesions that could represent either active enthesitis or enthesal changes secondary to previous inflammation.

<sup>1</sup>Rheumatology Department, CEDOC, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal and  
<sup>2</sup>Rheumatology Department, La Paz University Hospital, Madrid, Spain.

Submitted 10 March 2014; revised version accepted 7 August 2014.  
Correspondence to: Sandra Falcao, Hospital Egas Moniz, Rheumatology Department, Rua de Junqueira, 126, 1349-016 Lisbon, Portugal. E-mail: sfalcao78@gmail.com



Therefore the enthesitis US definition is still pending. In this sense, knowledge of which enthesal US lesions are related to other SpA disease activity outcomes could be relevant. The aim of the present study was to determine the construct validity of enthesitis US in the assessment of disease activity in SpA.

## Patients and methods

We performed a longitudinal enthesitis US study in patients with early SpA. Approval was obtained from the ethics committee of the Hospital Universitario La Paz. All patients signed an informed consent form.

### Patients

The sample included the baseline visit for 146 consecutive patients attending the Early SpA Unit as part of the Esperanza programme, the referral criteria of which have been previously published [13]. The patients were diagnosed with SpA according to accepted ASAS classification criteria [3–5]. All patients completed the Spanish version of the BASDAI and the BASFI. Peripheral joint count and the presence of heel pain were also registered on the same visit day. Laboratory tests included ESR, CRP and HLA-B27. The CRP version of the Ankylosing Spondylitis Disease Activity Score (ASDAS) [14, 15] and the BASRI were calculated.

### US examination

Patients underwent an Achilles US examination at baseline, and 6 and 12 months according to the Madrid Sonographic Enthesitis Index (MASEI) [16]. In this study, the only score was for the Achilles enthesitis. The ultrasonography was performed by one rheumatologist trained in enthesitis US using a Logiq 9 machine (General Electric, Wauwatosa, WI, USA) with a linear probe at 9–14MHz. The US examiner was blinded to the status of the subject.

The elemental lesions were defined according to OMERACT definitions [12] and the original MASEI publication [16]. To improve precision, erosion was defined as cortical breakages with step-downs of more than 1 mm in depth and width in both the longitudinal and transverse axes. Previous studies by our group have shown good to excellent reliability results for the MASEI score with an intraclass correlation coefficient range of 0.77 (95% CI 0.20, 0.95;  $P < 0.01$ ) to 0.97 (95% CI 0.90, 0.99;  $P < 0.0001$ ) [16, 17].

### Statistical analysis

The mean (s.d.) was used to describe the demographic characteristics of patients and ultrasonographic features. To compare quantitative and qualitative variables of clinical, biochemical and US data, an independent sample *t* test and chi-squared test were used, respectively. Pearson correlation coefficients were calculated to assess the relationships between disease activity measures and ultrasonographic features. *P*-values of  $< 0.05$

were considered statistically significant. All data analyses were performed with SPSS version 17.0 software (IBM, Armonk, NY, USA).

## Results

One hundred and forty-six early SpA patients (68 females) were examined. The subjects had a mean age of 32.4 years (s.d. 7.4, range 18–45). The average evolution time of disease was 10.9 months (s.d. 7.1). Forty-four per cent of patients had sacroiliitis on MRI and 10% fulfilled the modified New York AS criteria. Forty-seven per cent of patients were HLA-B27 positive, 27.6% had heel pain and 37.5% had peripheral arthritis. Thirty-eight per cent of patients with heel pain had Doppler signal compared with 24% of those without heel pain. There was no significant association between heel pain and Achilles Doppler signal ( $P = 0.34$ ). The baseline mean visual analogue scale for pain and patient global disease assessment was 5.15 (s.d. 2.5, range 0–10) and 2.98 (s.d. 1.56, range, 0–7), respectively. The mean BASFI measurement was 2.44 (s.d. 2.05, range 0–8) and the mean BASRI-spine measurement was 0.67 (s.d. 0.74, range 0–3). The baseline mean BASDAI, ASDAS, ESR and CRP measurements were 4.60 (s.d. 2.07, range 0–9.5), 2.51 (s.d. 1.16, range 0–5), 15.0 mm/h (s.d. 16.99, range 0–109) and 8.67 mg/l (s.d. 16.98, range 1–90), respectively. At baseline, all patients were treated with NSAIDs and 22 began classic DMARDs (SSZ or MTX). Associations between clinical and laboratory measurements of SpA patients' basal data and the Achilles enthesitis elemental lesions are reported in Table 1. At baseline, the Achilles Doppler signal and structure were significantly associated with higher CRP and ESR levels. Patients with Achilles Doppler signal at the baseline visit had a significantly higher total US score, not only at baseline but also at 6 and 12 months ( $P < 0.0001$ ). At baseline, none of the elemental Achilles lesions were consistently associated with the BASDAI, individual BASDAI questions, BASFI, BASRI, ASDAS or patient global disease assessment.

Patients who had very high disease activity at baseline assessed by ASDAS ( $> 3.5$ ) had a significantly higher Achilles total US score at baseline ( $P = 0.04$ ). The same Achilles total US score was not associated with other ASDAS cut-offs or BASDAI Overall. Achilles total US score was significantly higher in patients with higher baseline levels of CRP (baseline  $P = 0.04$ , 6 months  $P = 0.005$ , 12 months  $P = 0.03$ ) and ESR (baseline  $P = 0.02$ , 6 months  $P = 0.04$ , 12 months  $P = 0.005$ ) (Table 2). At baseline, ESR correlated weakly with baseline structure ( $r = 0.26$ ,  $P = 0.007$ ), Doppler signal ( $r = 0.28$ ,  $P = 0.004$ ) and total Achilles score ( $r = 0.31$ ,  $P = 0.01$ ). CRP had similar correlations (structure:  $r = 0.32$ ,  $P = 0.001$ ; Doppler:  $r = 0.29$ ,  $P = 0.002$ ; total Achilles score:  $r = 0.36$ ,  $P < 0.001$ ). None of the correlations described for ESR and CRP were consistently present for the ASDAS or BASDAI. Patients with baseline inactive disease assessed by ASDAS ( $< 1.3$ ) had no Doppler signal at 6 and 12 months. In the group treated with anti-inflammatory drugs in monotherapy, similar

Table 1 Activities US elemental lesions vs demographic, clinical and laboratory data

	Activities US elemental lesions																	
	Doppler			Erosion			Bursae			Bone proliferation			Structure			Thickness		
	Yes	No	P-value	Yes	No	P-value	Yes	No	P-value	Yes	No	P-value	Yes	No	P-value	Yes	No	P-value
Age, years	34.2 (6)	31.5 (7.5)	0.05	27.8 (8)	33 (7.4)	0.01	34.2 (7.5)	31.3 (7.7)	0.02	34 (7.7)	31.2 (7.5)	0.02	33.3 (8.1)	31.5 (7.2)	0.16	30.5 (6)	32.5 (7.6)	0.45
CRP	158 (30.2)	4.3 (0)	<0.001	13.6 (10.7)	7.1 (5.7)	0.2	11.3 (8.2)	6 (4.1)	0.32	10.9 (21.2)	6.2 (11.7)	0.14	12 (22.1)	4.3 (6)	0.01	14 (7.6)	7.7 (16.4)	0.32
ESR	21.3 (34.2)	11.2 (8.1)	<0.001	19.2 (24.3)	13.6 (14.4)	0.35	17.6 (9.9)	12.2 (11.6)	0.37	19.4 (7)	13.7 (15.9)	0.59	17.4 (20.5)	11.2 (6)	0.04	13.7 (5.5)	14.5 (16.4)	0.88
ASDAS	2.8 (0.3)	2.3 (1)	0.31	3 (1.9)	2.4 (1)	0.36	2.7 (1)	2.3 (1)	0.34	2.7 (1)	2.3 (1.2)	0.15	2.6 (1.1)	2.3 (0.2)	0.39	2.9 (0.2)	2.4 (1.1)	0.33
BASDAI	4.5 (2)	4.7 (1.2)	0.72	5 (2.5)	4.6 (2)	0.49	4.8 (2)	4.5 (2)	0.31	4.9 (1.6)	4.5 (2.3)	0.35	4.7 (1.6)	4.6 (2.4)	0.67	4.8 (0.5)	4.6 (2)	0.81
BASDAI 2	4.8 (2.9)	5.6 (2.7)	0.24	3.4 (3.6)	5.7 (2.6)	0.16	5 (1)	5.6 (2.7)	0.49	5.8 (2.4)	5.1 (2)	0.3	5.4 (2.7)	5.4 (2.7)	0.97	5.4 (2.8)	5.4 (2.8)	0.96
BASDAI 3	4.6 (1.4)	3.2 (3.1)	0.18	5.1 (4)	3.3 (3)	0.29	4.6 (1.4)	3 (3)	0.08	4.4 (2.6)	3 (3.5)	0.09	4 (3)	3.3 (3.1)	0.38	3.8 (3.6)	3.5 (3.2)	0.88
BASDAI 6	3.9 (1.5)	4.5 (3)	0.55	5 (4.2)	4.3 (3)	0.69	3.9 (1.4)	4.7 (2.9)	0.41	5 (3)	3.9 (3.1)	0.23	4.4 (3.5)	4.4 (2.9)	0.98	4.7 (3)	4.3 (2)	0.85
Disease activity	3.4 (1.6)	2.7 (1.4)	0.19	3.43 (2.3)	2.9 (1.9)	0.37	3.2 (1.6)	2.8 (1.3)	0.29	2.9 (1.3)	2.9 (1.7)	0.94	3.2 (1.6)	2.7 (1.3)	0.21	3.1 (1.8)	2.9 (1.5)	0.75
VAS (patient)	5 (1)	5.3 (2.4)	0.68	6.4 (2.4)	5.1 (2.5)	0.2	4.8 (2.8)	5.5 (2.3)	0.21	5.2 (2.2)	5.3 (2.8)	0.97	5.4 (2.5)	5.2 (2.6)	0.71	6.3 (1.7)	5.1 (2.4)	0.18
VAS (clin)	5 (2.1)	5 (2)	0.18	5 (2.4)	5.4 (2)	0.09	2.9 (2.2)	2.9 (2)	0.12	2.7 (2.3)	2.4 (2)	0.49	2.8 (1.9)	2.3 (2.3)	0.19	2.4 (1.8)	2.6 (2.2)	0.75
BASDAI-epsile	0.9 (0.8)	0.6 (0.6)	0.6	0.6 (0.7)	0.6 (0.7)	0.32	0.9 (0.8)	0.5 (0.7)	0.12	0.5 (0.7)	0.6 (0.6)	0.18	0.7 (0.8)	0.6 (0.7)	0.77	0.5 (0.5)	0.7 (0.6)	0.39
NSU	0.6 (0.7)	0.2 (0.7)	0.42	1.3 (2.4)	0.2 (0.7)	0.009	0.5 (0.5)	0.2 (0.6)	0.42	0.6 (0.6)	0.2 (0.5)	0.2	0.6 (1.6)	0.2 (0.4)	0.17	0.6 (0.4)	0.3 (1)	0.53

All values expressed as mean (s.d.). P-values in bold are significant. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI 2: BASDAI question 2 (How would you describe the overall level of AS neck, back or hip pain you have had?); BASDAI 3: BASDAI question 3 (How would you describe the overall level of pain/swelling in joints other than neck, back, and hips you have had?); BASDAI 6: BASDAI question 6 (How long does your morning stiffness last from the time you wake up?); NSU: number of swollen joints; VAS: Visual analogue scale for pain.

Table 2 US vs clinical and laboratory characteristics of SpA patients at baseline, 6 months and 12 months

Achilles US	CRP			ESR			BASDAI			ASDAS								
	>5	<5	P-value	>30	<30	P-value	>4	<4	P-value	>2.1	<2.1	P-value	>3.5	<3.5	P-value			
<b>Baseline</b>																		
Bone proliferation	2.9 (0.2)	2.5 (0.2)	0.1	3.3 (0.1)	2.6 (1.2)	0.05	2.8 (0.2)	2.5 (0.2)	0.30	2.7 (1)	1.7 (0.5)	0.001	2.6 (0.9)	2.4 (1.2)	0.4	2.8 (0.1)	2.5 (1)	0.46
Erosion	1 (0.9)	0.5 (0.5)	0.17	1.3 (0)	0.6 (1.6)	0.29	0.6 (0.5)	0.8 (0.8)	0.65	0.6 (1.6)	0.9 (2.3)	0.76	0.5 (1.6)	0.6 (1.7)	0.88	1.3 (0.4)	0.4 (1.4)	0.33
Structure	0.9 (0.9)	0.6 (0.8)	0.22	1.4 (0.8)	0.7 (0.8)	0.01	0.8 (0.8)	0.7 (0.8)	0.53	0.7 (0.8)	0.1 (0.4)	0.12	0.6 (0.8)	0.6 (0.9)	0.9	0.8 (0.8)	0.6 (0.8)	0.27
Thickness	0.2 (0.2)	0.07 (0.2)	0.19	0.2 (0.8)	0.1 (0.4)	0.74	0.1 (0.4)	0.06 (0.2)	0.3	0.2 (0.5)	0.1 (0.4)	0.77	0.2 (0.5)	0.1 (0.4)	0.47	0.3 (0.7)	0.1 (0.4)	0.23
Bursa	0.8 (0.9)	0.6 (0.8)	0.36	0.8 (0.9)	0.7 (0.8)	0.53	0.7 (0.8)	0.7 (0.8)	0.87	0.4 (0.6)	0.3 (0.5)	0.58	0.3 (0.6)	0.4 (0.7)	0.65	0.7 (0.8)	0.3 (0.6)	0.08
Doppler	2 (0.5)	1.3 (0.3)	0.14	3.3 (0.4)	1.3 (2.3)	0.02	1.5 (0.3)	1.9 (0.8)	0.42	1.2 (2.3)	0.9 (2.3)	0.7	1 (2)	1.2 (2.3)	0.98	2 (2.7)	0.9 (1.9)	0.13
Total Achilles	7.8 (5.1)	5.7 (4.4)	0.04	10.2 (5.2)	5.9 (4.4)	0.02	6.4 (4.5)	6.6 (4.8)	0.84	5.7 (4.7)	4 (0.9)	0.30	5.5 (4.6)	5.4 (4.7)	0.9	7.8 (5.4)	4.8 (3.8)	0.04
<b>6 months</b>																		
Bone proliferation	2.9 (0.4)	2 (1.5)	0.007	2.9 (0.4)	2.3 (1.5)	0.2	2.6 (0.6)	2 (1.5)	0.07	2.2 (1.4)	1.4 (0.8)	0.05	2 (1.5)	2 (0.4)	0.80	2.2 (0.2)	2 (1.4)	0.77
Erosion	0.9 (0.9)	0.5 (0.4)	0.17	1.3 (0.4)	0.5 (1.4)	0.15	0.6 (0.5)	0.6 (0.8)	0.98	0.6 (1.5)	0.9 (2.3)	0.76	0.6 (1.4)	0.7 (1.8)	0.88	0.8 (0.9)	0.5 (1.5)	0.76
Structure	0.8 (0.9)	0.6 (0.8)	0.21	0.9 (0)	0.6 (0.8)	0.19	0.7 (0.8)	0.3 (0.8)	0.01	0.7 (0.8)	0.3 (0.5)	0.08	0.7 (0.8)	0.5 (0.7)	0.38	0.7 (0.8)	0.6 (0.8)	0.85
Thickness	0.2 (0.4)	0.06 (0.3)	0.14	0 (0)	0.1 (0.3)	0.02	0.09 (0.3)	0.1 (0.4)	0.06	0.1 (0.3)	0 (0)	0.30	0.1 (0.3)	0.1 (0.3)	0.9	0.2 (0.4)	0.1 (0.3)	0.26
Bursa	0.8 (0.9)	0.3 (0.7)	0.005	0.8 (0.9)	0.5 (0.7)	0.28	0.5 (0.8)	0.4 (0.8)	0.67	0.3 (0.7)	0 (0)	0.19	0.4 (0.7)	0.2 (0.8)	0.23	0.8 (0.8)	0.1 (0.5)	0.001
Doppler	1.5 (0.2)	0.4 (0.2)	0.003	1.6 (0.2)	0.7 (1.5)	0.06	0.9 (0.7)	0.5 (0.7)	0.19	0.7 (1.7)	0 (0)	0.28	0.7 (1.7)	0.5 (1.8)	0.72	1.5 (0.4)	0.4 (1.2)	0.03
Total Achilles	6.9 (4.9)	4.1 (4)	0.006	7.4 (6)	4.6 (4.1)	0.04	5.4 (4.2)	3.9 (4.8)	0.43	4.6 (4.3)	2.6 (2.6)	0.45	4.6 (3.8)	4 (4.8)	0.73	6.2 (6)	3.8 (3.7)	0.14
<b>12 months</b>																		
Bone proliferation	2.8 (0.4)	2 (1.6)	0.009	3 (1.4)	2.3 (1.5)	0.16	2.4 (0.6)	2.2 (0.9)	0.44	2.2 (1.5)	1.7 (0.8)	0.22	2 (1.5)	2.2 (1.4)	0.90	2.4 (0.8)	2 (1.5)	0.48
Erosion	0.8 (0.8)	0.4 (0.3)	0.17	1.8 (0.4)	0.4 (1.3)	0.004	0.4 (0.3)	0.6 (0.8)	0.57	0.3 (1.3)	0 (0)	0.09	0.3 (1.2)	0.3 (1.2)	0.94	0.8 (0.8)	0.2 (0.9)	0.14
Structure	0.6 (0.7)	0.4 (0.7)	0.15	0.8 (0.8)	0.5 (0.7)	0.15	0.5 (0.7)	0.4 (0.8)	0.38	0.5 (0.8)	0.2 (0.4)	0.28	0.5 (0.8)	0.5 (0.7)	0.87	0.6 (0.8)	0.5 (0.7)	0.6
Thickness	0.3 (0.3)	0.07 (0.3)	0.002	0.4 (0.7)	0.1 (0.4)	0.03	0.2 (0.4)	0.1 (0.4)	0.30	0.2 (0.5)	0 (0)	0.29	0.2 (0.5)	0.09 (0.3)	0.34	0.3 (0.5)	0.2 (0.4)	0.5
Bursa	0.4 (0.7)	0.4 (0.7)	0.74	0.4 (0.7)	0.4 (0.7)	0.98	0.3 (0.6)	0.6 (0.8)	0.08	0.2 (0.5)	0.2 (0.4)	0.96	0.1 (0.3)	0.3 (0.6)	0.19	0.8 (0.3)	0.2 (0.5)	0.32
Doppler	1 (0.9)	0.5 (0.5)	0.11	1.5 (0.4)	0.6 (1.5)	0.07	0.8 (0.7)	0.5 (0.7)	0.52	0.5 (1.5)	0 (0)	0.01	0.4 (1)	0.5 (1.8)	0.73	0.5 (0.2)	0.5 (1.4)	0.9
Total Achilles	6 (6)	4 (3.8)	0.03	7.9 (6)	2.2 (2.7)	0.005	4.6 (4)	4.5 (4.8)	0.67	3.9 (4.2)	2 (0.3)	0.02	3.6 (3.7)	3.9 (4.8)	0.71	4.6 (4.8)	3.5 (3.8)	0.58

All values expressed as mean (s.d.). P-values in bold are significant. ASDAS: Ankylosing Spondylitis Disease Activity Score.



results were found for CRP and ASDAS. The Achilles total US score was significantly higher in patients with higher baseline levels of CRP (baseline  $P=0.05$ , 6 months  $P=0.03$ , 12 months  $P=0.02$ ). Patients with very high disease activity assessed by ASDAS ( $>3.5$ ) had significantly higher Achilles total US scores at baseline and 6 months ( $P=0.006$  and  $P=0.01$ , respectively). Furthermore, patients with high disease activity assessed by BASDAI ( $>4$ ) had a significantly higher Achilles total US score at 6 months ( $P=0.007$ ). SpA patients with positive HLA-B27 had significantly higher levels of BASRI ( $P=0.01$ ), but no correlation was found for other clinical, laboratory or US outcomes.

## Discussion

In general, assessment of patient disease activity is always difficult, particularly in SpA. The concept of disease activity, a reflection of the underlying inflammation, encompasses a wide range of measures and domains. For its assessment, we can use the patient and the physician perspective, single disease activity parameters (eg. ESR or CRP) or a composite index. It is likely that a composite disease activity index will capture multiple important aspects of disease activity and better represent the true disease state. The BASDAI, probably the most commonly used score in clinical practice, is composed of six domains with a high level of face validity; however, it represents only the subjective perspective of the patient [18]. To reduce the well-known limitations of subjective components based on patient perspective, ASAS has developed the ASDAS, with the hypothesis that a better selection of patient perspective components and an objective laboratory parameter will improve the composite score [14, 19].

The entheses, which is one of the more important targets in the pathogenesis of SpA, is undervalued in the assessment of disease activity. The inclusion of entheses as an outcome measure in SpA patients is represented in the BASDAI in question 4 but not in the ASDAS. The ASAS core set for clinical record keeping and for disease-controlling anti-rheumatic treatments validated an enthesitis score, such as the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), San Francisco or Berlin [20]. However, it is accepted that clinical examination lacks sensitivity and specificity for enthesitis detection and that imaging techniques such as US can be efficiently used for this purpose. This is why a large number of studies have been published on US enthesal alterations in SpA diseases in recent years [9–11, 16].

Disease activity in SpA patients is most likely related to at least three aspects: axial, synovial and enthesal involvement. Any composite score that is used as an outcome measure in SpA should include these domains. Our study explores a new perspective not previously reported about the construct validity of entheses US as a possible disease activity outcome measure in SpA. The question remains as to how US findings are related to

other well-known measures of disease activity and their relevance. In this sense, our results are exciting because they show that basal ESR and CRP are higher in patients with an entheses Doppler signal and that higher basal ESR, CRP and ASDAS predicted a higher Doppler signal (a US alteration accepted as representative of inflammation) 6 months later. This seems to represent a connection between classic biochemical or immunological aspects of inflammation and Doppler signal, not only simultaneously, but also in future months. Patients with higher ESR and CRP also had higher total Achilles scores at the baseline, 6 and 12 month examinations, which could be a predictor of poorer prognosis in these patients. A similar association was also found at baseline in patients with higher ASDAS. Remarkably, patients with inactive disease (ASDAS  $<1.3$ ) at baseline had no Doppler signal at 6 and 12 months, indicating a negative predictive value. Furthermore, the Doppler signal at the baseline visit predicted a higher total US score at 6 and 12 months. Interestingly, at baseline, patients with ASDAS  $<2.1$  had higher total Achilles scores when compared with patients with ASDAS  $<3.5$ . One possible explanation for this could be that the ASDAS measures other domains besides enthesitis, so axial or peripheral arthritis could influence the results. Nevertheless, during follow-up, the total Achilles score decreased to a greater extent in the group with higher ASDAS (ASDAS  $>3.5$  vs ASDAS  $<3.5$ ), which is likely related to more aggressive therapies (including biologic agents) in patients with higher levels of disease activity and the relative lack of efficacy of the treatment in patients with lower disease activity. These findings reinforce the potential use of entheses US for assessment of disease progression and prognosis. Nonetheless, the BASDAI does not show significant differences between different cut-offs for US lesions or Doppler signal when verified with the ASDAS. These results seem to indicate that the ASDAS better reflects enthesal disease activity than does the BASDAI.

One limitation of our study is the exploration of a single peripheral entheses. The challenge will be to verify if another single entheses or a composite US enthesal index has better validity than the Achilles tendon by itself. Even so, the consistency of our results using just one entheses is remarkable. Another limitation of our study is that we had incomplete data for follow-up in the longitudinal study; however, data for at least 80 patients remained for each variable. Another limitation is that the study was conducted by only one researcher with a US machine, thus these findings need to be replicated by others.

In conclusion, Doppler US is significantly associated with other commonly used disease activity measures and seems to be a valid tool for assessing enthesal inflammation in SpA patients. As a disease status measure, it seems that, compared with the BASDAI, the ASDAS better reflects enthesal inflammation. This study supports the construct validity of entheses US and provides

further evidence that enthesitis US could be a useful tool for disease assessment in patients with SpA.

#### Rheumatology key messages

- Doppler US seems to be a valid tool for assessing enthesitis inflammation in SpA patients.
- Doppler US can be used to identify a connection between clinical signs and biomarkers of inflammation in SpA.
- Compared with the BASDAI, the Ankylosing Spondylitis Disease Activity Score better reflects enthesitis inflammation and has predictive value for the Doppler signal in SpA patients.

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## DISCUSSION

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It is well established that enthesitis is a distinctive feature of SpA, is transversal to all SpA subtypes, and may sometimes be present several years as an isolated clinical manifestation. Despite the relevance of peripheral enthesitis assessment in the last years – as corroborated by its inclusion in the recent developed Assessment of SpondyloArthritis international Society (ASAS) new classification criteria for axial and peripheral SpA,<sup>35,36</sup> and in the last EULAR recommendations for the management of PsA<sup>108</sup> – it remains uncertain which is the best form to perform its diagnosis. Several studies on imaging of entheses showed that imaging techniques such as MRI or ultrasound are superior to clinical examination for enthesitis diagnosis, and some asymptomatic enthesitis might only be detected by imaging techniques. However, as the enthesitis diagnosis can be assessed by ultrasound, it is fundamental to study and define the elemental lesions that build the concept of enthesitis in SpA, and its relationship with other well-established SpA outcome measures. The aim of this dissertation thesis was to improve the knowledge of SpA enthesal lesions; namely, understand the behavior of enthesal erosion and the importance of the enthesal bursa that could be involved in futures scores of structural damage or disease activity; analyze the validity of entheses ultrasound in the quantification of SpA disease activity and to contribute for enthesitis ultrasound definition.

The first study of this thesis (part I) focused on the analysis of the reliability of inter-lector and inter-ultrasonography equipment of MASEI index. Fundamental data for the remaining unrolling project validity. This work represented the validation process for my incorporation in the research team. In addition, it has always been said that the main problem of ultrasound is the interobserver variability. These types of studies are fundamental to spread and generalize this technique. With the proper knowledge and training ultrasound has proven, in many cases, to be more reproducible than other oldest techniques used in clinical daily practice.

In part II we were concerned about the Achilles entheses erosions behavior over time. In literature erosions represent a permanent structural damage, being useful for

monitoring joint injury, disease activity and therapeutic response in many rheumatic diseases; and to date, this concept has been mostly applied in RA.<sup>109</sup> However, in this sense, it is important to emphasize that RA erosion and SpA enthesis erosions likely represent a different aetiopathogenic disease-response mechanism. Unquestionably, erosion is a tissue-related damage and a structural change. However, the important question is whether erosions represent a permanent structural change that can only grow and worsen over time, as occurs in RA, or a transitory alteration. The initial observation leading to the development of the hypothesis was based on the identification of the dynamic nature of the enthesal erosions. Unfortunately, this was just an observation in the daily practice that had to be tested. Initially, we also thought that this could be related with the variability of ultrasound image readings or patient enthesal ultrasound exploration; but in some cases we had collected pictures of erosions that we were not able to reproduce in later ultrasound examinations. This coupled with the fact that the vertebral erosions disappear in SpA patients made us hypothesize that these lesions might disappear over time. To avoid bias related with the lack of reliability of enthesal exploration or ultrasound image reading we used 3D technology that allowed us to observe the scan time and review as many times as necessary the images. Previous published data about enthesis ultrasound erosion in SpA classified this elementary enthesal alteration as a structural damage.<sup>70,73</sup> Nevertheless, our findings in the longitudinal study of Achilles enthesis in early SpA are consistent with the dynamic behavior of erosion over time (part II). Our results strongly suggest that previously detected erosions could disappear during the course of the disease. Furthermore, at six and twelve months of follow-up, 25% and 50% of basal erosions disappeared, respectively; and among the new erosions that appeared at six months, 40% disappeared six months later.<sup>110</sup> Based on these striking results it seems reasonable to suggest that the new-bone formation process in SpA could be associated with the resolution of cortical enthesal erosion over time. Consistent with these findings, prior results on spinal MRI showed that new syndesmophytes in SpA developed from inflammatory lesions in spinal vertebral corners into fat infiltration or erosion, and progressed to bone sclerosis and syndesmophyte formation.<sup>111</sup> This result could also be in agreement with the apparent failure of anti-TNF therapies to control bone proliferation in SpA; and with the relation of TNF, Dkk-1 and the regulatory

molecule of the Wnt pathway in the bone proliferation in SpA.<sup>51</sup> This can be important to the development of ultrasound activity and structural damage scores to improve assessment, treatment response and prognosis in SpA patients.

Following the study of ultrasound elementary enthesal lesions in SpA, another trend was to analyze the bursal enthesal area (part III). There are multiple studies that added the bursa to the elementary enthesal lesions considered in the OMERACT enthesopathy definition.<sup>19,68-73</sup> In fact, bursa was not included in the OMERACT enthesopathy definition,<sup>67</sup> but was included in 46% of the enthesis studies in a recently systematic literature review,<sup>103</sup> being in agreement with the concept of “synovio-enthesal complex” that includes the link between enthesitis and osteitis in SpA. It has been clarified in recent data that there is not only a close functional integration of the enthesis with the neighboring bone, but also a connection between enthesitis and synovitis.<sup>29</sup> Additionally, enthesal morphologic abnormalities, Doppler signal and bursa were the only elementary lesions that were associated with anti-TNF therapies response.<sup>81,82</sup> Therefore, bursa may be important in quantifying the therapeutic response in SpA patients, and may be related with disease activity. Consequently, bursa was another of the injuries of interest in our ultrasound enthesis SpA third study draft. Therefore, we tried to assess the prevalence and relevance of the bursa-synovial lesion in SpA. Our findings showed a significant increase of Achilles bursa presence and thickness in SpA patients compared to controls (healthy/mechanical controls and RA controls). Furthermore, when bursa’s thickness was measured, our results showed an increase in SpA patients with statistical significant differences. The ROC curve analysis showed 60.4% sensitivity and 68.5% specificity, for SpA diagnosis, when bursa was >1 mm, and 34% sensitivity and 87% specificity when bursa was >1.5 mm. A cut-off of bursa >2 mm showed a low sensitivity of 19.8% with a specificity of 97.8% in front of the overall group, and a sensitivity of 19.8% and a specificity of 95.7% with a positive likelihood ratio of 4.6 in front of healthy controls. A likelihood ratio between 2 and 5 generates small, but sometimes important changes in probability. In this study, a striking finding was the relatively low prevalence and thickness of bursa in RA control group (21.7% in RA control group versus 58.7% in healthy controls;  $p < 0.01$ ).<sup>112</sup> One possible explanation could be that this control population was composed by RA



patients all treated with disease modifying anti-rheumatic drugs without advanced deformities, and low disease activity. On the other hand in the healthy control population the higher bursa presence could be related with overuse. In agreement with what has been shown by other authors, the presence of Doppler signal seems to have a high significance in the correct classification of SpA patients.<sup>68,71,83,84</sup> Doppler signal was also associated with other clinical measures accepted for assessment of SpA disease activity (CRP, heel pain, patient VAS for pain and global disease activity evaluation, number of swollen joints and BASDAI question 3), but not with axial question of BASDAI, it even had a negative association with spine pain (BASDAI question 2). The association with the number of swollen joints, BASDAI question 3 and CRP is in agreement with the idea that bursal-synovial specific factors could trigger innate immune responses and may be pivotal players in the phenotypic expression of SpA, as suggested by the synovio-entheseal complex concept proposed by McGonagle and colleagues.<sup>29,32,39</sup> In this sense, and supporting the idea of the importance of the participation of the synovial bursal tissue in enthesitis damage, previous reported data have demonstrated that erosions typically occur in the bursal proximal portion of the enthesitis in SpA patients, possibly establishing a link between these lesions.<sup>110,113</sup> Therefore, after analyzing the available data in our cohort of patients our study effectively can conclude that the entheseal bursa can be seen in other pathologies than in SpA. Although, bursa has some power to discriminate between SpA and other diseases, mainly if is used in combination with other elementary lesions. Moreover, its correlation with other activity parameters makes it a significant injury to be included in future scores of disease activity; for monitoring response to treatment purposes, and to be included in the definition of enthesitis.

In general, patient disease activity assessment is always difficult, particularly in SpA. The concept of disease activity, a reflection of the underlying inflammation, encompasses a wide range of measures and domains. To its assessment we can use both the patient and the physician's perspectives, single disease activity parameters (e.g., ESR or CRP) or a composite index. Probably, a disease activity composite index can capture multiple important aspects of disease activity and better represent the truth. In general, and referring to the OMERACT initiative, such indices should be

truthful, discriminative and feasible.<sup>114</sup> The BASDAI is an example of an expected based index, composed by six domains (fatigue, back pain, peripheral joint pain and swelling, enthesitis, and severity and duration of morning stiffness) with a high level of face validity, but represents only the subjective perspective of the patient. Nonetheless, BASDAI is probably the most commonly used score in clinical practice, and for therapeutic guidance in SpA.<sup>115</sup> In order to reduce the well-known limitations of subjective components based in the patient perspective – or currently used indices, such as BASDAI – ASAS has developed ASDAS (statistically derived in analogy with the development of DAS in RA), focusing on the hypothesis that a better selection of patient perspective components and an objective laboratory parameter could improve the composite score.<sup>116</sup> Based on feasibility, the ASAS membership selected the ASDAS version, which included back pain, duration of morning stiffness, patient global assessment, peripheral joint complaints and CRP as the preferred version. The entheses, one of the more important targets in the pathogenesis of SpA, are undervalued in the assessment of disease activity. The inclusion of entheses as an outcome in SpA patients is represented in BASDAI as question 4, but not in ASDAS. However, ASAS core set for clinical record keeping and for disease-controlling anti-rheumatic treatments validated enthesitis score, such as MASES, San Francisco and Berlin.<sup>117</sup> Furthermore, it is consensual that clinical examination lacks sensitivity and specificity for enthesitis detection; and that imaging technics, such as ultrasound, can be efficiently used for this purpose. This is the reason why in recent years a large number of studies have been published on ultrasound enthesal alterations in SpA diseases.<sup>118-121</sup> Activity in SpA patients is probably related with at least three aspects: axial, synovial and entheses involvement. Whatever composite score used as an outcome in SpA should include these domains. The fourth study of this thesis (part IV) explored new perspectives, not previously reported, about construct validity of entheses ultrasound as a possible activity outcome in SpA.<sup>122</sup> The question remains of how are ultrasound findings related with other well-known measures of disease activity, and its relevance. In this sense, our results were exciting because they showed that basal ESR and CRP are higher in patients with Doppler signal in entheses, and even that higher basal ESR, CRP and ASDAS predicted a higher Doppler signal (an ultrasound alteration accepted as representative of inflammation) six months later. This seems to

represent a connection between classical biochemical or immunological aspects associated with inflammation and Doppler signal, not only at the same time, but also for the following months. Patients with higher values of ESR and CRP had also higher total Achilles score at basal visit, six and twelve months examinations; this could be a predictor of worst prognosis in these patients, as the score included also structural damage lesions. The same correlation was also established at baseline in patients with higher levels of ASDAS; and, remarkably, patients with inactive disease (ASDAS < 1.3) at baseline had no Doppler signal at six and twelve months. Furthermore, Doppler signal at basal visit predicted a higher total ultrasound score at six and twelve months. These findings reinforce the potential use of ultrasound related techniques for disease progression assessment and prognosis purposes. Nonetheless, BASDAI didn't show significant differences between different cut-offs concerning ultrasound lesions or Doppler signal, while verified with ASDAS. These results seem to indicate that ASDAS reflects better than BASDAI what happens in the enthesis. In conclusion, Doppler seems to be a valid tool to assess enthesal inflammation in SpA patients, and has significant correlation with other commonly used disease activity measures. As a status measure, it seems that ASDAS better reflects the enthesal inflammatory disease process in SpA than BASDAI. Our last study strengthens the construct validity of enthesis ultrasound and provides further evidence that enthesis ultrasound could be a useful tool for disease assessment in patients with SpA. Therefore local promotion of this technique constitutes a medical intervention that is worth being tested in SpA patients for diagnosis, monitoring and prognosis purposes.

## CONCLUSION

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In the last decade ultrasound has been shown to be remarkably attractive in the evaluation of rheumatic diseases. Nevertheless, it is with some surprise that this technique continues to be ignored by many physicians. The independence that it provides in assisting diagnosis, as well as in the practice of ultrasound guided procedures, makes it a unique technique. Perhaps as disadvantage, we can consider the operator dependency and the relatively long learning process, when compared with other techniques. Similarly to Fernando Pessoa *Coke* description, I can define it as: *"First you find it strange. Then you cannot get enough of it."* or, in a good Portuguese way, *"Primeiro estranha-se. Depois, entranha-se"*. This slogan led to the banning of Coca-Cola by the Portuguese authorities, for about 50 years, allegedly for being a product capable of creating addiction. The expression still in use today and it is just a small slice of the masterpiece left by Fernando Pessoa.

The OMERACT definition of enthesopathy is a broad concept that includes a wide range of structural lesions found in inflammatory and degenerative diseases. With this work we intended to open new horizons in order to understand the importance of other structural entheses lesions not included in this definition, such as the enthesal bursa; but also the behavior of lesions that were empirically considered as permanent structural damage, namely the enthesal cortical erosions. In the latter case, with the demonstration of the dynamic behavior of enthesal erosions in SpA patients, we not only revolutionized the classical erosion concept, but also reinforced the importance of the new bone formation in the pathophysiologic process in SpA. This work seeks to add objective data for a better definition of enthesopathy in SpA.

As physicians researchers we try to awaken consciousness towards the use of Doppler ultrasound in the assessment of patients with SpA. The SpA for many years have been forgotten at the expense of other inflammatory diseases, such as RA. Perhaps this was related with the relatively lack of therapeutic options to change the disease course, or even to efficiently improve the patient's quality of life. The increasing development of new pharmacological tools for the treatment of this condition boosted the

development of new concepts for early diagnosis, as well as the creation of new mechanisms for patients' disease assessment. This is clearly evident in new developed concepts, such as pre-radiographic AS or ASDAS. Despite the consistent data of this work supporting the use of Doppler ultrasound in the assessment of disease activity, the results obtained using just one enthesis as a model are remarkable. This fact is certainly in straight connection with the wide enthesal involvement in SpA, and the chosen enthesis. The Achilles is a complex and well-structured superficial enthesis, with excellent acoustic window, that can be easily assessable by Doppler ultrasound.

As people with dreams we hope that the work herein discussed makes some helpful contribution in the Doppler ultrasound history, underwriting towards the spread of this technique in the daily practice of rheumatology. Fernando Pessoa's *Coke* slogan could be easily applied here. My personal experience has shown me that, as time-consuming as it might be in the beginning, using Doppler ultrasound has become essential in my daily practice to the point where I "cannot get enough of it."

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## ***Muere lentamente***

*Muere lentamente quien se transforma en esclavo del hábito,  
repetiendo todos los días los mismos trayectos,  
quien no cambia de marca, no arriesga vestir un color nuevo  
y no le habla a quien no conoce.*

*Muere lentamente quien evita una pasión, quien prefiere el negro sobre blanco  
y los puntos sobre las "íes" a un remolino de emociones,  
justamente las que rescatan el brillo de los ojos,  
sonrisas de los bostezos, corazones a los tropiezos y sentimientos.*

*Muere lentamente quien no voltea la mesa cuando está infeliz en el trabajo,  
quien no arriesga lo cierto por lo incierto para ir detrás de un sueño,  
quien no se permite por lo menos una vez en la vida, huir de los consejos sensatos.*

*Muere lentamente quien no viaja, quien no lee,  
quien no oye música, quien no encuentra gracia en sí mismo.*

*Muere lentamente quien destruye su amor propio, quien no se deja ayudar.*

*Muere lentamente, quien pasa los días quejándose de su mala suerte o de la lluvia  
incesante.*

*Muere lentamente, quien abandona un proyecto antes de iniciarlo,  
no preguntando de un asunto que desconoce  
o no respondiendo cuando le indagan sobre algo que sabe.*

*Evitemos la muerte en suaves cuotas, recordando siempre que estar vivo  
exige un esfuerzo mucho mayor que el simple hecho de respirar.*

*Solamente la ardiente paciencia hará que conquistemos una espléndida felicidad.*

*Pablo Neruda*