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"DIAGNOSTIC IMAGING TECHNIQUES AND PREDICTIVE FACTORS IN SPONDYLOARTHRITIS AND PSORIATIC ARTHRITIS"

Mª CONCEPCIÓN CASTILLO GALLEGO

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- ABSTRACT

The work in this Thesis explores the role of different diagnostic imaging techniques in the characterization and early diagnosis of Spondyloarthritis and Psoriatic Arthritis and studies imaging and clinical indicators of prognosis in these diseases.

First, we studied the prevalence of bone marrow oedema on magnetic resonance imaging (MRI) in patients with axial Psoriatic Arthritis compared to patients with non-radiographic axial Spondyloarthritis and Ankylosing Spondylitis in relation to HLA-B27 status. In this study, it was shown that patients with Psoriatic Arthritis who were HLA-B27 positive had a comparable amount of inflammatory burden to patients with Ankylosing Spondylitis.

Using ultrasound, several studies were performed in relation to the enthesis. Firstly, focused in the ultrasound assessment of the retro-calcaneal bursa at the Aquilles enthesis showing that this is a commonly affected entheseal site in early Spondyloarthritis when compared to healthy individuals. Secondly, we demonstrated the utility of Doppler ultrasound in the assessment of disease activity in patients with early Spondyloarthritis and as an objective outcome measure for enthesitis. Finally, we explored the role of ultrasound in the assessment of the sacroiliac joints in patients with Spondyloarthritis, demonstrating its usefulness in the detection of active sacroiliitis.

Nail involvement in psoriasis is associated with functional impairment. In this part of the Thesis, we explored the possible link of the nail and the underlying enthesis in two studies involving subjects affected with psoriasis and Psoriatic Arthritis. In the

first study, using high resolution ultrasound, the link between the extensor tendon and the nail, as well as the importance of enthesopathy associated with nail involvement, regardless of the presence of arthritis, are demonstrated. In the second study, optic coherence tomography (OCT), a novel non-invasive imaging technique without irradiation was used in addition to ultrasound to characterize nail involvement in psoriasis and Psoriatic Arthritis showing that OCT is a promising tool for the systematic characterization of psoriatic nail changes and suggesting its possible role as a diagnostic and outcome measure.

In the final part of this work, we sought to identify predictors of prognosis in patients with Psoriatic Arthritis and Spondyloarthritis. For this purpose, we evaluated the enthesis of patients with Psoriatic Arthritis and patients with psoriasis, all asymptomatic. We observed more inflammation in patients with psoriatic arthritis, which may help to understand the progression of the disease from the skin to the joint. Finally, we explored the long term outcome of a cohort of early oligoarthritis in which an early treatment intervention was performed, finding that at 10 years a third of subjects were in drug-free remission.

- RESUMEN

En esta tesis doctoral estudiamos diferentes técnicas de imagen para el diagnóstico y la caracterización de las Espondiloartritis y de la artritis psoriásica, así como para su diagnóstico precoz. Además, se estudian también diferentes indicadores clínicos y de imagen para poder conocer el pronóstico de estas enfermedades.

En el primer lugar estudiamos la prevalencia de edema óseo en resonancia magnética en pacientes con artritis psoriásica axial comparado con pacientes con Espondiloartritis axial no radiográfica y Espondilitis Anquilosante en relación al estatus del HLA-B27. En este estudio se demostró que los pacientes con artritis psoriásica que eran HLA-B27 positivo tenían una afectación inflamatoria comparable a de los pacientes con Espondilitis Anquilosante.

En cuanto a ecografía, hemos realizado varios trabajos en relación a la entesis. En primer lugar hemos estudiado la valoración ecográfica de la bursa retrocalcánea de la entesis aquilea en la Espondiloartritis precoz, demostrando que es una localización frecuentemente afectada en estos pacientes. En segundo lugar, hemos demostrado la utilidad de la ecografía en la valoración de la actividad de la enfermedad en pacientes con Espondiloartritis precoz y como medida objetiva de actividad de entesitis. Finalmente, hemos explorado ecográficamente las articulaciones sacroilíacas de pacientes con Espondiloartritis, demostrando su utilidad en la detección de sacroileítis activa.

La afectación ungueal en la psoriasis está asociada con discapacidad funcional. En esta parte de la tesis hemos investigado el posible vínculo ente la uña y la entesis subyacente en dos estudios en los que se incluyen pacientes con psoriasis cutánea y

pacientes con artritis psoriásica. En el primer estudio se demuestra el vínculo existente entre la entesis del tendón extensor y la uña, así como la importancia de la entesopatía asociada a afectación ungueal, independientemente de la presencia de artritis, utilizando la ecografía de alta resolución. En el segundo utilizamos, además de la ecografía, la tomografía de coherencia óptica, una novedosa técnica de diagnóstico por imagen no invasiva y sin irradiación. Los hallazgos son prometedores como técnica para la caracterización de las lesiones ungueales de los pacientes con psoriasis y sugieren su posible papel como técnica de diagnóstico y de medida de desenlace.

Como parte final de esta Tesis, hemos intentado identificar factores predictivos de la enfermedad en pacientes con Artritis Psoriásica y Espondiloartritis. Para ello valoramos ecográficamente la entesis de pacientes con artritis psoriásica y de pacientes con psoriasis, todos ellos asintomáticos. Observamos más inflamación en los pacientes con artritis psoriásica, lo cual podría ayudar a entender la progresión de la afectación cutánea a la articular. Finalmente hemos analizado los resultados de seguimiento de una Cohorte de Oligoartritis en los que se realizó una intervención precoz, encontrándose que a los 10 años un tercio de ellos se mantienen en remisión y sin tratamiento.

INDEX

- ABBREVIATIONS

ACR: American College of Rheumatology

Anti-CCP: anti-cyclic citrulined peptid

Anti-TNF: Anti tumor necrosis factor

AS: Ankylosing spondylitis

ASAS: Assessment of SpondyloArthritis international Society

ASDAS: Ankylosing spondylitis disease activity score

BASDAI: Bath ankylosing spondylitis disease activity index

BASFI: Bath Ankylosing Spondylitis Functional Index

BASRI: Bath Ankylosing Spondylitis Radiology Index

CASPAR: classification criteria for psoriatic arthritis

CD: Crohn disease

CDUS: Colour Doppler Ultrasound

CRP: C-reactive protein

DAS28: Disease activity score 28

DIP: distal interphalangeal

DIPJ: DIP joint

EULAR: European league against rheumatism

ESR: erythrocyte sedimentation rate

GS: grey-scale

GUESS: Glasgow ultrasound enthesitis scoring system

HC: healthy controls

HLA: human leucokyte antigen

Hz: herz

ICC: intraclass-correlation coefficient

IBP: inflammatory back pain

LR: likehood ratio

L-spine: lumbar spine

MASEI: Madrid Sonographic Enthesis Index

MASES: Maastricht Ankylosing Spondylitis Enthesitis Score

mNAPSI: modeified nail psoriasis severity index

MHz: megaherz

MRI: Magnetic Resonance Imaging

NAPSI: nail psoriasis severity index

NSAIDs: non-steroidal anti-inflammatory drugs

OCT: optical coherence tomography

OMERACT: Outcome Measures in Rheumatology Clinical Trials

PASI: psoriasis area and severity index

PsA: Psoriatic Arthritis

RA: Rheumatoid arthritis

RF: Rheumatoid factor

RI: resistive index

ROC: receiver operating characteristic

SSZ: sulphasalazine

SpA: Spondyloarthritis

IBD: inflammatory bowel diseases

SPARCC: spondyloarthritis research consortium of Canada

SJC: swollen joint counts

TJC: tender joint counts

TNF: tumour necrosis factor

US: ultrasound

2D: two-dimensional

3D: three-dimensional

1. INTRODUCTION

1.1. Imaging Diagnostic Techniques in Spondyloarthritis and Psoriatic Arthritis

1.1.1. MRI in the assessment of axial Psoriatic Arthritis and Spondyloarthritis

Psoriatic arthritis (PsA) is a heterogeneous disease with a variable, sometimes evolving clinical phenotype. An estimated 25–70% of patients may have spinal involvement, which varies from largely asymptomatic to severe inflammatory back pain, that may be indistinguishable from ankylosing spondylitis (AS). It is sometimes difficult to establish the presence of inflammatory back pain in patients with PsA, who generally report less pain than patients with AS (1). Previous studies have demonstrated that AS differs from axial PsA radiographically, with the latter having some distinctive features such as asymmetry, less severe structural damage, and distinctive syndesmophytes (2). The utility of magnetic resonance imaging (MRI) in the diagnosis and assessment of spinal disease in AS and non-radiographic axial SpA is now well proven (3). However, data are sparse on spinal MRI in non-radiographic axial SpA, and it is unclear whether MRI appearances of spinal involvement differ between patients with nonradiographic axial SpA or AS and patients with PsA-related spondylitis (4).

HLA–B27 shows a striking relationship with AS and is associated with the

severity of MRI-evident osteitis in the axial and peripheral skeleton (5-7). In patients with early inflammatory back pain, a combination of severe sacroiliitis and HLA–B27 has a high specificity for the future development of AS. In contrast, there is a very low likelihood that AS will develop in patients with mild or no osteitis, regardless of HLA–B27 status (8). It is also known that positive MRI findings at baseline in patients with early inflammatory back pain predict positive MRI findings during followup in HLA–B27–positive patients (9). However, it is unclear whether such a relationship between HLA–B27 and inflammation can be seen on the spine and sacroiliac (SI) joint MRI of PsA patients.

1.2. Ultrasound in Spondyloarthritis and Psoriatic Arthritis

1.2.1. Ultrasonography of the Achilles bursa in early Spondyloarthritis

The diagnosis of SpA is often made several years after the disease begins. The absence of both radiographic sacroiliitis and impaired spinal mobility at early stages of the disease contributes to the long delay (5–10 years) in the diagnosis of AS in many patients.

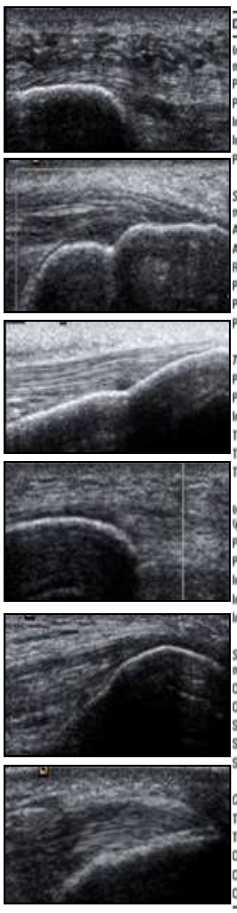
Enthesitis, inflammatory involvement of the enthesis, is a distinctive feature of SpA regarded as the primary lesion in this disease. The central importance of the enthesis in understanding SpA pathophysiology has remerged in the last decade relating structural entheseal damage with inflammation, regional microanatomy and biomechanics, and its correlation with entheseal new bone formation, and erosion (10-

13). Considering the cardinal role of enthesis 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) (14-16), 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 enthesis. Furthermore, US elemental lesions included in enthesis pathology have been described (17, 18) and consensus about definitions initiated.

The importance of enthesitis in SpA is growing, since the new ASAS classification criteria for peripheral SpA includes enthesitis as one of the three entry criteria (the other two being arthritis and dactylitis (19). It is also included in the EULAR recommendation for psoriatic arthritis management (20), 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. 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 (21). 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 (22). 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” (23). This definition includes the principal

lesions of the enthesis at bone and enthesis 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 entheseal lesions considered in the OMERACT enthesopathy definition (14-16, 24-26).

We have previously developed and validated an enthesis US score index, the MASEI (**M**adrid **S**onographic **E**nthesis **I**ndex) that includes de Achilles bursa, see figure 1 (24).



Data	Value
Inferior pole of the calcaneus: plantar aponeurosis enthesis	
Plantar aponeurosis structure	(0 or 1)
Plantar aponeurosis thickness >4.4 mm	(0 or 1)
Inferior pole of calcaneus erosion	(0 or 3)
Inferior pole of calcaneus enthesis calcification	(0, 1, 2 or 3)
Plantar aponeurosis enthesis power Doppler	(0 or 3)
Superior pole of the calcaneus: Achilles tendon enthesis	
Achilles tendon structure	(0 or 1)
Achilles tendon thickness >5.29 mm	(0 or 1)
Retrocalcaneal bursitis	(0 or 1)
Posterior pole of calcaneus erosion	(0 or 3)
Posterior pole of calcaneus enthesis calcification	(0, 1, 2 or 3)
Posterior pole of calcaneus power Doppler	(0 or 3)
Tibial tuberosity: distal patellar ligament enthesis	
Patellar ligament structure	(0 or 1)
Patellar ligament thickness >4 mm	(0 or 1)
Infrapatellar bursitis	(0 or 1)
Tibial tuberosity erosion	(0 or 3)
Tibial tuberosity enthesis calcification	(0, 1, 2 or 3)
Tibial tuberosity enthesis power Doppler	(0 or 3)
Inferior pole of the patella: proximal patellar ligament enthesis	
Patellar ligament structure	(0 or 1)
Patellar ligament thickness >4 mm	(0 or 1)
Inferior pole of patella erosion	(0 or 3)
Inferior pole of patella enthesis calcification	(0, 1, 2 or 3)
Inferior pole of patella enthesis power Doppler	(0 or 3)
Superior pole of the patella: quadriceps tendon enthesis	
Quadriceps tendon structure	(0 or 1)
Quadriceps tendon thickness >6.1 mm	(0 or 1)
Superior pole of patella erosion	(0 or 3)
Superior pole of patella enthesis calcification	(0, 1, 2 or 3)
Superior pole of patella enthesis power Doppler	(0 or 3)
Olecranon tuberosity: triceps tendon enthesis	
Triceps tendon structure	(0 or 1)
Triceps tendon thickness >4.3 mm	(0 or 1)
Olecranon erosion	(0 or 3)
Olecranon enthesis calcification	(0, 1, 2 or 3)
Olecranon enthesis power Doppler	(0 or 3)

Figure 1 Images on the left: ultrasonographic appearance of entheseal insertions, from the top: plantar aponeurosis insertion, calcaneal Achilles tendon insertion, distal patellar enthesis, proximal patellar enthesis, quadriceps tendon enthesis, triceps tendon enthesis. On the right side, The MASEI: ach item scores one point, except for calcification (0, 1, 2 or 3) and erosion and Doppler signal (0 or 3). The total possible score on both sides (12 entheses) is 136. Sensitivity 83.3%, specificity 82.8%, positive predictive value 80.8%, negative predictive value 85.7%, positive likelihood ratio (LR+) 4.87, negative likelihood ratio (LR-) 0.19

In fact, bursa was included in 46% of enthesis studies in a recently systematic literature review (17). This is in agreement with the concept of "synovio-entheseal 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 enthesis with neighbouring bone, but also the connection between enthesitis and synovitis (12, 13, 27-29). 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 entheseal lesion, and is often mistaken for sport and overuse pathology (30).

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. In this sense, knowledge of which entheseal US lesions are related to other SpA disease activity outcomes could be relevant.

In this Thesis work we use two-dimensional (2D), in grey scale and Doppler, and three-dimensional (3D) US to assess the prevalence and relevance of the bursa-synovial lesión in SpA, using as model the Achilles enthesis. We also determine the construct validity of enthesis US in the assessment of disease activity in SpA.

1.2.2. Ultrasonography of the Sacroiliac Joints in Spondyloarthritis

Sacroiliac joint (SIJ) involvement is a distinctive and characteristic feature of SpA. The diagnosis of AS relies on a combination of clinical symptoms with

unequivocal radiographic sacroiliitis (31). X-ray radiography reveals structural damage caused by inflammation but cannot detect active inflammatory lesions, and the diagnosis of AS is commonly delayed by an average of 6–9 years after the onset of symptoms (32, 33). Moreover, at 10 years from the first presentation of the disease, 25–35% of patients still do not have radiographic sacroiliitis (3). Therefore, new imaging techniques are required for the early diagnosis and assessment of inflammatory activity in SpA.

In the last decade, MRI has been increasingly used to visualize inflammation in the SIJs, and it has now been included in the new ASAS criteria for the classification of axial SpA (34). It has become clear in recent years that active inflammatory lesions are visible on MRI long before definite lesions on plain radiographs are detectable (8). Although MRI can shorten the interval between the onset of symptoms and the radiographic diagnosis of sacroiliitis, the availability of MRI is limited in many countries, and the technique is relatively time-consuming and cost-intensive.

Enthesis ultrasound has demonstrated that it is useful for discriminating patients with long-standing SpA from those with early SpA (14, 24, 35, 36). However, even in a less explored field, such as inflammation in the SIJs, US can be used by applying different methods, including grayscale or colour Doppler ultrasound (CDUS), spectral Doppler resistive index (RI) and contrast-enhanced media (37-43).

Thus far, there have been very few studies published assessing active inflammatory lesions in the SIJs using ultrasound.

In this Thesis work we study the validity of CDUS, compared to physical examination as the gold standard, in the assessment of active inflammation of the SIJs in patients with SpA.

1.2.3. Ultrasonography of the Nail and the extensor tendon enthesis

The importance of nail disease in subjects with psoriasis is being increasingly recognised (44). Clinically, nail disease is associated with pain, functional loss, disfigurement and psychological distress (45). From the rheumatological perspective, the presence of nail disease is a predictor for the development of PsA (46). In PsA patients, nail disease is associated with arthritis of the distal interphalangeal (DIP) joint (47, 48). The nail is directly anchored to the underlying bone by structures including the extensor tendon (49-51). Enthesopathy is a generalised feature of both psoriasis and PsA and we have recently demonstrated that in psoriasis patients, nail disease is associated with a greater degree of systemic enthesopathy (52) (see figure 2).

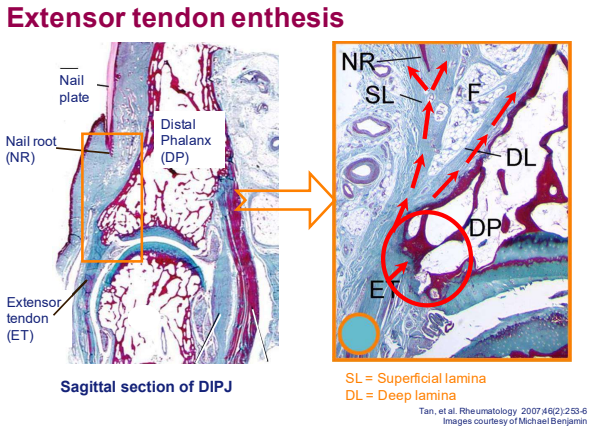


Figure 2 This is the extensor tendon enthesis on histology. We see that the extensor tendon is not only attached to the dorsal aspect of the base of the distal phalanx, but also extended more distally as the superficial lamina of dense fibrous connective tissue to connect with the nail root. A further deep lamina forms a thick periosteum on the distal phalanx

Presently, assessment of nail disease is difficult given the limited utility of clinical assessment tools for the nail, which include the nail psoriasis severity index

(NAPSI) and the modified NAPSI (mNAPSI) (53, 54). Recently MRI, ultrasonography (US) and optical coherence tomography have been reported as possible tools for a more objective assessment of nail disease (55-58). US has wide availability in the rheumatology setting, modest costs, a high resolution and allows good visualisation of tendons and entheses. With respect to the nail matrix region, we were especially interested to determine whether US had the capability to detect local DIP joint enthesopathy in PsA and psoriasis patients. No USbased imaging study of the nail has considered the matrix region before.

Therefore in this Thesis work we assess the utility of US for the assessment of psoriatic nail disease including both the nail plate and nail matrix region.

1.3. OCT and US in the assessment of nail disease in Psoriasis and Psoriatic Arthritis

Nail disease represents both a clinically and pathophysiologically important aspect of both psoriasis and PsA. In psoriasis, nail involvement may be associated with significant pain and functional impairment (45). The pathogenesis of several matrix and plate lesions including pitting, leuconychia and onycholysis is still not clearly defined. The historical difficulties in assessing treatments for nail psoriasis have in part stemmed from the lack of objective assessment tools, as well as the duration of treatment needed to see a response. Currently these lesions may be clinically scored and evaluated using the Nail Psoriasis Severity Index (NAPSI) or the modified NAPSI (mNAPSI) system (53, 54).

The advent of biological therapies which effectively treat psoriasis, PsA and nail disease has further heightened the importance of understanding nail involvement. Nail disease scores are one of the outcome measures used to assess the success of therapy, and therefore it is important to have a measure which is objective and sensitive to change. From the rheumatological viewpoint, nail disease is important since it is a predictor of future PsA development (46). Nail disease is also more common in PsA compared to psoriasis without arthritis (59-62). The basis for this observation has now become more clear as entesitis (inflammation at tendon and ligament insertions) has been shown to be a key feature of the skeletal manifestations of PsA (63, 64). It has been suggested that the normal nail is anchored to the skeleton via a network of entheses (50). Patients with nail disease also have more subclinical enthesitis both at the distal interphalangeal joint level as well as at remote sites (52, 65), although the link between the different patterns of nail disease and subclinical entesitis remains enigmatic (66, 67). A combination of these dermatological and rheumatological issues has led to an increased interest in imaging of the nail to better understand disease mechanisms.

Our group previously used both conventional and high-resolution MRI to image nail disease and to show that the nail is functionally integrated with the skeleton, as outlined above (68, 69). Whilst MRI is good for demonstrating the bone and soft tissues around the nail, the nail itself is very poorly visualised due to its low water content. Several studies have reported the use of US in nail evaluation. Given the accessibility and low cost of US, it may become the method of choice for nail disease evaluation (56, 65, 70, 71). Nevertheless, there is a need for improved nail imaging techniques for making a diagnosis, understanding disease mechanisms and monitoring the response to

therapy.

Recently our group reported on our preliminary experience with optical coherence tomography (OCT) for the assessment of nail disease in psoriasis (55). The accuracy of OCT for measuring nail thickness has previously been reported (57). OCT is a non-invasive optical imaging technique that has the advantage of incredibly high spatial resolution compared to other clinically available methods. It is already in dermatological use for the assessment of skin tumours (72-75).

Figure 3 Image of an OCT machine (Michelson Diagnostics, Orpington, UK)

Figure 4 Image of the OCT probe used (VivoSight Topical OCT probwe (multibeam frequency-domain type OCT with a central wavelength of 1,305nm and a sweep range of 150nm

As the light-based analogue of US pulse-echo imaging, OCT systems focus a

low-intensity infrared beam in tissue and analyse scattered light to provide tomograms and 3D volumes of morphology up to 2 mm below the surface. While ophthalmic OCT has been in use since the early 1990s, advanced laser technology and multibeam modalities have enabled the development of high-speed and ultra-highsensitivity 'frequency-domain OCT' which provides the superior contrast necessary to create dermatological images with <10 μm resolution at video rate (76, 77).

In this Thesis work we compare OCT and US of the nail to ascertain which of them is the best imaging modality and how they compare to clinical assessment. We also describe in detail the anatomical location of the different psoriasis-associated nail lesions.

1.4. Predictive Factors in Spondyloartrhitis and Psoriatic Arthritis

1.4.1. Association between enthesitis and nail disease in Psoriatic Arthritis

Psoriasis affects approximately 2% of the population and up to 30% of these will develop PsA (78-81). As dermatologists usually see patients with psoriasis before arthritis develops they are well placed to diagnose PsA early. Now that effective therapies for the suppression of PsA exist, the early recognition of PsA has important consequences for optimal patient management.

Currently, the conceptual basis for the link between psoriasis and nail disease and subsequent PsA is poorly understood. It has been suggested that enthesitis is the

primary lesion that underscores the diverse skeletal manifestations of PsA (82). It has also been demonstrated that subclinical enthesopathy and associated osteitis is present in up to 50% of patients with psoriasis with no arthritis (46, 83, 84). Another stream of research has shown that the presence of nail disease is a harbinger for the future development of PsA (46). These findings are noteworthy because it has been shown that psoriatic nail disease in PsA is intimately associated with enthesopathy of the distal interphalangeal joint and that the nail is functionally integrated with the enthesis (49, 50, 69).

During the past decade it has emerged that enthesitis and associated osteitis are the common denominators underlying the multifaceted skeletal manifestations of PsA that include axial and appendicular disease (63). In keeping with the importance of enthesitis as the key pathological lesion in PsA, some studies have shown enthesopathy in asymptomatic large insertions of the lower limbs in patients with SpA including PsA (15). This is reminiscent of studies in inflammatory oligoarthritis, in which US detected synovitis in joints that were clinically uninvolved (85). Of even greater importance is that several studies have shown subclinical enthesopathy or osteitis in up to 50% of psoriasis patients with no skeletal symptoms (84).

These combined clinical and imaging observations suggest that there may be a link between systemic enthesopathy and psoriatic nail disease. Therefore, we posed the question as to whether nail disease in psoriasis is linked to a greater degree of systemic enthesopathy compared with psoriasis patients without nail disease in a previous study (52). In that study, we confirm that enthesopathy is common in psoriasis patients without clinical arthritis. Moreover, subclinical enthesopathy is especially associated

with nail involvement in a cross-sectional analysis. Those findings suggested that nail disease is in some way linked to the expression of enthesitis including subclinical disease.

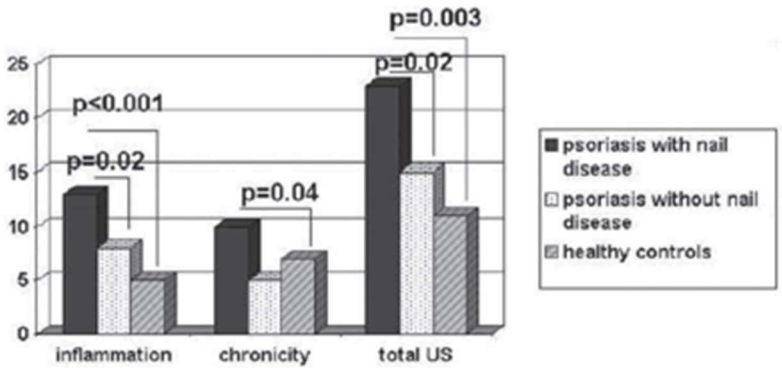


Figure 5 Comparison of median US scores related to inflammation and chronicity in psoriasis patients with and without nail disease and healthy controls:

Figure 6 Photograph of a thumb nail of a patient with psoriasis, showing onycholysis and an oil drop spot

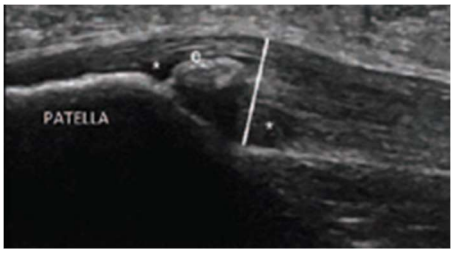


Figure 7 Longitudinal US scan of the origin of the patellar tendon of the same patient showing severe thickening (White line 0.7mm), hypoechogenicity (*) and a large enthesophyte

Ultrasonography is well suited to the assessment of entheses and is able to depict soft tissue thickening and oedema in addition to new bone formation and erosions (23). In recent years, power Doppler (PD) ultrasonography has been increasingly used in rheumatology as it identifies vascular abnormalities known to be associated with inflammation. PD ultrasound to some extent provides a reflection of the degree of angiogenesis, which is critically related to joint damage and therapeutic responses to drugs (86-88). An extra-articular PD signal has been demonstrated in both PsA and psoriasis patients (89-91). However, there is limited work directly comparing PD changes at the insertions between patients with PsA and psoriasis. Such a link would offer a novel unifying concept for nail disease, systemic enthesopathy and the future development of PsA.

The purpose of this part of the Thesis work is to undertake ultrasonography of symptomatic and asymptomatic insertions in cases with PsA and cases with psoriasis, the latter having no clinical arthritis. The hypothesis tested was that the imaging phenotypes might differ between PsA patients and psoriasis cases without clinical arthritis. In particular, we hypothesised that the enthesopathy associated with PsA would have a greater degree of vascularisation compared to that seen in psoriasis without arthritis. We also postulated that subclinical vascular changes at the entheses might be associated with more widespread disease activity in PsA. Such an imaging biomarker could be helpful in understanding and predicting the disease evolution from psoriasis to PsA, which at the present time is not fully understood.

1.4.2. Predictors of outcome in Oligoarthritis and Spondyloarthritis

Oligoarthritis is an inflammatory arthritis affecting ≤4 joints (92, 93). It represents either an early clinical presentation or a unique disease phenotype within the conditions collectively termed the seronegative spondyloarthropathies. Oligoarthritis typically affects young people causing high morbidity (94, 95) and it may have a variable outcome although long term follow up data are sparse (96-98).

The majority of published studies have only reported on short/middle term outcomes. Some reports have described as many as 75% of patients with ReA having persistent disease at 6 months (96), whereas other cohort studies have suggested rates of persistence as low as 15%. In our first study, at 12 months of follow up, 51% of patients satisfied criteria for complete response (absence of synovitis) (92). In the second study, at 12 months, up to 81% of the patients in the early intervention group had no clinical evidence of synovitis compared with 57% of the patients in the conservative group (93). Both reports indicated a significant benefit from an early intervention protocol in the short term, with better results in the second study, suggesting that this may have been due to the early use of sulphasalazine (SSZ) as a DMARD.

As part of the Thesis work, we aim to assess the long term follow up of these patients. We were interested in particular, to assess the prognostic role of an early intervention.

2. HYPOTHESIS

1. HLA–B27 status determines the severity of bone marrow oedema lesions in PsA patients with inflammatory back pain. A link between bone marrow oedema and HLA–B27 in axial PsA would have implications both for an improved understanding of the disease process and for MRI interpretation in the clinical setting.

2. The bursa-synovial of the Achilles enthesis is a relevance lesion in SpA and it US examination can be useful in the assessment of disease activity in early SpA.

3. CDUS can be a useful tool in the assessment of active inflammation of the SIJs in patients with SpA.

4. Nail involvement is specifically linked to extensor tendon enthesopathy.

5. The US imaging phenotypes might differ between PsA patients and psoriasis cases without clinical arthritis. In particular, we hypothesise that the enthesopathy associated with PsA will have a greater degree of vascularisation compared to that seen in psoriasis without arthritis. We also postulate that subclinical vascular changes at the entheses might be associated with more widespread disease activity in PsA. Such an imaging biomarker could be helpful in understanding and predicting the disease evolution from psoriasis to PsA, which at the present time is not fully understood.

6. An early treatment intervention in an Early Oligoartrhitis Cohort should lead to a better long term prognosis.

3. OBJECTIVES

The main objectives of this Thesis work are:

1. To determine the prevalence, on MRI, of bone marrow oedema lesions in symptomatic axial PsA, and to compare this prevalence with that in nonradiographic axial SpA and ankylosing spondylitis (AS) and its relationship to HLA–B27 status.
2. To assess the prevalence and relevance of the bursa-synovial lesion in SpA and to evaluate the construct validity of enthesis US in the assessment of disease activity in early SpA.
3. To assess the validity of CDUS in SIJ in SpA.
4. To investigate the nail plate, nail matrix and adjacent tendons in subjects with psoriatic nail disease with ultrasonography and to compare those findings with OCT images.
5. To test the hypothesis that subclinical enthesopathy in PsA was associated with an 'inflammatory' or vascular phenotype compared to that seen in psoriasis using ultrasonography with power Doppler (PD).
6. To report the long-term outcome in the Leeds Early Oligoarthritis Cohort and to assess the prognostic role of an early treatment intervention in these patients.

4. OVERVIEW

Research hypothesis	Aims	Theme	Page	Publication
1. HLA–B27 status determines the severity of bone marrow oedema lesions in PsA patients with inflammatory back pain	1. To determine the prevalence, on MRI of bone marrow oedema lesions in symptomatic axial PsA and its relationship to HLA–B27 status	MRI in the assessment of axial psoriatic arthritis and spondyloarthritis	34	1.Magnetic Resonance imaging assessment of axial psoriatic arthritis: extent of disease relates to HLA-B27. **Castillo-Gallego C**, Aydin SZ, Emery P, McGonagle DG, Marzo-Ortega H. Arthritis Rheum. 2013 Sep;65(9):2274-8
2. The bursa-synovial of the Achilles enthesis is a relevant site of disease in SpA and its characterization using US may be of value in the assessment of disease activity in SpA	2.1 To assess the prevalence and relevance of the bursa-synovial lesion in SpA	US in Spondyloarthritis and Psoriatic Arthritis	42	2. Can we use enthesis ultrasound as an outcome measure of disease activity in spondyloarthritis? A study at the Achilles level. Falcao S, **Castillo-Gallego** C, Peiteado D, Branco J, Martín Mola E, de Miguel E. Rheumatology (Oxford). 2015 Sep;54(9):1557-62
	2.2 To evaluate the construct validity of enthesis US in the assessment of disease activity in SpA	US in Spondyloarthritis and Psoriatic Arthritis	51	3. Achilles enthesis ultrasound: the importance of the bursa in spondyloarthritis. Falcao S, de Miguel E, **Castillo-Gallego C,** Peiteado D, Branco J, Martin Mola E. Clinical Experimental Rheumatology, 2013 May-Jun; 31(3): 422-7
3. Colour Doppler US can be a useful tool in the assessment of active inflammation of the SIJs in patients with SpA	3. To assess the validity of Colour Doppler US in the SIJ	US in Spondyloarthritis and Psoriatic Arthritis	59	4. Colour Doppler and spectral Doppler ultrasound detection of active sacroiliitis in spondyloarthritis compared with physical examination. **Castillo-Gallego C**, De Miguel E, García-Arias M, Plasencia Ch, Lojo-Oliveira L, Martín-Mola E. Rheumatology International (submitted, under revision)
4. Nail involvement is specifically linked to extensor tendon enthesopathy	4. To investigate the nail plate, matrix and adjacent tendons in subjects with psoriatic nail disease	US in the assessment of nail disease in Psoriasis and Psoriatic Arthritis	79	5. Ultrasonographic Assessment of nail in Psoriatic Disease Shows a Link Between Onychopathy and Distal Interphalangeal Joint Extensor Tendon Enthesopathy. Aydin SZ, **Castillo-Gallego C**, Ash ZR, Marzo-Ortega H, Wakefield RJ, Wittmann M, McGonagle D. Dermatology 2012 nov; 225: 231-235
		OCT and US in the assessment of nail disease in Psoriasis and Psoriatic Arthritis	89	6. Potential use of optical coherence tomography and high-frequency ultrasound for the assessment of nail disease in psoriasis and psoriatic arthritis. Aydin SZ, **Castillo-Gallego** C, Ash ZR, Abignano G, Marzo-Ortega H, Wittmann M, Del Galdo F, McGonagle D. Dermatology. 2013;227(1):45-51
5. The US imaging phenotypes might differ between PsA patients and psoriasis cases without clinical arthritis.	5. To test the hypothesis that subclinical enthesopathy in PsA is associated with an 'inflammatory' or vascular phenotype compared to that seen in psoriasis using ultrasonography with PD	Predictive factors in Psoriatic Arthritis and Spondyloarthritis	101	7. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. Aydin SZ, As ZR, **Castillo-Gallego C**, Kwok C, Wilson C, Goodfield M, Gisondi P, Tan AL, Marzo-Ortega H, Emery P, Wakefield RJ, McGonagle DG. Annals of Rheumatic Diseases 2013 Jun;72(6):992-5
6. An early intervention assess in early Oligoarthritis Cohort should lead to a better prognosis in the future	6. To report the long-term outcome of the Leeds Early Oligoarthritis Cohort and to assess the prognostic role of an early intervention in these patients	Predictive factors in Psoriatic Arthritis and Spondyloarthritis	118	8. Long Term follow up of an early Oligoarthritis cohort shows that early aggressive intervention leads to drug free remission after 10 years: results from the LoTO study. **Castillo-Gallego C**, Green MJ, Aydin SZ, Nizam S, Emery P, Marzo-Ortega H. International Journal of Clinical Rheumatology 2017: 12(2), 012-015 ISSN 1758-4272

5. PUBLICATIONS

5.1. MRI in the assessment of axial Psoriatic Arthritis and Spondyloarthritis

5.1.1. ARTICLE 1

TITLE: *"*Magnetic Resonance imaging assessment of axial psoriatic arthritis: extent of disease relates to HLA-B27"

JOURNAL: Arthritis and Reumatism, 2013 Sep; 65(9): 2274-8

AUTHORS: Castillo-Gallego C, Aydin SZ, Emery P, McGonagle, Marzo-Ortega H.

The aim of this study was to determine the prevalence, on MRI, of bone marrow oedema lesions in symptomatic axial PsA, and to compare this prevalence with that in non-radiographic axial SpA and AS and its relationship to HLA–B27 status.

5.1.1.1. PATIENTS AND METHODS

5.1.1.1.1. MRI scan selection procedure

The study was a cross-sectional audit of MRI scans of the lumbar spine (L-spine) and SI joints performed consecutively between May 2007 and February 2011 in the Rheumatology department of a large teaching hospital, to reflect service development. MRI scans were requested for diagnostic purposes in symptomatic patients with inflammatory back pain and a background clinical suspicion or diagnosis of PsA, non-radiographic axial SpA, or AS. Eligible scans were retrieved from the

hospital intranet computer system for scoring. The audit had the approval of the local governance committee.

5.1.1.1.2. Patient groups

The clinical diagnosis according to the requesting clinician, HLA–B27 status, and demographic data were retrieved from the clinical notes. Subjects were categorized into 3 groups: patients with PsA (patients meeting the Classification of Psoriatic Arthritis Study Group criteria), patients with nonradiographic axial SpA (patients fulfilling the ASAS criteria for axial SpA but not the modified New York criteria for AS), and patients with AS (patients fulfilling the modified New York criteria for AS).

5.1.1.1.3 MRI scoring

MRI scans were scored independently by 2 expert readers (HMO and DGM) who were blinded to the clinical characteristics of the patients. The readers used the semiquantitative Leeds Scoring System for bone marrow oedema lesions representative of inflammation in the spine and SI joints. This scoring system allows for estimation of the severity of a lesion by combining the concepts of extent and intensity in one definition with lesions ranked on a scale of 0–3 as described by the Leeds MRI Scoring Index. A lesion graded as severe (grade 2) is considered clinically significant. For analysis, concordant data from the 2 readers were used to report on definite lesions. An overall score for inflammatory activity was calculated as the sum of bone marrow oedema scores.

5.1.1.1.4 Statistical analysis

Data are expressed either as frequencies or as the median and range. The total

MRI scores of the 3 different groups of patients and patients with or without HLA–B27 were compared using the Mann-Whitney U test. The prevalences of severe MRI lesions (grade 2) were compared using the chi-square test. Statistical analysis was performed using SPSS software, version 11.5.

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BRIEF REPORT

Magnetic Resonance Imaging Assessment of Axial Psoriatic Arthritis: Extent of Disease Relates to HLA–B27

Concepción Castillo-Gallego, Sibel Z. Aydin, Paul Emery, Dennis G. McGonagle, and Helena Marzo-Ortega

Objective. **To determine the prevalence, on magnetic resonance imaging (MRI), of bone marrow edema lesions in symptomatic axial psoriatic arthritis (PsA), and to compare this prevalence with that in nonradiographic axial spondyloarthritis (SpA) and ankylosing spondylitis (AS) and its relationship to HLA–B27 status.**

Methods. **We performed a cross-sectional audit of MRI scans of lumbar spine (L-spine) and sacroiliac (SI) joints. Using the semiquantitative Leeds Scoring System in which bone marrow edema is graded from 0 to 3 according to severity of the lesions, MRI scans were scored independently by 2 expert readers who were blinded to the clinical characteristics of the patients. Concordant data from the 2 readers were used to report on definite lesions.**

Results. **MRIs from 76 patients with comparable age ranges were categorized into 3 groups: those from PsA patients, those from patients with nonradiographic axial SpA, and those from AS patients. HLA–B27 positivity was similar in PsA patients (10 of 33) and patients with nonradiographic axial SpA (10 of 24) and higher in AS patients (18 of 19). Total MRI scores (L-spine plus SI joints) were higher in AS patients than in PsA patients ($P = 0.025$) or in patients with nonradiographic axial SpA ($P = 0.007$). A relationship was seen between the severity and extent of disease and HLA–B27 positivity in PsA patients, which was comparable to that in AS patients. HLA–B27–negative PsA patients had lower MRI scores than HLA–B27–positive PsA patients ($P = 0.03$) and AS patients ($P = 0.006$), whereas scores were similar in HLA–B27–positive PsA patients and AS patients. Similarly, MRI scores of HLA–B27–negative patients with nonradiographic axial SpA were lower than those of AS patients ($P = 0.01$).**

Conclusion. **HLA–B27 positivity defines a group of patients with more severe axial bone marrow edema that is likely related to the classic AS phenotype. Clinically, HLA–B27–negative PsA is more likely to be reported as a "negative" MRI examination result.**

Psoriatic arthritis (PsA) is a heterogeneous disease with a variable, sometimes evolving clinical phenotype. An estimated 25–70% of patients may have spinal involvement, which varies from largely asymptomatic to severe inflammatory back pain, that may be indistinguishable from ankylosing spondylitis (AS). It is sometimes difficult to establish the presence of inflammatory back pain in patients with PsA, who generally report less pain than patients with AS (1). Previous studies have demonstrated that AS differs from axial PsA radiographically, with the latter having some distinctive features such as asymmetry, less severe structural damage, and distinctive syndesmophytes (2). The utility of magnetic resonance imaging (MRI) in the diagnosis and assessment of spinal disease in AS and nonradiographic axial spondyloarthritis (SpA) is now well proven (3). However, data are sparse on spinal MRI in nonradiographic axial SpA, and it is unclear whether MRI appearances of spinal involvement differ between patients with nonradiographic axial SpA or AS and patients with PsA-related spondylitis (4).

HLA–B27 shows a striking relationship with AS and is associated with the severity of MRI-evident

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Dr. Aydin has received speaking fees from Abbott and Pfizer (less than $10,000 each).

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osteitis in the axial and peripheral skeleton (5–7). In patients with early inflammatory back pain, a combination of severe sacroiliitis and HLA–B27 has a high specificity for the future development of AS. In contrast, there is a very low likelihood that AS will develop in patients with mild or no osteitis, regardless of HLA–B27 status (8). It is also known that positive MRI findings at baseline in patients with early inflammatory back pain predict positive MRI findings during followup in HLA–B27–positive patients (9). However, it is unclear whether such a relationship between HLA–B27 and inflammation can be seen on the spine and sacroiliac (SI) joint MRI of PsA patients.

The aim of this study was to test the hypothesis that HLA–B27 status determines the severity of bone marrow edema lesions in PsA patients with inflammatory back pain. A link between bone marrow edema and HLA–B27 in axial PsA would have implications both for an improved understanding of the disease process and for MRI interpretation in the clinical setting.

PATIENTS AND METHODS

MRI scan selection procedure. The study was a cross-sectional audit of MRI scans of the lumbar spine (L-spine) and SI joints performed consecutively between May 2007 and February 2011 in the rheumatology department of a large teaching hospital, to reflect service development. MRI scans had been requested for diagnostic purposes in symptomatic patients with inflammatory back pain and a background clinical suspicion or diagnosis of PsA, nonradiographic axial SpA, or AS. Eligible scans were retrieved from the hospital intranet computer system for scoring. The audit had the approval of the local governance committee.

Patient groups. The clinical diagnosis according to the requesting clinician, HLA–B27 status, and demographic data were retrieved from the clinical notes. Subjects were categorized into 3 groups: patients with PsA (patients meeting the Classification of Psoriatic Arthritis Study Group criteria [10]), patients with nonradiographic axial SpA (patients fulfilling the Assessment of SpondyloArthritis international Society criteria for axial SpA [11] but not the modified New York criteria for AS [12]), and patients with AS (patients fulfilling the modified New York criteria for AS).

MRI scoring. MRI scans were scored independently by 2 expert readers (HMO and DGM) who were blinded to the clinical characteristics of the patients. The readers used the semiquantitative Leeds Scoring System for bone marrow edema lesions representative of inflammation in the spine and SI joints. This scoring system allows for estimation of the severity of a lesion by combining the concepts of extent and intensity in one definition with lesions ranked on a scale of 0–3 as previously described (13). A lesion graded as severe (grade ≥2) is considered clinically significant. For analysis, concordant data from the 2 readers were used to report on definite lesions. An overall score for inflammatory activity was calculated as the sum of bone marrow edema scores.

Statistical analysis. Data are expressed either as frequencies or as the median and range. The total MRI scores of the 3 different groups of patients and patients with or without HLA–B27 were compared using the Mann-Whitney U test. The prevalences of severe MRI lesions (grade ≥2) were compared using the chi-square test. Statistical analysis was performed using SPSS software, version 11.5.

RESULTS

Demographic and clinical data. A total of 76 scans were available for analysis. There were 33 PsA patients, 24 patients with nonradiographic axial SpA, and 19 AS patients. Three PsA patients (9%) fulfilled the modified New York radiographic criterion for AS (2 had bilateral grade 2 sacroiliitis, and 1 had unilateral grade 3 sacroiliitis). Due to poor scan quality, L-spine MRIs could not be scored in 1 patient with PsA and 2 patients with nonradiographic axial SpA, and SI joint MRIs could not be scored in 2 patients with PsA and 1 patient with AS. Total MRI scores were calculated and compared only for patients for whom we had paired L-spine and SI joint data (n = 70). For comparison of number of lesions and number of severe lesions (grade ≥2), L-spine and SI joint scans were analyzed separately. The median (range) age was comparable in all groups (for patients with PsA, 39 years [18–60 years]; for patients with nonradiographic axial SpA, 34.5 years [19–47 years]; for patients with AS, 35.5 years [23–61 years]). There were more women in the group with PsA (75.8%) than in the groups with nonradiographic axial SpA (38.1%) and AS (31.6%). HLA–B27 positivity was similar in PsA patients (30.3%, 10 of 33) and patients with nonradiographic axial SpA (41.7%, 10 of 24) and higher in AS patients (94.7%, 18 of 19).

MRI findings. The majority of scans were normal or negative, showing no inflammatory lesions, and this was more common in the groups with PsA and nonradiographic axial SpA (70% for both, versus 50% in the group with AS). When scoring the abnormal scans, total MRI scores (L-spine plus SI joints) were higher in AS patients than in PsA patients ($P = 0.025$) or in patients with nonradiographic axial SpA ($P = 0.007$) (see Figure 1). A comparable extent of disease was shown by similar total numbers of bone marrow edema lesions at both the SI joints and L-spine in all 3 groups, but the number of severe lesions at the SI joints (grade ≥2) was higher in AS patients and PsA patients than in patients with nonradiographic axial SpA ($P = 0.01$ and $P = 0.03$, respectively).

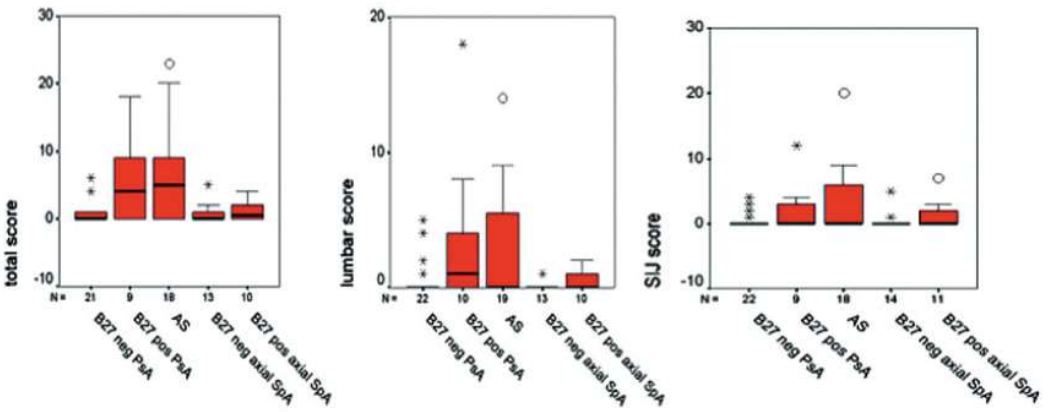

Figure 1. Comparison of total numbers of inflammatory (bone marrow edema) lesions on magnetic resonance imaging of the lumbar spine and sacroiliac joint (SIJ) between patients with psoriatic arthritis (PsA), patients with ankylosing spondylitis (AS), and patients with nonradiographic axial spondyloarthritis (SpA) in relation to HLA–B27 status (negative [neg] or positive [pos]). Data are shown as box plots. Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes represent the 10th and the 90th percentiles. Circles and asterisks indicate outliers.

When the groups were subanalyzed according to HLA–B27 status, disease severity in terms of total MRI scores was found to be related to the presence of HLA–B27. HLA–B27–negative PsA patients had lower MRI scores than HLA–B27–positive PsA patients ($P = 0.03$) and AS patients ($P = 0.006$), whereas HLA–B27–positive PsA patients and AS patients had similar scores. Similarly, the MRI scores of HLA–B27–negative patients with nonradiographic axial SpA were lower than those of AS patients ($P = 0.01$) (see Figure 1). No differences were seen between women and men, who had similar MRI scores for both L-spine and SI joints in all groups (data not shown).

The extent of disease, as assessed by the overall number of bone marrow edema lesions, was also related to the presence of HLA–B27, as HLA–B27–negative PsA patients had a lower number of L-spine lesions than AS patients ($P = 0.028$) and HLA–B27–positive PsA patients ($P = 0.039$), whereas there were no differences between AS patients and HLA–B27–positive PsA patients. The number of severe lesions (grade ≥2) was not different in any group pairs (Table 1).

Table 1. Characteristics of L-spine and SI joint inflammatory involvement on magnetic resonance imaging according to the different clinical groups*

	HLA–B27–negative PsA	HLA–B27–positive PsA	AS	HLA–B27–negative nonradiographic axial SpA	HLA–B27–positive nonradiographic axial SpA
L-spine					
No. of patients	22	10	19	13	9
Any grade ≥1 lesion, no. (%)	4 (18.2)	6 (60)	9 (47.4)	3 (23.1)	3 (33.3)
At least 1 grade 2 lesion, no. (%)	3 (14.6)	3 (30)	5 (26.3)	0 (0)	0 (0)
SI joints					
No. of patients	22	9	18	14	10
Any grade ≥1 lesion, no. (%)	5 (22.7)	4 (44.4)	8 (44.4)	2 (14.3)	4 (40)
At least 1 grade 2 lesion, no. (%)	2 (9.1)	3 (33.3)	6 (33.3)	1 (7.1)	2 (20)
Bilateral lesions, no. (%)	3 (13.6)	1 (11.1)	8 (44.4)	1 (7.1)	2 (20)

* There were no statistically significant differences between any group pairs. L-spine = lumbar spine; SI = sacroiliac; PsA = psoriatic arthritis; AS = ankylosing spondylitis; SpA = spondyloarthritis.

DISCUSSION

This study investigated the role of the HLA–B27 gene on the MRI phenotypes in PsA and axial SpA including AS. Our findings confirm that the HLA–B27 gene has a major effect on both the severity of axial lesions and the number of different distinct lesions. In accordance with previous studies, we have shown that the majority of patients with axial PsA and nonradiographic axial SpA are HLA–B27 negative (14). In addition, we show that HLA–B27–positive axial PsA and AS have the same pattern of bone marrow edema. Conversely, HLA–B27–negative axial disease including PsA has a much lower extent of bone marrow edema. Collectively, these findings support the concept of the key role of the HLA–B27 gene as a determinant of the extent of osteitis in SpA.

These findings have important implications for understanding SpA. There is now a link established between MRI-determined bone marrow edema and subsequent disease progression at diseased segments. Given that symptomatic PsA has less bone marrow edema, it might be expected that there is less diffuse spinal disease. Indeed, historical radiographic imaging studies have shown asymmetric, less severe disease in PsA compared to classic AS, but the studies in question did not note the HLA–B27 status (2).

It is interesting to note that AS, psoriasis, and PsA are all class I major histocompatibility complex–associated diseases. In the case of psoriasis, the HLA–Cw0602 gene is a severity factor for the extent of skin disease but does not appear to be linked to the joint disease. It seems that HLA–B27 is a marker for the extent of bone marrow edema in SpA irrespective of the presence of skin psoriasis. Just as T cells appear to be associated with the dissemination of disease in HLA–Cw0602–positive skin psoriasis, T cells may be associated with the development of disease at different bony sites. This hypothesis has never been tested, and the role of the affected bone in SpA and the basis for disease in relation to HLA–B27 have not been evaluated at this site.

These findings also have a practical aspect for consideration. The majority of PsA patients who were HLA–B27 negative were reported as having a normal MRI scan. This may reflect the fact that MRI may be insensitive at picking up subtle soft tissue changes at entheses (15).

Our study has some limitations. First, this is a retrospective audit of MRI scans requested in daily clinical practice, and data on clinical outcomes such as the Bath Ankylosing Spondylitis Disease Activity Index (16) or Ankylosing Spondylitis Disease Activity Score (17) were not systematically collected to allow for a correlation with clinical symptoms. Previous studies on early inflammatory back pain have shown a higher level of disease activity as shown by clinical outcomes in patients with psoriasis (14), suggesting a possible role of psoriasis as an independent contributor to disease activity. Taken together, these results suggest a role for HLA–B27 and psoriasis as partly independent contributors to inflammation and disease activity in axial PsA. Second, the sample size was small, which represents an important limitation to conducting a multivariate analysis of the data. Third, only the lumbar portion of the spine in addition to the SI joints was imaged as opposed to the whole spine. Ideally, the whole spine should have been imaged to allow for the assessment of cervical and thoracic sites where a significant proportion of lesions may have been missed. Further, we have looked at inflammatory bone lesions only as represented by bone marrow edema, but a "positive" MRI result reflecting disease may need to incorporate other features of structural change such as fatty degeneration, sclerosis, or erosions. The presence of structural lesions in the absence of inflammation would help us to understand why axial PsA is indeed more asymptomatic than AS and can go largely undiagnosed. Larger, prospective MRI studies of the whole spine with associated genotypes are needed to confirm these results.

In conclusion, HLA–B27–related active axial PsA shows an extent of inflammation on MRI comparable to that of AS and superior to that of HLA–B27–negative PsA. These results suggest that this subgroup of PsA shares common etiopathogenic mechanisms of disease with AS and may carry a comparable disease burden.

ACKNOWLEDGMENT

We honor the memory of Dr. Jóse Luis Fernández Sueiro for his unfailing belief in the concept of axial PsA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Marzo-Ortega had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Castillo-Gallego, Aydin, Emery, McGonagle, Marzo-Ortega.

Acquisition of data. Castillo-Gallego, Marzo-Ortega.

Analysis and interpretation of data. Castillo-Gallego, Aydin, Emery, McGonagle, Marzo-Ortega.

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5.2. US in Spondyloarthritis and Psoriatic arthritis

5.2.1. ARTICLE 2:

TITLE: "Achilles enthesis ultrasound: the importance of the bursa in spondyloarthritis"

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5.2.1.1 PATIENTS AND METHODS

5.2.1.1.1. Patients group

This part of the Thesis work is a blind and controlled Achilles enthesis bursitis US study performed on early-stage SpA patients. The patient sample was selected consecutively from individuals attending the Early Spondyloarthritis Unit (forty-six patients), as part of the ESPERANZA programme. 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. Patients were classified as SpA

according to accepted classification criteria. 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.

5.2.1.1.2. Controls group

Forty-six sex-matched controls (92 Achilles enthesis) were included.

5.2.1.1.3. Ultrasound scanning protocol

Ultrasonography was performed by an experienced rheumatologist, who 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. The same protocol was used for both 2D and 3D examinations.

5.2.1.1.4. 2D US and 3D US 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. 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. 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. 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.

5.2.1.1.5. Statistical analysis

Mean ± standard deviation was used to describe the demographic characteristics of patients and US features. To compare quantitative and qualitative variables of clinical, biochemical and US data, the independent sample t -test and the chi-square 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).

Achilles enthesis ultrasound: the importance of the bursa in spondyloarthritis

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Abstract

Objectives

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

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.

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-spine 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 enthesis (67.4%) vs. 27/46 enthesis (58.7%) of healthy controls ($p<0.01$), and 10/46 enthesis (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 enthesis 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 ($p<0.01$).

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.

Key words

spondyloarthritis, ultrasonography, power Doppler, enthesis

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Introduction

Enthesitis is a distinctive feature of spondyloarthritis (SpA) (1). The central importance of the enthesis in understanding SpA pathophysiology has remerged in the last decade relating structural entheseal damage with inflammation, regional microanatomy and biomechanics, and its correlation with entheseal new bone formation, and erosion (2-5). Considering the cardinal role of enthesis 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 enthesis. Furthermore, US elemental lesions included in enthesis 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 enthesis at bone and enthesis 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 entheseal lesions considered in the OMERACT enthesopathy definition (6-8, 14-16). In fact, bursa was included in 46% of enthesis studies in a recently systematic literature review (9). This is in agreement with the concept of "synovio-entheseal 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 enthesis 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 entheseal 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 enthesis.

Patients and methods

A blind and controlled Achilles enthesis 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

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 enthesis) were included. Half of the controls were patients who fulfilled 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 Electrics 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 ± 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 enthesis of 66 early SpA patients (34 female, 32 male) were studied. Mean age was 32.5±7.66 (range 18–45) years. Mean disease evolution

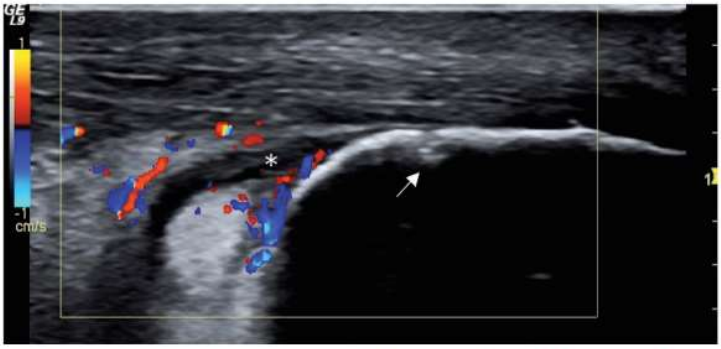

Fig. 1. Ultrasonographic appearance of entheseal Achilles insertion. Bursal enlargement with Doppler signal (*), and erosion (arrow) in a longitudinal view.

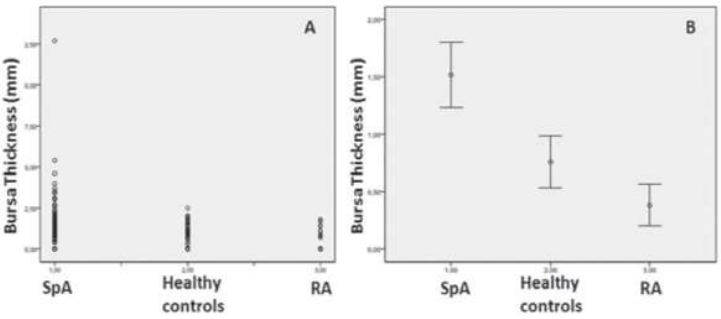

Fig. 2. Ultrasound bursa measures in spondyloarthritis (SpA) and controls. **A**. Scattergram dots distribution in SpA, healthy controls and rheumatoid arthritis (RA) control group. **B**. Mean and 95%CI of bursa thickness in SpA, healthy controls and RA controls.

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±2.08 (0–8.8), 2.16±1.95 (0–7.4) and 0.65±0.77 (0–3), respectively. Mean erythrocyte sedimentation rate (ESR) was 10.93±12.35 mm/h (range 1–53) and C-reactive protein (CRP) was 6.46±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±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 enthesis bursa was 0.98 (95%CI 0.97–0.99; $p<0.0001$).

Validity. Bursas were visualised in 89/132 SpA enthesis (67.4%) *versus* 27/46 enthesis (58.7%) of healthy controls ($p<0.01$), and 10/46 enthesis (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±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 ($p<0.0001$). 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 enthesis of control groups and SpA patients. No Doppler signal was detected in any bursa of control patients, but 6.6% of SpA Achilles enthesis had Doppler bursitis.

The correlation between bursas >2mm 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±1.24 mm in SpA patients with heel pain compared with 1.31±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 affectation on enthesis could be relevant as elemental lesion in the concept of entheseal 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 enthesis 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 affectation 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 I. 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	43.5	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 enthesis 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 ≥2mm 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 I 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 enthesis damage, previous reported data have demonstrated that erosions typically occur in the bursal proximal portion of the enthesis 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 enthesis 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 enthesis 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 enthesis. 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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5.2.2. ARTICLE 3

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

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5.2.2.1. PATIENTS AND METHODS:

In this part of the Thesis work we performed a longitudinal enthesis 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.

5.2.2.1.1. Patients

The sample included the baseline visit for 146 consecutive patients attending the Early SpA Unit as part of the ESPERANZA programme. The patients were diagnosed with SpA according to accepted ASAS classification criteria. 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) and the BASRI were calculated.

5.2.2.1.2. US examination

Patients underwent an Achilles US examination at baseline, and 6 and 12 months according to the Madrid Sonographic Enthesitis Index (MASEI) (24). In this study, the only score was for the Achilles enthesis. The US was performed by one rheumatologist trained in enthesis US using a Logiq 9 machine (General Electric, Wauwatosa, WI, USA) with a linear probe at 9-14 MHz. The US examiner was blinded to the status of the subject. The elemental lesions were defined according to OMERACT definitions and the original MASEI publication. To improve precision, erosion was defined as cortical breakages with step-downs of more than 1mm 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).

5.2.2.1.3. Statistical analysis

The mean (S.D.) was used to describe the demographic characteristics of patients and US 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 US 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).

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

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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 $P = 0.03$) 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 entheseal affectation, 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 entheseal changes secondary to previous inflammation.

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Therefore the enthesitis US definition is still pending. In this sense, knowledge of which entheseal 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 enthesis US in the assessment of disease activity in SpA.

Patients and methods

We performed a longitudinal enthesis 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 enthesis. The ultrasonography was performed by one rheumatologist trained in enthesis US using a Logiq 9 machine (General Electric, Wauwatosa, WI, USA) with a linear probe at 9–14 MHz. 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 enthesis 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 $P = 0.006$, 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 Achilles US elemental lesions *vs* demographic, clinical and laboratory data

	Achilles US elemental lesions																	
	Doppler			Erosion			Bursa			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 (8)	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 (9)	32.5 (7.6)	0.45
CRP	15.8 (26.3)	4.3 (5)	<**0.001**	13.6 (19.7)	7.1 (15.7)	0.2	11.3 (19.2)	6 (14.1)	0.12	10.9 (21.2)	6.2 (11.7)	0.14	12 (22.1)	4.3 (5)	**0.01**	14 (17.6)	7.7 (16.4)	0.32
ESR	21.3 (24.2)	11.2 (9.1)	<**0.005**	19.2 (24.3)	13.6 (14.4)	0.35	17.6 (20.9)	12.2 (11.6)	0.07	15.4 (17)	13.7 (15.9)	0.59	17.4 (20.5)	11.2 (9)	**0.04**	13.7 (15.5)	14.5 (16.4)	0.88
ASDAS	2.8 (1.3)	2.3 (1)	0.31	3 (1.5)	2.4 (1)	0.36	2.7 (1.4)	2.3 (1)	0.34	2.7 (1)	2.3 (1.2)	0.15	2.6 (1.1)	2.3 (1.2)	0.39	2.9 (1.2)	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)	0.51	4.9 (1.6)	4.5 (2.3)	0.35	4.7 (1.6)	4.6 (2.4)	0.67	4.8 (1.5)	4.6 (2)	0.81
BASDAI 2	4.8 (2.9)	5.6 (2.7)	0.34	3.4 (3.6)	5.7 (2.6)	0.16	5 (3)	5.6 (2.7)	0.49	5.8 (2.4)	5.1 (3)	0.3	5.4 (2.7)	5.4 (2.9)	0.97	5.4 (2.8)	5.4 (2.8)	0.96
BASDAI 3	4.6 (3.4)	3.2 (3.1)	0.18	5.1 (4)	3.3 (3)	0.29	4.6 (3.4)	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 (3.5)	4.5 (3)	0.55	5 (4.2)	4.3 (3)	0.68	3.9 (3.4)	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 (3.9)	4.3 (3)	0.85
Disease activity (patient)	3.4 (1.8)	2.7 (1.4)	0.19	3.43 (2.3)	2.9 (1.5)	0.37	3.2 (1.6)	2.8 (1.5)	0.29	2.9 (1.3)	2.9 (1.7)	0.94	3.2 (1.6)	2.7 (1.5)	0.21	3.1 (1.8)	2.9 (1.5)	0.75
VAS (patient)	5 (3)	5.3 (2.4)	0.68	6.4 (2.4)	5.1 (2.5)	0.2	4.8 (2.8)	5.5 (2.3)	0.31	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 (2.6)	0.18
BASFI	3 (2.3)	2.4 (2)	0.18	3.5 (2.4)	2.4 (2)	0.09	2.9 (2.2)	2.3 (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
BASRI-spine	0.9 (0.9)	0.6 (0.6)	0.18	1 (0.7)	0.6 (0.7)	0.32	0.9 (0.8)	0.5 (0.7)	0.12	0.5 (0.7)	0.8 (0.8)	0.18	0.7 (0.8)	0.6 (0.7)	0.77	0.5 (0.5)	0.7 (0.8)	0.39
NSJ	0.6 (1.7)	0.2 (0.7)	0.42	1.3 (2.4)	0.2 (0.7)	**0.009**	0.5 (1.5)	0.2 (0.8)	0.42	0.6 (1.6)	0.2 (0.5)	0.13	0.6 (1.6)	0.2 (0.5)	0.17	0.6 (1.4)	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?); NSJ: 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

	Clinical and laboratory baseline data of SpA patients																	
	CRP			ESR			BASDAI			ASDAS								
Achilles US	>5	<5	*P*-value	>30	<30	*P*-value	>4	<4	*P*-value	>1.3	<1.3	*P*-value	>2.1	<2.1	*P*-value	>3.5	<3.5	*P*-value
Baseline																		
Bone proliferation	2.9 (1.2)	2.5 (1.2)	0.1	3.3 (1.1)	2.6 (1.2)	**0.05**	2.8 (1.2)	2.5 (1.2)	0.33	2.7 (1)	1.7 (0.5)	**0.001**	2.6 (0.9)	2.4 (1.2)	0.4	2.8 (1.1)	2.5 (1)	0.46
Erosion	1 (1.9)	0.5 (1.5)	0.17	1.3 (2)	0.6 (1.6)	0.29	0.6 (1.5)	0.8 (1.8)	0.65	0.6 (1.6)	0.9 (2.3)	0.76	0.5 (1.6)	0.6 (1.7)	0.88	1.3 (2.4)	0.4 (1.4)	0.13
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 (0.5)	0.07 (0.3)	0.19	0.2 (0.6)	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 (0.9)	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 (2.5)	1.3 (2.3)	0.14	3.3 (2.4)	1.3 (2.3)	**0.02**	1.5 (2.3)	1.9 (2.6)	0.42	1.2 (2.1)	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 (3.9)	0.33	5.5 (4.6)	5.4 (4.7)	0.9	7.8 (6.4)	4.8 (3.8)	**0.04**
6 months																		
Bone proliferation	2.9 (1.4)	2 (1.5)	**0.007**	2.9 (1.4)	2.3 (1.5)	0.2	2.6 (1.6)	2 (1.5)	0.07	2.2 (1.4)	1.4 (0.8)	0.06	2 (1.3)	2 (1.4)	0.89	2.2 (1.2)	2 (1.4)	0.77
Erosion	0.9 (1.9)	0.5 (1.4)	0.17	1.3 (2.4)	0.5 (1.4)	0.15	0.6 (1.5)	0.6 (1.8)	0.98	0.6 (1.5)	0.9 (2.3)	0.76	0.6 (1.4)	0.7 (1.8)	0.88	0.8 (1.9)	0.5 (1.5)	0.76
Structure	0.8 (0.9)	0.6 (0.8)	0.21	0.9 (1)	0.6 (0.8)	0.19	0.7 (0.8)	0.3 (0.6)	**0.01**	0.7 (0.8)	0.3 (0.5)	0.09	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)	0.66	0.1 (0.3)	0 (0)	0.33	0.1 (0.3)	0.1 (0.3)	0.9	0.2 (0.4)	0.1 (0.3)	0.36
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 (0.5)	0.23	0.8 (0.8)	0.1 (0.5)	**0.001**
Doppler	1.5 (2.2)	0.4 (1.2)	**0.003**	1.6 (2.2)	0.7 (1.5)	**0.05**	0.9 (1.7)	0.5 (1.4)	0.19	0.7 (1.7)	0 (0)	0.28	0.7 (1.7)	0.5 (1.5)	0.72	1.5 (2.4)	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 (4.5)	0.43	4.6 (4.3)	2.6 (2.6)	0.45	4.6 (3.8)	4 (4.6)	0.73	6.2 (5)	3.8 (3.7)	0.14
12 months																		
Bone proliferation	2.8 (1.4)	2 (1.6)	**0.009**	3 (1.4)	2.3 (1.5)	0.16	2.4 (1.6)	2.2 (1.5)	0.44	2.2 (1.5)	1.7 (0.8)	0.22	2 (1.5)	2.2 (1.4)	0.69	2.4 (1.6)	2 (1.5)	0.48
Erosion	0.8 (1.9)	0.4 (1.3)	0.17	1.8 (2.4)	0.4 (1.3)	**0.004**	0.4 (1.3)	0.6 (1.6)	0.57	0.3 (1.3)	0 (0)	0.09	0.3 (1.2)	0.3 (1.2)	0.94	0.8 (1.9)	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 (0.6)	0.39	0.5 (0.8)	0.2 (0.4)	0.26	0.5 (0.8)	0.5 (0.7)	0.87	0.6 (0.8)	0.5 (0.7)	0.6
Thickness	0.3 (0.5)	0.07 (0.3)	**0.002**	0.4 (0.7)	0.1 (0.4)	**0.03**	0.2 (0.4)	0.1 (0.4)	0.89	0.2 (0.5)	0 (0)	0.29	0.2 (0.5)	0.09 (0.3)	0.24	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)	**0.03**	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 (1.9)	0.5 (1.5)	0.11	1.5 (2.4)	0.6 (1.5)	0.07	0.8 (1.7)	0.5 (1.7)	0.52	0.5 (1.5)	0 (0)	**0.01**	0.4 (1)	0.5 (1.8)	0.73	0.5 (1.2)	0.5 (1.4)	0.9
Total Achilles	6 (5)	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 (1.3)	**0.02**	3.6 (3.7)	3.9 (4.5)	0.71	4.6 (4.6)	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 (e.g. 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 enthesis, which is one of the more important targets in the pathogenesis of SpA, is undervalued in the assessment of disease activity. The inclusion of enthesitis 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 entheseal 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 entheseal 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 enthesis 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 enthesis 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 enthesis 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 entheseal disease activity than does the BASDAI.

One limitation of our study is the exploration of a single peripheral enthesis. The challenge will be to verify if another single enthesis or a composite US entheseal index has better validity than the Achilles tendon by itself. Even so, the consistency of our results using just one enthesis 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 entheseal inflammation in SpA patients. As a disease status measure, it seems that, compared with the BASDAI, the ASDAS better reflects entheseal inflammation. This study supports the construct validity of enthesis US and provides

further evidence that enthesis 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 entheseal 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 entheseal inflammation and has predictive value for the Doppler signal in SpA patients.

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Disclosure statement: The authors have declared no conflicts of interest.

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5.2.3. ARTICLE 4

TITLE: "Colour Doppler and spectral Doppler ultrasound detection of active sacroileitis in spondyloarthritis compared with physical examination"

JOURNAL: Rheumatology International (submitted, under revision)

AUTHORS: Castillo-Gallego C, De Miguel E, García-Arias M, Plasencia Ch, Lojo-Oliveira L, Martín-Mola E.

5.2.3.1. PATIENTS AND METHODS:

5.2.3.1.1. Patients

This part of the Thesis work was a cross-sectional, blinded and controlled study of the SIJs, in which three populations were compared. We studied 108 patients, who were divided into three groups: a) 53 patients diagnosed with SpA who had IBP; b) 28 patients diagnosed with SpA who did not have IBP or SIJ tenderness but had normal physical examinations of the SIJs; and c) a group of 27 subjects, including 19 healthy controls and 8 subjects, with mechanical lumbar pain. All of the patients included who were diagnosed with SpA met the ASAS classification criteria for axial SpA. Inflammatory back pain (IBP) was defined as pain in the lumbosacral according to ASAS criteria, assessed by a rheumatologist.

The study was conducted according to local regulations and the Declaration of Helsinki, and the ethical committee of our hospital granted approval for the study.

5.2.3.1.2. Physical examination

A rheumatologist, who previously had performed the clinical history, assessed the patients. The physical examinations of the SIJs included the following: sacral sulcus tenderness, iliac compression, the midline sacral thrust test, Gaenslen's and Patrick's tests. The results of these tests were reported as positive if any of these manoeuvres provoked pain in the right or left SIJ or as negative if none of them provoked pain. Both right and left SIJs were assessed and scored independently in each patient.

5.2.3.1.4. CDUS

CDUS examination of the SIJs was performed using a Logiq 9 equipment (General Electrics Medical Systems, Milwaukee, Wisconsin, USA) fitted with a 9-14 MHz lineal probe. The ultrasonographer was blinded to the clinical data of the patient. The color Doppler settings were the same for all of the participants, with a gain setting just below the noise level and 5 MHz of Doppler frequency. The cases and the controls were examined in the prone position. The probe, in the transverse position, was moved from the cephalic origin of the SIJ to the end of the SIJ, caudal to the second sacral foramen (figure 8). Vascularization within the SIJs was explored by the presence of a CDUS signal. The sacral foramen, with its vessels, was always identified, but a Doppler signal in this area was not considered to be a Doppler signal in the SIJs (figure 9).

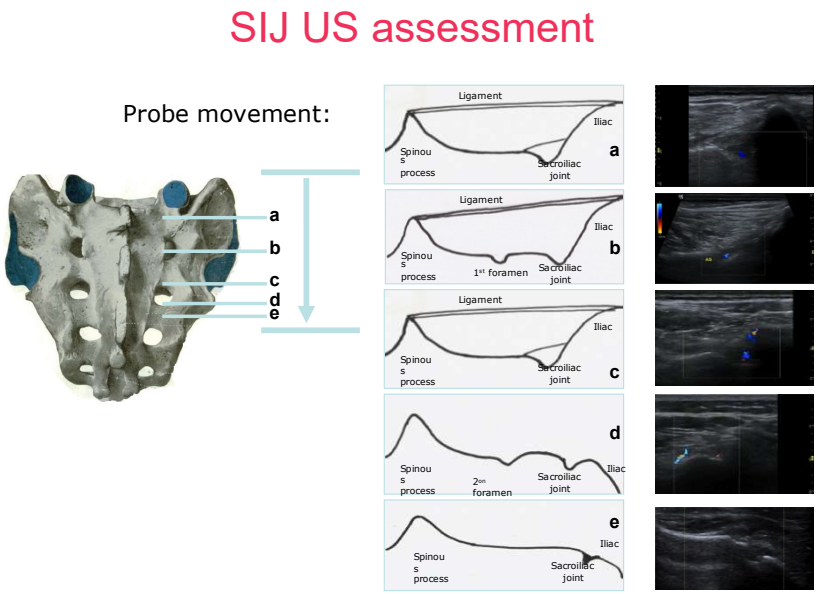

Figure 8 Movement of the US probe, in transverse position, from the cephalic origin of the SIJ to the end of the SIJ, caudal to the second sacral foramen. end of sacroiliac joint.

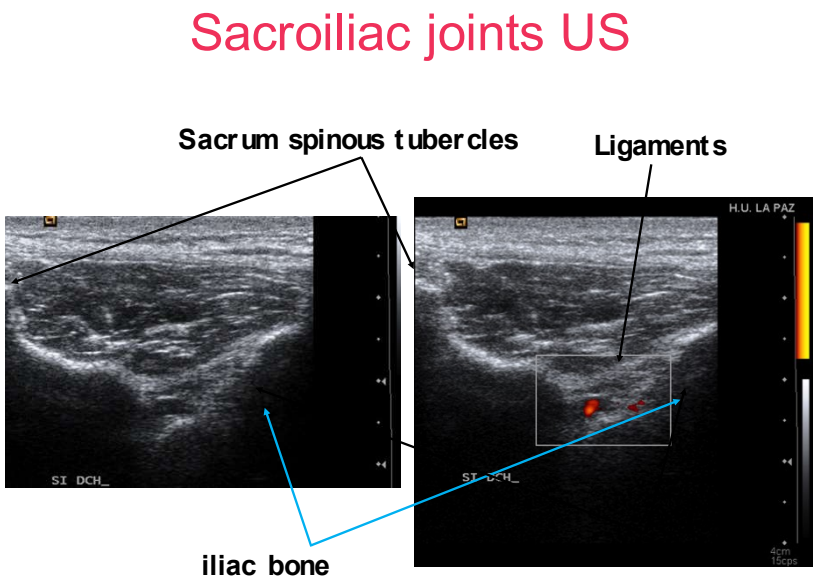

Figure 9 Images of SIJ US, the left one only grey scale and the right one with colour Doppler

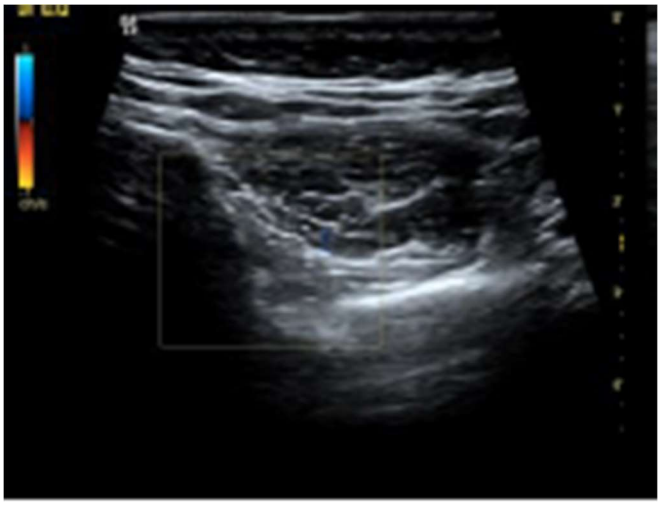

Figure 10 Image of CDUS of the left SI joints: no Doppler signal detected

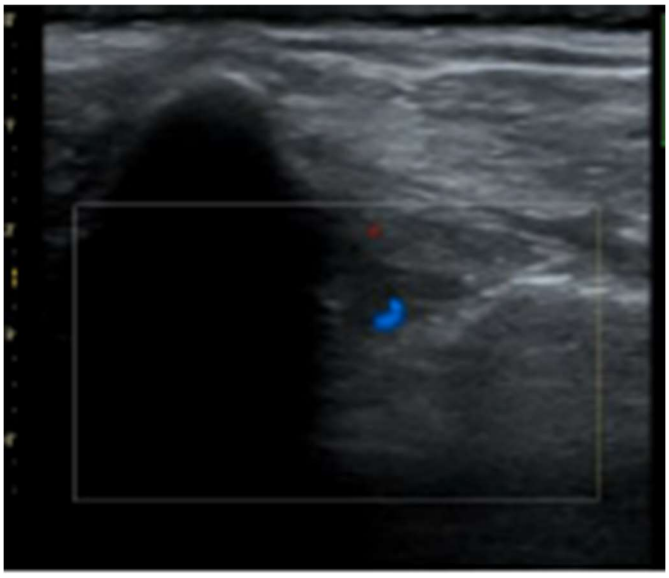

Figure 11 Image of CDUS of the left SI joints: Doppler signal detected

5.2.3.1.5. Spectral Doppler

If any Doppler signals were detected within the SIJs, the RI was measured. The US flow patterns in the SIJs with activity on CDUS were evaluated using quantitative spectral Doppler with automatic calculation of the RI (RI = [peak systolic flow - end diastolic flow/peak systolic flow]). The values of the RI ranged between 0 and 1. Measurements in each examination area were repeated at least twice, and the mean values of those measurements were used as the results. If there was no Doppler signal within the SIJs, the RI was calculated from the subcutaneous vessels above the SIJ. Doppler of each SIJ was classified, after calculation of the cut-off point with ROC curves (see results), as positive when both CDUS and RI were < 0.75 within the SIJ area.

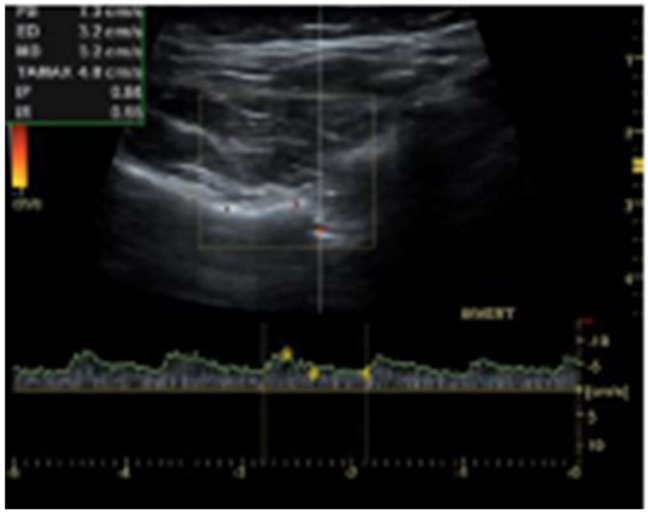

Figure 12 Image of CDUS and Spectral Doppler of the Right sacroiliac joint with a Doppler signal and spectral Doppler with a resistive index of 0.55

5.4.1.5. Statistical analysis

Means ± standard deviations were used to describe the demographic characteristics. A statistical analysis was performed, estimating the sensitivity and specificity against the gold standard, and ROC curves were constructed to calculate the sensitivity, specificity, accuracy and best cut-off point of the spectral Doppler RI to distinguish physiological from pathologic SIJ flow. A chi-square test for the comparison of categorical variables and paired and unpaired t tests for continuous variables were applied.

Rheumatology International

COLOUR DOPPLER AND SPECTRAL DOPPLER ULTRASOUND DETECTION OF ACTIVE SACROILIITIS IN SPONDYLOARTHRITIS COMPARED TO PHYSICAL EXAMINATION

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Abstract:	Objective: Sacroiliac joint (SIJ) involvement is a distinctive feature of spondyloarthritis (SpA). The main objective of this study was to assess the validity of colour Doppler ultrasound (CDUS) in SIJ. Methods: This was a cross-sectional, blinded, case-control study of 108 cases divided into three groups: a) 53 SpA patients with inflammatory back pain (IBP); b) 28 SpA patients with no IBP; and c) 27 healthy mechanical lumbar pain subjects. Physical examinations of the SIJs were assessed as positive or negative in each SIJ and were used as the gold standard. SIJs were examined with CDUS and spectral Doppler, and the SIJs were assessed as positive when both color Doppler and the resistance index (RI) were less than the cut-off point within the SIJs area. Results: A total of 108 cases (53 female; mean age 3610 years old) were studied. The physical examination of the SIJs was positive in 38 patients (59 SIJs). Ultrasound detected Doppler signal within the SIJs in 37 cases (58 SIJs): 33 of them had symptomatic SpA (52 SIJs), 3 of them had asymptomatic SpA (5 SIJs), and 1 was a healthy control (1 SIJ). The accuracy of CDUS, when compared to physical SIJ examination, at the patient level in the overall group had a sensitivity of 70.3%, a specificity of 85.7%, a positive likelihood ratio of 4.9 and a negative likelihood ratio of 0.36. For the spectral Doppler RI, with an optimal cut-off point ≤ 0.75, the sensitivity was 76.2%, and the specificity was 77.8%. Conclusions: CDUS of SIJs seems to be a feasible and valid method for detecting active inflammation in patients with SpA.

COLOUR DOPPLER AND SPECTRAL DOPPLER ULTRASOUND DETECTION OF ACTIVE SACROILIITIS IN SPONDYLOARTHRITIS COMPARED TO PHYSICAL EXAMINATION

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Keywords

Ultrasound

Spondyloarthritis

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Sacroiliitis

Diagnosis

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Conclusions: CDUS of SIJs seems to be a feasible and valid method for detecting active inflammation in patients with SpA.

Conflict of interest: C Castillo-Gallego has received an unrestricted grant from Spanish Foundation of Rheumatology and Pfizer (Esperanza Program).

Introduction

Sacroiliac joint (SIJ) involvement is a distinctive and characteristic feature of spondyloarthritis (SpA). The diagnosis of AS relies on a combination of clinical symptoms with unequivocal radiographic sacroiliitis (1). X-ray radiography reveals structural damage caused by inflammation but cannot detect active inflammatory lesions, and the diagnosis of ankylosing spondylitis (AS) is commonly delayed by an average of 6–9 years after the onset of symptoms (2, 3). Moreover, at 10 years from the first presentation of the disease, 25–35% of patients still do not have radiographic sacroiliitis (4). Therefore, new imaging techniques are required for the early diagnosis and assessment of inflammatory activity in SpA.

In the last decade, magnetic resonance imaging (MRI) has been increasingly used to visualize inflammation in the SIJs, and it has now been included in the new Assessment of SpondyloArthritis International Society (ASAS) criteria for the classification of axial SpA (5). It has become clear in recent years that active inflammatory lesions are visible on MRI long before definite lesions on plain radiographs are detectable (6). Although MRI can shorten the interval between the onset of symptoms and the radiographic diagnosis of sacroiliitis, the availability of MRI is limited in many countries, and the technique is relatively time-consuming and cost-intensive.

Enthesis ultrasound has demonstrated that it is useful for discriminating patients with long-standing SpA from those with early SpA (7-10). However, even in a less explored field, such as inflammation in the SIJs, US can be used by applying different methods, including grayscale or colour Doppler ultrasound (CDUS), spectral Doppler resistive index (RI) and contrast-enhanced media (11-17).

Thus far, there have been very few studies published assessing active inflammatory lesions in the SIJs using ultrasound. The main purpose of this study was to assess the validity of color Doppler ultrasound (CDUS), compared to physical examination as the gold standard, in the assessment of active inflammation of the SIJs in patients with SpA.

Patients and Methods

Patients

This was a cross-sectional, blinded and controlled study of the SIJs, in which three populations were compared. We studied 108 patients, who were divided into three groups: a) 53 patients diagnosed with SpA who had IBP; b) 28 patients diagnosed with SpA who did not have IBP or SIJ tenderness but had normal physical examinations of the SIJs; and c) a group of 27 subjects, including 19 healthy controls and 8 subjects, with mechanical lumbar pain. All of the patients included who were diagnosed with SpA met the ASAS classification criteria for axial SpA (5). Inflammatory back pain (IBP) was defined as pain in the lumbosacral according to ASAS criteria (18), assessed by a rheumatologist.

The study was conducted according to local regulations and the Declaration of Helsinki, and the ethical committee of our hospital granted approval for the study.

Physical examination

A rheumatologist, who previously had performed the clinical history, assessed the patients. The physical examinations of the SIJs included the following: sacral sulcus tenderness, iliac compression, the midline sacral thrust test, Gaenslen's and Patrick's tests. The results of these tests were reported as positive if any of these maneuvers provoked pain in the right or left SIJ or as negative if none of them provoked pain. Both right and left SIJs were assessed and scored independently in each patient.

specificity against the gold standard, and receiver operating characteristic (ROC) curves were constructed to calculate the sensitivity, specificity, accuracy and best cut-off point of the spectral Doppler RI to distinguish physiological from pathologic SIJ flow. A chi-square test for the comparison of categorical variables and paired and unpaired t tests for continuous variables were applied.

Results

A total of 108 cases (53 female, 55 male; mean age 36±10 years old) were studied. There were no significant differences between the groups related to age or sex. The physical examinations of the SIJs were positive in 38 patients (59 sacroiliac joints). Doppler signals were detected in 58 SIJs of 37 subjects, of whom 33 were from the symptomatic SpA group (52 SIJs), three patients (5 SIJs) were from the asymptomatic SpA group, and one was a healthy control (1 SIJ) (figure 1). The accuracy of the CDUS of the SIJs, when compared to SIJ physical examination as the gold standard, at the patient level in the overall group had a sensitivity of 70.3%, a specificity of 85.7%, a positive predictive value of 70.5% and a negative predictive value of 85.7%. The positive likelihood ratio obtained was 4.9, and the negative likelihood ratio was 0.36. The calculated RI area under the ROC curve was 0.794 (95% confidence interval 0.721-0.866). For the spectral Doppler RI, with an optimal cut-off point ≤ 0.75, the sensitivity was 76.2%, and the specificity was 77.8% (see table 1). The RI was used to distinguish patients with active SIJ inflammation, and the mean RI was 0.54 for positive SIJ examinations and 0.94 for negative SIJ examinations ($p<0.0001$). When we analyzed the value of ultrasound in patients with IBP, CDUS showed a sensitivity of 62.26% and a specificity of 92.59%, and the VPP and VPN were 89.19% and 71.43%, respectively, with a positive LR of 8.402 and a negative LR of 0.408.

CDUS

CDUS examination of the SIJs was performed using Logiq 9 equipment (General Electrics Medical Systems, Milwaukee, Wisconsin, USA) fitted with a 9-14 MHz lineal probe. The ultrasonographer was blinded to the clinical data of the patient. The color Doppler settings were the same for all of the participants, with a gain setting just below the noise level and 5 MHz of Doppler frequency. The cases and the controls were examined in the prone position. The probe, in the transverse position, was moved from the cephalic origin of the SIJ to the end of the SIJ, caudal to the second sacral foramen (19, 20). Vascularization within the SIJs was explored by the presence of a CDUS signal. The sacral foramen, with its vessels, was always identified, but a Doppler signal in this area was not considered to be a Doppler signal in the SIJs.

Spectral Doppler

If any Doppler signals were detected within the SIJs, the RI was measured. The US flow patterns in the SIJs with activity on CDUS were evaluated using quantitative spectral Doppler with automatic calculation of the RI (RI = [peak systolic flow - end diastolic flow/peak systolic flow]). The values of the RI ranged between 0 and 1. Measurements in each examination area were repeated at least twice, and the mean values of those measurements were used as the results. If there was no Doppler signal within the SIJs, the RI was calculated from the subcutaneous vessels above the SIJ. Doppler of each SIJ was classified, after calculation of the cut-off point with ROC curves (see results), as positive when both color Doppler and RI were < 0.75 within the SIJ area.

Statistical analysis

Means ± standard deviations were used to describe the demographic characteristics. A statistical analysis was performed, estimating the sensitivity and

specificity against the gold standard, and receiver operating characteristic (ROC) curves were constructed to calculate the sensitivity, specificity, accuracy and best cut-off point of the spectral Doppler RI to distinguish physiological from pathologic SIJ flow. A chi-square test for the comparison of categorical variables and paired and unpaired t tests for continuous variables were applied.

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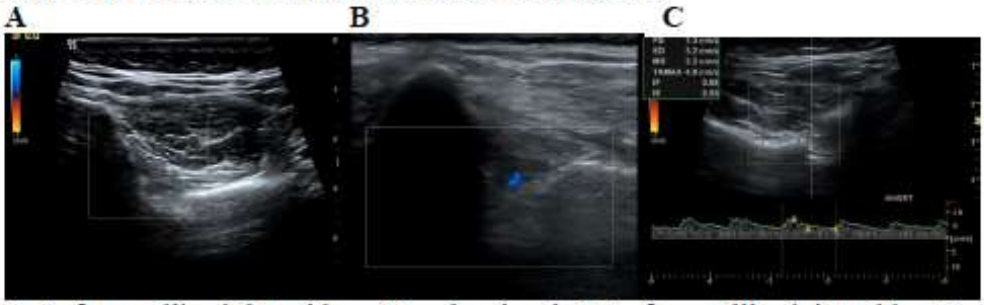
Figure 1: Ultrasound images of the sacroiliac joints



A. Left sacroiliac joint with no Doppler signal. **B.** Left sacroiliac joint with a Doppler signal. **C.** Right sacroiliac joint with a Doppler signal and spectral Doppler with a resistive index of 0.55

Table 1: Determination of the resistive index cut-off level (receiver operating characteristic area under the curve)

Resistive Index	Sensitivity	Specificity
<.20	0.960	0.978
<.30	0.952	0.956
<.35	0.929	0.889
<.40	0.913	0.822
<.45	0.897	0.756
<.50	0.873	0.689
<.5050	0.873	0.667
<.55	0.849	0.600
<.60	0.825	0.511
<.650	0.794	0.333
<.70	0.778	0.244
<.75	0.762	0.222
<.80	0.730	0.133
<.85	0.667	0.089
<.90	0.627	0.089
.95	0.611	0.089
2.0	0.000	0.000

The examination time for each patient was 3-5 minutes for both the localization of the SIJs in grayscale and CDUS, with 2 additional minutes for the spectral Doppler examination. No adverse events occurred in any of the participants.

Discussion

Currently, there is little available knowledge on the use of ultrasound on the SIJs or the applicability of US in the diagnosis and monitoring of SpA. In this sense, conducting new studies in this field is important. Previous studies have provided initial evidence of the validity of SIJ US (11-17). Analyses of these data showed that US could provide an opportunity to assess the SIJs. There have been different research end points used in these studies, using grayscale mode, color Doppler, ultrasound-enhanced media and RI. Contrast-enhanced studies have shown very good results in terms of validity, but it is an invasive technique that increases the time and cost of examinations and can lead to adverse events in patients.

To determine the real possibilities for the use of US SIJ examinations in clinical practice, it is interesting to note that an LR greater than 10 or less than 0.1 is considered to be sufficiently strong evidence to confirm or disprove, respectively, a diagnosis in most circumstances. LRs of 5-10 and 0.1-0.2 generate moderate shifts in pre-test and post-test probabilities, respectively, and LRs of 2-5 and 0.5-0.2 generate smaller (but sometimes important) changes in these probabilities. In our study, the positive LR achieved by US in the SIJs was 4.9, meaning that US could be a useful test to assess active sacroiliitis in clinical practice. This result was better than the previously reported data of 4.25 (12) and 2.67 (14) but was lower than the results when enhanced ultrasound media were used, for which the positive LR was 6.71 (12).

Zhu *et al*,(17) studied the complex appearance of vascularity of the SIJs in AS and commented that most of the color flow signs corresponded to venous flow in active AS patients. In our study, spectral Doppler tracing was obtained to confirm that each color Doppler signal represented a true arterial or venous flow pattern, and the inflammatory patterns were also checked using the RI to improve the accuracy. In the evaluation of the RI, our study had similar RI results to those achieved by previous publications (12, 14, 17), demonstrating statistically significant differences between SpA patients and controls. However, we went one step further with the calculation of the better cut-off for the RI (≤ 0.75) to differentiate clinical activity from normality using flow pattern assessment.

Furthermore, the presence of IBP is a key symptom of axial involvement in SpA, and it is present in the majority of patients (5). Therefore, we studied whether CDUS assessment could answer a relevant question in clinical practice, i.e., whether IBP is related to the diagnosis of SpA. In our study, the presence of Doppler signals in the SIJs resulted in a high positive LR value when compared to patients with or without IBP. The combination with IBP increased the post-test probability of SI joint US examination to a positive LR of 8.4; thus, CDUS of the SIJs could be of relevance in the detection of active sacroiliitis and in the diagnosis of SpA, but these data need to be confirmed in further studies.

There were some limitations to our study. First, an increased body mass index can reduce the sensitivity of CDUS. It was difficult to detect CDUS signals with our US equipment when the SIJs were deeper than 4 cm. This fact could have resulted in some false negatives cases. Second, we compared US results to physical examination as the gold standard. There are many physical examination tests for the SIJs, and all of them have been advocated as useful tools in identifying patients with SIJ pain; however, none

of the available SIJ tests appears to be clearly superior to the others (18). To reduce this limitation, we used several of these tests. Moreover, physical examination has been accepted as the gold standard in previous studies (14, 17), although it is probably not the actual gold standard. Histopathology is the most accurate gold standard, but it is difficult to perform. MRI is accepted as a good technique to assess sacroiliitis, but its correlation with histopathology has a relative lack of sensitivity (19).

CDUS can also be used to perform US-guided sacroiliac joint injection in the treatment of sacroiliitis (20) and to detect the changes of sacroiliitis and peripheral enthesitis in AS patients under biologic therapy (21).

In conclusion, CDUS is a promising imaging technique for the detection of active sacroiliitis and could be a less expensive and easier-to-apply alternative method to MRI for detecting inflammation secondary to increased SIJ vascularization. Our results showed good sensitivity and high specificity of CDUS combined with RI, especially when they were associated with IBP. CDUS might be as cost-effective a technique as an initial imaging assessment in the study of inflammatory lower back pain.

Compliance with Ethical Standards:

- **Disclosure of potential conflicts of interest:** This study was funded by an unrestricted grant from Spanish Foundation of Rheumatology and Pfizer (Esperanza Program).
- **Research involving human participants and/or animals:**
    - **Ethical approval:** all procedures performed in this study were in accordance with the ethical standards of the institutional research

committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

  - This article does not contain any studies with animals performed by any of the authors.

- **Informed consent:** informed consent was obtained from all indivicual participants included in the study.

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5.2.4. ARTICLE 5

TITLE: "Ultrasonographic Assessment of nail in Psoriatic Disease Shows a Link Between Onychopathy and Distal Interphalangeal Joint Extensor Tendon Enthesopathy"

JOURNAL: Dermatology 2012 nov; 225: 231-235

AUTHORS: Aydin SZ, **Castillo-Gallego C**, Ash ZR, Marzo-Ortega H, Wakefield RJ, Wittmann M, McGonagle D.

5.2.4.1. PATIENTS AND METHODS

5.2.4.1.1. Patient groups and clinical assessment

This part of the Thesis work was approved by the Leeds (East) Research Ethics Committee. Informed consent was obtained from all participants. A total of 86 psoriasis patients with or without PsA (169 nails) and 20 healthy controls (HC) (40 nails) were assessed for the purpose of this study. Macroscopic nail features were assessed by clinical examination. Abnormalities including onycholysis, pits, nail plate crumbling, leuconychia, splinter haemorrhages, nail bed hyperkeratosis and red spots in the lunula were recorded and scored by using the mNAPSI scoring system by a rheumatologist experienced in this assessment. This assessor was blinded to the US findings.

5.2.4.1.2. Ultrasonography

An US scan of patients' nails was performed by a rheumatologist fully trained in musculoskeletal US (S.Z.A.), using a Logiq E9 machine (General Electric, Wauwatosa, Wisc., USA) and a linear probe at 18–10 MHz. Two nails per patient were scanned by

US. The clinician performing the mNAPSI selected the most severely involved nail and the corresponding nail on the other hand (irrespective of involvement) to be scanned. The ultrasonographer was unaware of the presence or absence of nail disease and was only informed which finger was to be scanned. The nail plate and nail matrix were scanned in every patient. A thick gel layer allowed for appropriate transmission of ultrasound without any additional device. All US assessments were performed using a multiplanar technique, scanning the nail from medial to lateral sites and from the lunula to the distal nail in order to provide as complete coverage as possible. Particular attention was paid to blind the sonographer from the clinical findings; the room was completely darkened during the US assessment and the patients and controls were asked not to talk to the sonographer prior to or during the US assessment. The sonographer did not perform a physical examination, therefore sites other than those involved in the US scan were not seen by the sonographer. The light of the US machine alone is not enough for the sonographer to see the nails clearly. Nail Plate Region. A dorsal longitudinal scan of the distal phalanx at the midline was used for thickness measurements. The thickness of the nail was measured as the maximum distance between the dorsal and ventral nail plates. The sonographic trilaminar appearance of the nail plate was evaluated. The trilaminar structure (two hyperechogenic bands with a hypo/anechogenic band in the middle) was documented as either present or absent.

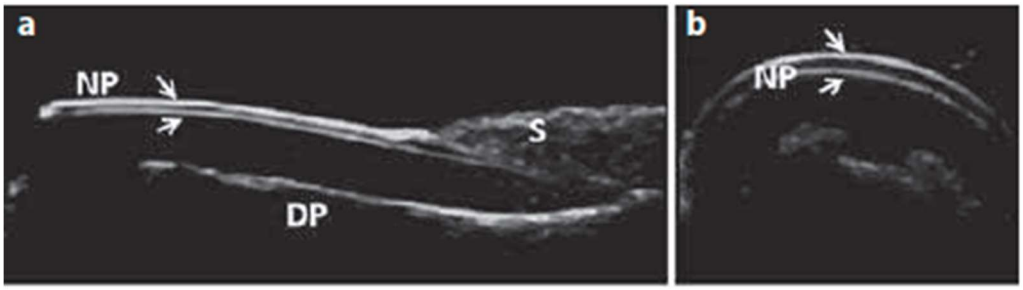

Figure 13 US images of the nail. Longitudinal (a) and transverse (b) scan of the healthy nail demonstrating the trilaminar structure as two hyperechoic lines (arrows) surrounding an anechoic line. (NP= nail plate; S= skin; DP= distal phalanx)

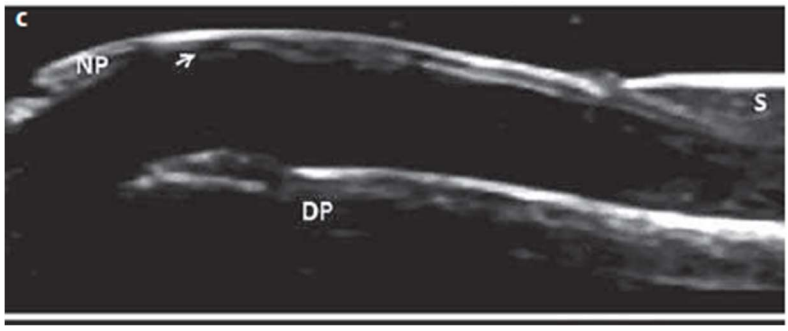

Figure 14 US image of the nail. Loss of the trilaminar appearance at the ventral plate seen as the irregularity and absence of the deeper hyperechoic line (arrow) (NP= nail plate; S= skin; DP= distal phalanx)

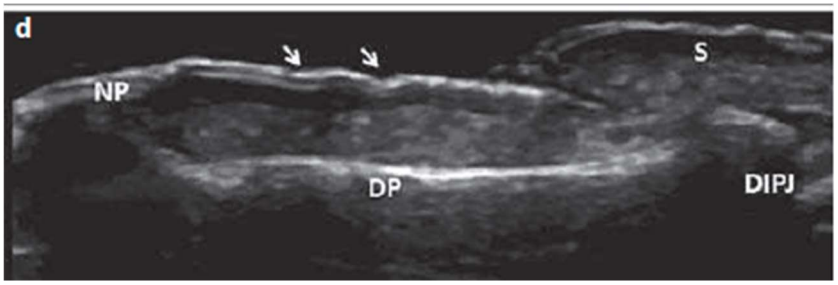

Figure 15 US image of the nail. Pitting and irregularity of the nail plate (arrows). (NP= nail plate; S= skin; DP= distal phalanx; DIPJ= DIP joint)

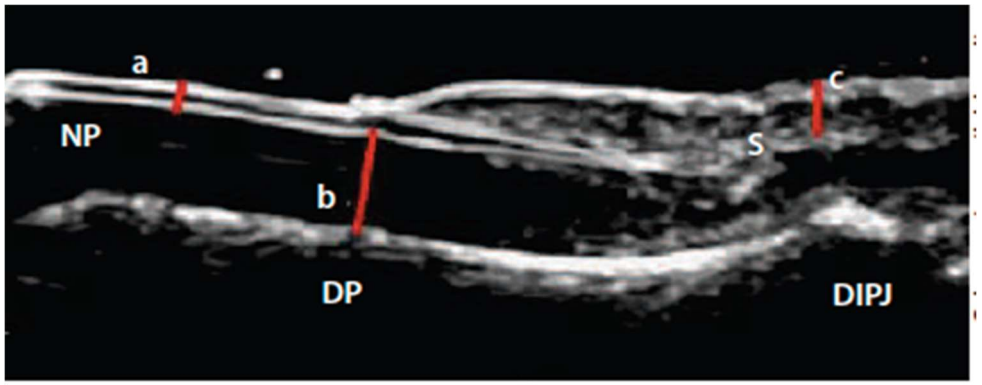

Figure 16 US image of the nail. Measurements of the thickness:

a: nail thickness; the maximum distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix.

b: nail matrix thickness; the distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix.

c: skin thickness; the maximum thickness of the hyperechoic epidermis and hypoechoic dermis around the level of the DIPJ.

(NP= nail plate; S= skin; DP= distal phalanx; DIPJ= DIP joint)

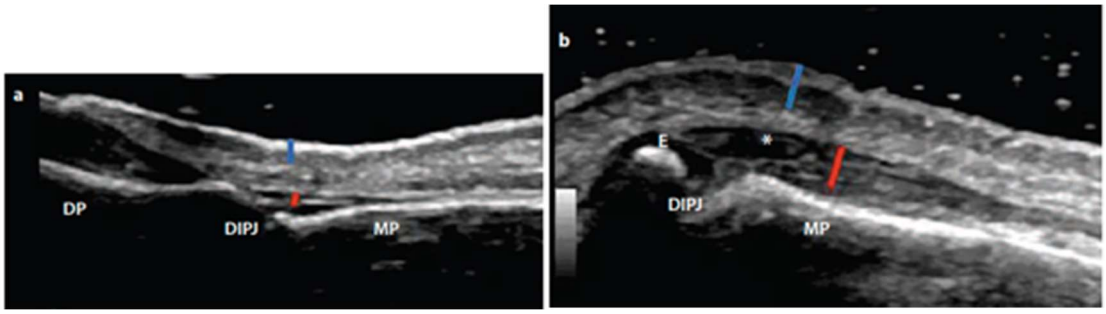

Figure 17 US images of the nail. An example of different enthesal and skin thickness (blue line) in a healthy control (a) and in a patient with psoriasis (b).

The thickening of the extensor tendón (red line) and enthesis is seen in addition to hypoechogenicity (*) and an enthesophyte (E) (b) as well as the increased thickness of the skin.

(DIPJ= DIP joint; DP= distal phalanx; MP: middle phalanx)

Pits and irregularities of the nail plate surface were noted as regions where the normal convexity of the nail plate was lost. Nail Matrix Region. The skin thickness was measured as the maximum thickness of the hyperechoic epidermis and hypoechoic dermis around the level of the DIP joint. The thickness of the matrix was measured as the distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix, determined by a line perpendicular to the bone profile. With respect to the nail matrix region, the thickness of the extensor tendon at the level of insertion was assessed as normal or thickened by comparing it to the proximal part of the tendon. The grey-scale settings used for nail assessment were: frequency at 14 MHz, gain at 18 dB and a dynamic range at 36 dB.

5.2.4.1.4. Statistics

Data are expressed either as frequencies or medians (range). The concordance between US and physical examination was evaluated using absolute agreements and kappa analysis and the prevalence of findings was compared using the x 2 test. The measurements of the HC and patients were compared using the Mann-Whitney U test. To test the differences between subgroups for the presence or absence of nail disease, the Kruskal-Wallis test was applied followed by the Mann-Whitney U test. To assess reproducibility, the images of randomly chosen 100 extensor tendons were reassessed for the presence or absence of thickening by the same investigator blinded to the nail plate findings, and this revealed a moderate agreement with a kappa value of 0.58. Statistical analysis was performed using SPSS version 11.5.

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Ultrasonographic Assessment of Nail in Psoriatic Disease Shows a Link between Onychopathy and Distal Interphalangeal Joint Extensor Tendon Enthesopathy

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Key Words
Psoriasis · Nail disease · Ultrasonography

Abstract
Objective: We compared ultrasonography (US) with the modified nail psoriasis severity index (mNAPSI) to investigate the nail plate, nail matrix and adjacent tendons in subjects with psoriatic nail disease and to test the hypothesis that nail involvement was specifically linked to extensor tendon enthesopathy. ***Methods:*** 86 psoriatic patients (169 nails) and 20 healthy controls (HC) (40 nails) were assessed with both the mNAPSI and US. The thickness of the nail plate, nail matrix region and adjacent extensor tendon were assessed and compared with physical examination findings. ***Results:*** A good agreement between clinical and sonographic nail findings was noted (kappa value = 0.52, $p < 0.0001$). Enthesseal thickening of the extensor tendon on US was more frequent in patients with clinical nail disease compared to patients without clinical nail disease in both psoriasis and psoriatic arthritis (38 vs. 16%, $p = 0.03$, and 47 vs. 19%, $p = 0.008$, respectively). Nail thickness, nail matrix and adjacent skin thickness were higher in psoriatic patients compared to HC. ***Conclusion:*** US and clinical findings show good correlation for the assessment of the nail in psoriatic disease. The demonstration of extensor tendon enthesopathy in both psoriasis and psoriatic arthritis supports the importance of enthesopathy in nail disease pathogenesis whether or not clinical arthritis is present.

Introduction

The importance of nail disease in subjects with psoriasis is being increasingly recognised [1]. Clinically, nail disease is associated with pain, functional loss, disfigurement and psychological distress [2]. From the rheumatological perspective, the presence of nail disease is a predictor for the development of psoriatic arthritis (PsA) [3]. In PsA patients, nail disease is associated with arthritis of the distal interphalangeal (DIP) joint [4, 5]. The nail is directly anchored to the underlying bone by structures including the extensor tendon [6–8]. Enthesopathy is a generalised fea-

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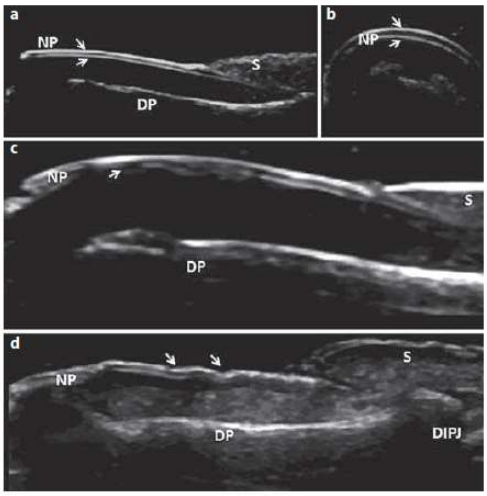

Fig. 1. Longitudinal (**a**) and transverse (**b**) scan of the healthy nail demonstrating the trilaminar structure as two hyperechoic lines (arrows) surrounding an anechoic line. **c** Loss of the trilaminar appearance at the ventral plate seen as the irregularity and absence of the deeper hyperechoic line (arrow). **d** Pitting and irregularity of the nail plate (arrows). NP = Nail plate; S = skin; DP = distal phalanx; DIPJ = DIP joint.

ture of both psoriasis and PsA and we have recently demonstrated that in psoriasis patients, nail disease is associated with a greater degree of systemic enthesopathy [9].

Presently, assessment of nail disease is difficult given the limited utility of clinical assessment tools for the nail, which include the nail psoriasis severity index (NAPSI) and the modified NAPSI (mNAPSI) [10, 11]. Recently magnetic resonance imaging, ultrasonography (US) and optical coherence tomography have been reported as possible tools for a more objective assessment of nail disease [12–15]. US has wide availability in the rheumatology setting, modest costs, a high resolution and allows good visualisation of tendons and entheses. With respect to the nail matrix region, we were especially interested to determine whether US had the capability to detect local DIP joint enthesopathy in PsA and psoriasis patients. No US-based imaging study of the nail has considered the matrix region before. Therefore in the present study, we assessed the utility of US for the assessment of psoriatic nail disease including both the nail plate and nail matrix region.

Methods

Patient Groups and Clinical Assessment

This study was approved by the Leeds (East) Research Ethics Committee. Informed consent was obtained from all participants. A total of 86 psoriasis patients with or without PsA (169 nails) and 20 healthy controls (HC) (40 nails) were assessed for the purpose of this study.

Macroscopic nail features were assessed by clinical examination. Abnormalities including onycholysis, pits, nail plate crumbling, leuconychia, splinter haemorrhages, nail bed hyperkeratosis and red spots in the lunula were recorded and scored by using the mNAPSI scoring system [10] by a rheumatologist experienced in this assessment. This assessor was blinded to the US findings.

Ultrasonography

An US scan of patients' nails was performed by a rheumatologist fully trained in musculoskeletal US (S.Z.A.), using a Logiq E9 machine (General Electric, Wauwatosa, Wisc., USA) and a linear probe at 18–10 MHz. Two nails per patient were scanned by US. The clinician performing the mNAPSI selected the most severely involved nail and the corresponding nail on the other hand (irrespective of involvement) to be scanned. The ultrasonographer was unaware of the presence or absence of nail disease and was only informed which finger was to be scanned. The nail plate and nail matrix were scanned in every patient. A thick gel layer allowed for appropriate transmission of ultrasound without any additional device.

All US assessments were performed using a multiplanar technique, scanning the nail from medial to lateral sites and from the lunula to the distal nail in order to provide as complete coverage as possible. Particular attention was paid to blind the sonographer from the clinical findings; the room was completely darkened during the US assessment and the patients and controls were asked not to talk to the sonographer prior to or during the US assessment. The sonographer did not perform a physical examination, therefore sites other than those involved in the US scan were not seen by the sonographer. The light of the US machine alone is not enough for the sonographer to see the nails clearly.

Nail Plate Region. A dorsal longitudinal scan of the distal phalanx at the midline was used for thickness measurements. The thickness of the nail was measured as the maximum distance between the dorsal and ventral nail plates. The sonographic trilaminar appearance of the nail plate was evaluated [13]. The trilaminar structure (two hyperechogenic bands with a hypo/anechogenic band in the middle) was documented as either present or absent. Pits and irregularities of the nail plate surface were noted as regions where the normal convexity of the nail plate was lost (fig. 1).

Nail Matrix Region. The skin thickness was measured as the maximum thickness of the hyperechoic epidermis and hypoechoic dermis around the level of the DIP joint. The thickness of the matrix was measured as the distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix, determined by a line perpendicular to the bone profile (fig. 2). With respect to the nail matrix region, the thickness of the extensor tendon at the level of insertion was assessed as normal or thickened by comparing it to the proximal part of the tendon. The grey-scale settings used for nail assessment were: frequency at 14 MHz, gain at 18 dB and a dynamic range at 36 dB.

Statistics

Data are expressed either as frequencies or medians (range). The concordance between US and physical examination was evaluated using absolute agreements and kappa analysis and the prevalence of findings was compared using the χ^2 test. The measurements of the HC and patients were compared using the Mann-Whitney U test. To test the differences between subgroups for the presence or absence of nail disease, the Kruskal-Wallis test was applied followed by the Mann-Whitney U test.

To assess reproducibility, the images of randomly chosen 100 extensor tendons were reassessed for the presence or absence of thickening by the same investigator blinded to the nail plate findings, and this revealed a moderate agreement with a kappa value of 0.58.

Statistical analysis was performed using SPSS version 11.5.

Results

Of the psoriatic patients, 33/86 (38.4%) were female, compared to 11/20 (55.0%) of the HC. 52 of the psoriatic patients (60.5%) had clinical nail disease and 42 patients (48.8%) had arthritis. Median (range) of disease duration in patients with psoriasis was 16 (1–55) months and mNAPSI score was 15 (1–56) in patients with nail disease. None of the HC had any known clinical nail disease, psoriasis nor arthritis.

Nail Plate Findings by US and Comparison with Clinical Assessment

Patients with psoriasis had significantly more US findings of the nail than HC (42/86 [48.8%] vs. 2/20 [10.0%], $p < 0.002$). There were more abnormal nail US findings in nails with clinical findings (57/101 [56.4%] vs. 6/68 [8.8%], $p < 0.0001$). mNAPSI scores were higher in the presence of any nail abnormality by US (14 [0–50] vs. 1 [0–56], $p < 0.0001$).

The absolute agreement between US and clinical assessment in the 169 nails of the psoriatic patients was 76.3% with a kappa value of 0.52 ($p < 0.0001$). US detected abnormalities in 10 nails where clinical examination was normal. Conversely, US failed to demonstrate any lesions in 30 nails despite the presence of a positive clinical finding. These patients had either onycholysis or pitting but collectively their nails had milder abnormalities with lower mNAPSI scores than nails that were abnormal on US (mNAPSI 10 [1–56] vs. 17 [1–50], $p = 0.03$).

Nail thickness was greater in patients in the psoriasis group compared to HC (0.56 mm [0.3–1.9] vs. 0.5 mm [0.3–0.6], $p < 0.0001$). Nail thickness was higher in those nails with clinical abnormalities (0.6 mm [0.3–1.9] vs. 0.5 mm [0.3–0.9], $p < 0.0001$).

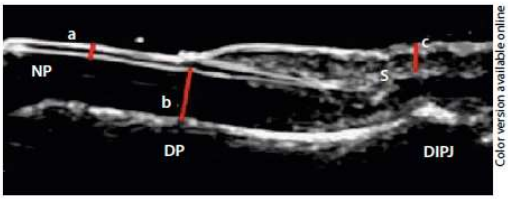

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Fig. 2. Measurements of the thickness and comparison between groups. **a** Nail thickness: The maximum distance between the dorsal and ventral nail plates. **b** Nail matrix thickness: The distance between the ventral nail plate and the cortex of the distal phalanx at the level of the matrix. **c** Skin thickness: The maximum thickness of the hyperechoic epidermis and hypoechoic dermis around the level of the DIP joint (DIPJ). NP = nail plate; S = skin; DP = distal phalanx.

Nail Matrix Findings

Whereas US and clinical examination were broadly similar in the assessment of the nail plate, the US assessment of the nail matrix, skin and DIP joint region was very revealing. Entheseal thickening of the extensor tendon insertion region was more frequent in patients in whom there was an abnormality in the adjacent nail by physical examination (35/83 vs. 15/86, $p = 0.001$). When different clinical nail findings were analysed separately, onycholysis (26/50 [52.0%] vs. 34/119 [28.6%], $p = 0.005$), pitting (23/50 [46.0%] vs. 36/119 [30.3%], $p = 0.05$) and nail crumbling (7/50 [14.0%] vs. 3/119 [2.5%], $p = 0.008$) were found more frequently in patients with extensor tendon entheseal thickening. Likewise entheseal thickening of the extensor tendon insertion region was more frequent in patients in whom there was an abnormality in the adjacent nail by US, but this difference was not statistically significant (24/63 [38.1%] vs. 26/106 [24.5%], $p = 0.08$).

Both sonographically determined nail matrix and skin thickness were higher in patients with psoriasis compared to HC (nail matrix thickness: 1.9 mm [1.1–3.9] in psoriasis vs. 1.8 mm [1.2–2.2] in HC, $p = 0.003$; skin thickness: 1.1 mm [0.7–1.9] in psoriasis vs. 1 mm [0.6–1.6] in HC, $p < 0.0001$). Of note, skin thickness in psoriasis was not higher in those with clinical nail disease compared to those without nail disease (table 1). The thickness of the matrix was higher if there was clinical nail disease (2 mm [1.2–3.9] vs. 1.8 mm [1.1–2.5], $p < 0.0001$).

However, with respect to the extensor tendon insertion region we noted that tendon enthesopathy was often

Table 1. Comparison of extensor tendon thickening, skin, nail and nail matrix thickness between different disease groups

	Psoriasis		Psoriatic arthritis		Healthy controls
	nail disease	normal nails	nail disease	normal nails	
Extensor tendon thickening, frequency (%)	17/45 (38)	7/43 (16)	18/38 (47)	8/43 (19)	0/40 (0)
Median skin thickness, mm (range)	1.1 (0.8–1.9)	1.05 (0.7–1.7)	1.07 (0.7–1.7)	1.1 (0.7–1.9)	1 (0.6–1.6)
Median matrix thickness, mm (range)	1.9 (1.2–3.9)	1.8 (1.2–2.4)	2 (1.5–3.5)	1.7 (1.1–2.5)	1.8 (1.2–2.2)
Nail plate thickness (range)	0.6 (0.3–1.2)	0.5 (0.3–0.7)	0.7 (0.4–1.9)	0.5 (0.3–0.9)	0.5 (0.3–0.6)

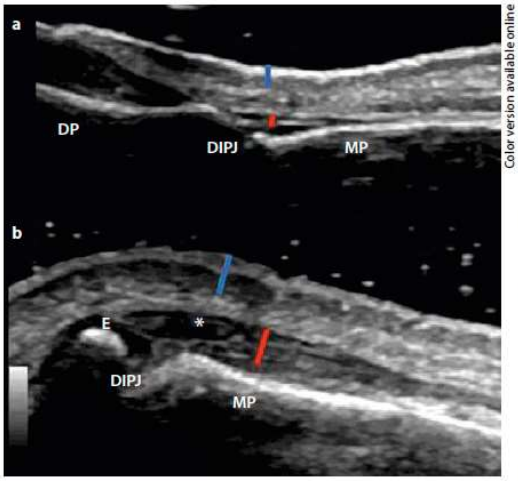

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Fig. 3. An example of different entheseal and skin thickness (blue line) in a HC (**a**) and in a patient with psoriasis (**b**). The thickening of the extensor tendon (red line) and enthesis is seen in addition to hypoechogenicity (*) and an enthesophyte (E) (**b**) as well as the increased thickness of the skin. DIPJ = DIP joint; DP = distal phalanx; MP = middle phalanx.

associated with thickening of the adjacent epidermis and oedema of the dermis (skin thickness in patients with entheseal thickening 1.2 mm [0.7–1.9] compared to those without entheseal thickening 1.02 mm [0.7–1.9], p = 0.009) (fig. 3).

To ascertain whether the extensor tendon thickening was related to clinical DIP arthropathy or whether it could be linked to psoriasis and nail disease without clinical arthropathy, we looked at both groups separately. Patients with or without PsA had similar thicknesses of the skin, nail and matrix. Similarly, the relationship between extensor tendon thickening and clinical nail disease was seen in both psoriasis and PsA (table 1).

In patients with clinical DIP disease (with tenderness or swelling), extensor tendon thickening was more frequent (11/18 [61.1%] in active DIP joints vs. 39/151 [25.8%] in non-active DIP joints, p = 0.005). The thickness of the skin (1.3 mm [0.8–1.9] vs. 1.1 mm [0.7–1.9], p = 0.04) and the matrix (2.1 mm [1.4–2.9] vs. 1.9 mm [1.1–3.9], p = 0.05) were higher in those with clinical DIP disease whereas nail thicknesses were similar (0.55 mm [0.3–0.9] vs. 0.56 mm [0.3–0.9], p = 0.8).

Discussion

This is the first study using US to assess the entire nail apparatus including the nail plate and nail matrix region, where it is now known that the nail is integrated with the skeleton [6]. Both US and clinical examination were broadly similar for the assessment of the nail plate region. In the evaluation of the nail matrix region we noted an association between extensor tendon enthesopathy and nail disease. This enthesopathy was specifically associated with nail disease but not clinical PsA. These findings are relevant for the development of US for the assessment of the nail disease and also point towards the importance of the enthesis in nail involvement.

These findings have implications for a better understanding of nail disease in psoriasis. The link between enthesopathy on US and clinical nail disease was not confined to pitting, a recognised matrix-specific abnormality, but was also seen with onycholysis (thought to be a nail plate lesion) which therefore would not be expected to be related to extensor tendon disease. These findings raise the possibility that nail pain and loss of function seen in the dermatological setting may in part be related to microenthesopathy-related pain. The relevance of

these changes for the development of PsA and their relevance for the prognosis of nail disease awaits further study.

Another noteworthy finding of the present study was that the DIP enthesopathy was associated with both epidermal thickening and dermal oedema. This is interesting since it suggests a very close link between the pathology in the skin and the adjacent enthesis and to the best of our knowledge has not being recognised before. Perhaps the skin changes may be secondary to extension of the inflammatory processes to the adjacent dermis with secondary epidermal changes, or they may reflect common mechanical stretching responses to the skin and enthesis during finger flexion.

There are some potential limitations to this study. As with all US studies on psoriasis, it is not technically possible to be completely blinded to the skin findings if the patient has very severe disease. We tried to avoid this situation by avoiding conversation between the patient and the ultrasonographer about their disease and by having the room completely darkened from the beginning of the assessment.

In conclusion, this study confirms that US is helpful to objectively assess psoriatic nail disease and compares favourably with clinical assessment. Given that only superficial changes can be detected by physical examination, US proved to be informative in the nail matrix and adjacent extensor tendon region. In particular the US findings in this study showed a link between extensor tendon enthesopathy and nail disease. This supports the concept that nail disease in psoriasis is more than skin deep, and is linked to enthesopathy. This has broad implications for further studies into nail disease in psoriasis.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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5.3. OCT and US in the assessment of nail disease in Psoriasis and Psoriatic Arthritis

5.3.1. ARTICLE 6

TITLE: *"*Potential use of optical coherence tomography and high-frecuency ultrasound for the assessment of nail disease in psoriasis and psoriatic arthritis"

JOURNAL: Dermatology 2013 Aug; 227: 45-51

AUTHORS: Aydin SZ, **Castillo-Gallego C**, Ash ZR, Abignano G, Marzo-Ortega H, Wittmann M, Del Galdo F, McGonagle D.

5.3.1.1. PATIENTS AND METHODS

5.3.1.1.1. Patient Groups and Clinical Assessment

This part of the Thesis work was a 'real-life' evaluation of imaging performed within the clinics of the Leeds Teaching Hospitals. A total of 300 finger nails of 18 patients with at least one diseased nail (5 psoriasis, 13 PsA) and 12 healthy controls (HCs) were assessed. All patients were aged >18 years. Macroscopic nail features including onycholysis, pitting, nail plate crumbling, leuconychia, splinter haemorrhages, nail bed hyperkeratosis and red spots in the lunula were scored using the mNAPSI scoring system by a rheumatologist who was blinded to the US and OCT findings.

5.3.1.1.2. Ultrasound

An US scan of finger nails was performed in patients with psoriasis by a

rheumatologist fully trained in musculoskeletal US (C.C.G.), using a Logiq E9 machine (General Electric, Wauwatosa, Wisc., USA) and a linear probe at 9–14 MHz. The US assessment was performed in a darkened room and the sonographer was blinded as far as possible to the presence or absence of arthritis and nail disease. Patients were asked not to communicate with the sonographer. All US assessments were performed using a multiplanar technique, scanning the nail from the medial to the lateral side and from the lunula to the distal nail in order to provide as complete coverage as possible. The nail plate, nail matrix and nail bed of all fingers of the hands were scanned. A thick gel layer allowed for appropriate transmission of US without any additional device.

The nail plate is seen in normal nails as two hyperechogenic bands with a hypoechogenic band in the middle, which is thus called a trilaminar appearance. The loss of this trilaminar appearance of the nail plate and the presence of pits or irregularities in the nail surface were noted using grey-scale US.

5.3.1.1.3. OCT Assessment

All patients and controls were scanned using OCT by a different investigator (S.Z.A.) blinded to the clinical details using a VivoSight optical OCT Probe (Michelson Diagnostics, Orpington, UK) which is a multibeam frequency-domain type OCT with a central laser wavelength of 1,305 nm and a sweep range of 150 nm. The nail plates were assessed longitudinally from the lunula to the distal nail and from the lateral to the medial side. The OCT probe was applied directly to the nail without intermediate gel. The scanning of each nail lasted less than 1 min and did not cause dis- comfort to the subjects studied. OCT provided images of the nail plate, the nail bed and the matrix up to a depth of 2 mm and a width of 4 mm. The multislice mode was used, recording 100 slices per nail with interslice spacing of 4 μm to provide densely sampled 3D ‘bread

slice' image volumes. In standard OCT the nail plate appeared as a layered structure containing a number of horizontal homogeneous bands of varying intensity and thickness. At the lunula and at sites of leuconychia, distinct horizontal white bands were seen at the deep end of the nail plate and within the nail plate, respectively. We assessed these lesions as well as other findings within the nail plate and surface abnormalities that have not been described previously.

5.3.1.1.4. Nail OCT images

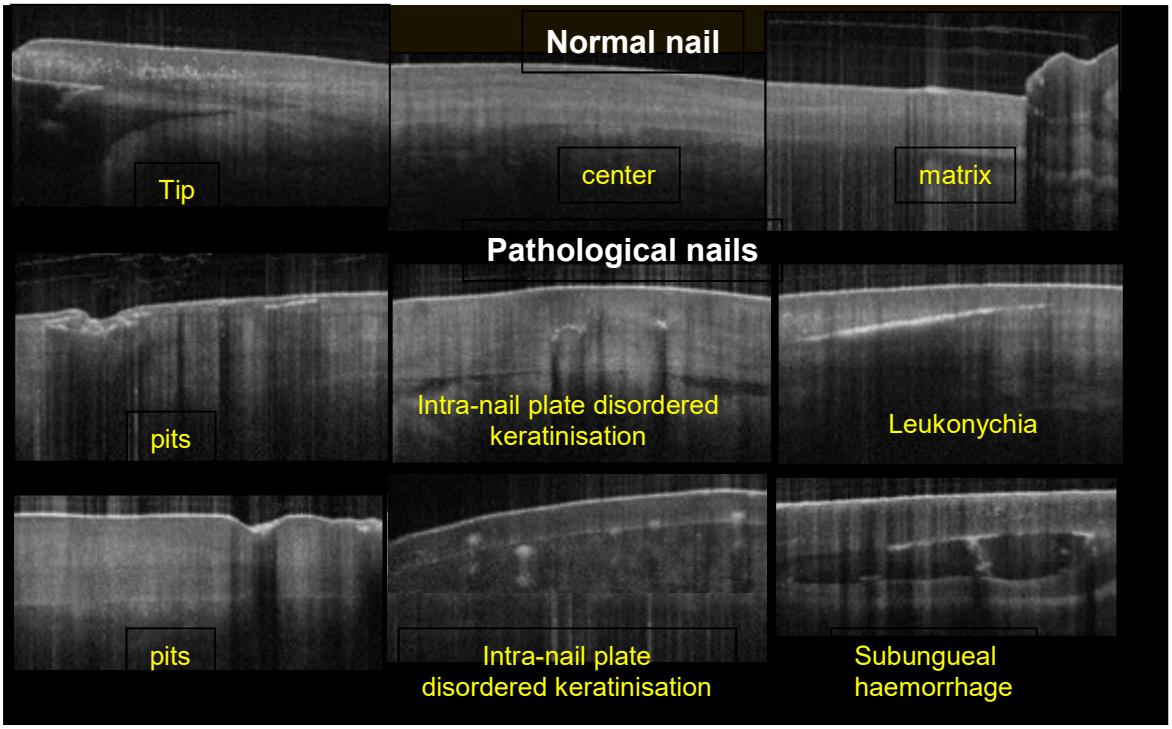

Figure 18 Nail OCT images (normal and pathological nails)

OCT showed remarkably high quality images of the nail, the adjacent nail matrix and the subungual epidermis and vessels.
The most striking finding was that of leuconychia, manifesting as diffuse "white" lines running obliquely along the middle third of the nail.
Pits were very superficial and were associated with disorders of the nail matrix keratinisation.
OCT also showed other nail lesions as intra-nail plate disordered queratinisation and subungueal haemorrhage.

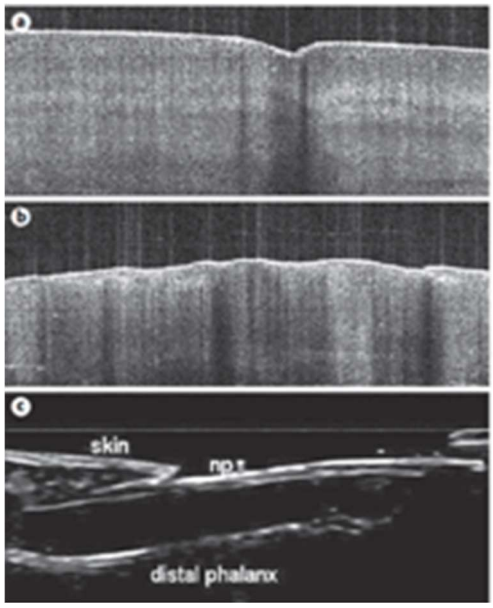

Figure 19 Nail OCT and corresponding US images

OCT of the nails in psoriasis and PsA. Pitting is seen as an irregularity of the superficial nail plate, sometimes associated with an underlying shadow. **a** Focal pitting. **b** A more diffuse lesion seen as waving of the superficial nail plate. **c** Corresponding US image of the nail seen in **a** . NP = Nail plate.

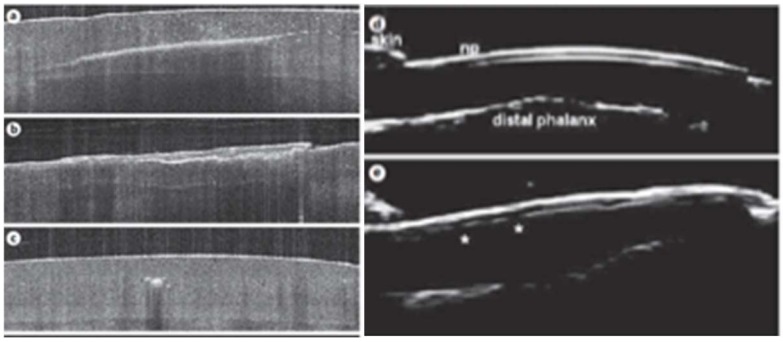

Figure 20 Appearance of hyperreflective lesions on OCT and the corresponding US images:

a–c Appearance of hyperref lective lesions on OCT.
a Linear regular stripes (seen clinically as leuconychia) located in between the two borders of the nail plate. **b** Thickening and irregularity of the superficial layer. **c** Hyperref lective spots, sometimes with an underlying shadow, depending on the density of the calcification.

d, **e** Corresponding US images.
d US image corresponding to **a**, demonstrating the well-depicted trilaminar appearance [nail plates seen as two white (hyperechoic) lines with a black line (anechoic) in between. **e** US image corresponding to **c**, with local losses of trilaminar appearance, but no focal lesions are seen in between the nail plates. Asterisks indicate loss of the trilaminar appearance.

5.3.1.1.5. Statistics

Data are expressed either as frequencies or means (± standard deviation). The concordance between OCT, US and physical examination was evaluated using absolute agreements and kappa analysis and the prevalence of findings was compared by χ 2 test. The sensitivities, specificities and likelihood ratios of different OCT findings to differentiate psoriasis were calculated. Statistical analysis was performed using SPSS version 11.5.

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Potential Use of Optical Coherence Tomography and High-Frequency Ultrasound for the Assessment of Nail Disease in Psoriasis and Psoriatic Arthritis

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Key Words
Validation · Optical coherence tomography · Ultrasound · Psoriasis · Nail disease

Abstract
Background: Psoriatic nail disease is increasingly recognised to be of major clinical and research relevance. Clinical assessment remains the current gold standard for its evaluation. ***Objective:*** We compared optical coherence tomography (OCT) and ultrasound (US) for nail disease assessment in psoriatic disease. ***Methods:*** 18 patients with at least one involved nail and 12 healthy controls were scanned using OCT; psoriatic patients also had an US scan (using a linear probe at 9–14 MHz). Nail and contour abnormalities were documented. Clinical onychopathy was scored independently using the modified Nail Psoriasis Severity Index. ***Results:*** Among 180 nails, 67.8% had clinical findings whereas 33.9% were abnormal by US and 44.4% had abnormalities on OCT. A positive OCT had a sensitivity and specificity of 44.4 and 95.8%, respectively, with a positive likelihood ratio of 10.7 for nail disease. OCT demonstrated 76.3% absolute agreement compared with clinical assessment and 65% with US. OCT detected subtle abnormalities in 12 clinically normal nails and in 41 nails with normal US findings. ***Conclusion:*** These findings show that OCT has a potential for the systematic characterisation of psoriatic nail changes and could be useful in diagnosis and more objective assessment of treatment response.

Introduction

Nail disease represents both a clinically and pathophysiologically important aspect of both psoriasis and psoriatic arthritis (PsA). In psoriasis, nail involvement may be associated with significant pain and functional impairment [1]. The pathogenesis of several matrix and plate lesions including pitting, leuconychia and onycholysis is still not clearly defined. The historical difficulties in assessing treatments for nail psoriasis have in part stemmed from the lack of objective assessment tools, as well as the duration of treatment needed to see a response. Currently these lesions may be clinically scored and evaluated using the Nail Psoriasis Severity Index (NAPSI) or

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the modified NAPSI (mNAPSI) system [2, 3]. The advent of biological therapies which effectively treat psoriasis, PsA and nail disease has further heightened the importance of understanding nail involvement. Nail disease scores are one of the outcome measures used to assess the success of therapy, and therefore it is important to have a measure which is objective and sensitive to change.

From the rheumatological viewpoint, nail disease is important since it is a predictor of future PsA development [4]. Nail disease is also more common in PsA compared to psoriasis without arthritis [5–8]. The basis for this observation has now become more clear as enthesitis (inflammation at tendon and ligament insertions) has been shown to be a key feature of the skeletal manifestations of PsA [9, 10]. It has been suggested that the normal nail is anchored to the skeleton via a network of entheses [11]. Patients with nail disease also have more subclinical enthesitis both at the distal interphalangeal joint level as well as at remote sites [12, 13], although the link between the different patterns of nail disease and subclinical enthesitis remains enigmatic [14, 15].

A combination of these dermatological and rheumatological issues has led to an increased interest in imaging of the nail to better understand disease mechanisms. We have previously used both conventional and high-resolution MRI to image nail disease and to show that the nail is functionally integrated with the skeleton, as outlined above [16, 17]. Whilst MRI is good for demonstrating the bone and soft tissues around the nail, the nail itself is very poorly visualised due to its low water content. Several studies have reported the use of ultrasound (US) in nail evaluation. Given the accessibility and low cost of US, it may become the method of choice for nail disease evaluation [13, 18–20].

Nevertheless, there is a need for improved nail imaging techniques for making a diagnosis, understanding disease mechanisms and monitoring the response to therapy. Recently we reported on our preliminary experience with optical coherence tomography (OCT) for the assessment of nail disease in psoriasis [21]. The accuracy of OCT for measuring nail thickness has previously been reported [22]. OCT is a non-invasive optical imaging technique that has the advantage of incredibly high spatial resolution compared to other clinically available methods. It is already in dermatological use for the assessment of skin tumours [23–26]. As the light-based analogue of US pulse-echo imaging, OCT systems focus a low-intensity infrared beam in tissue and analyse scattered light to provide tomograms and 3D volumes of morphology up to 2 mm below the surface. While ophthalmic OCT has been in use since the early 1990s, advanced laser technology and multibeam modalities have enabled the development of high-speed and ultra-high-sensitivity 'frequency-domain OCT' which provides the superior contrast necessary to create dermatological images with <10 μm resolution at video rate [27, 28].

Here we compare OCT and US of the nail to ascertain which of them is the best imaging modality and how they compare to clinical assessment. We also describe in detail the anatomical location of the different psoriasis-associated nail lesions.

Subjects and Methods

Patient Groups and Clinical Assessment

This was a 'real-life' evaluation of imaging performed within the clinics of the Leeds Teaching Hospitals. A total of 300 finger nails of 18 patients with at least one diseased nail (5 psoriasis, 13 PsA) and 12 healthy controls (HCs) were assessed. All patients were aged >18 years. Macroscopic nail features including onycholysis, pitting, nail plate crumbling, leuconychia, splinter haemorrhages, nail bed hyperkeratosis and red spots in the lunula were scored using the mNAPSI scoring system by a rheumatologist who was blinded to the US and OCT findings.

Ultrasound

An US scan of finger nails was performed in patients with psoriasis by a rheumatologist fully trained in musculoskeletal US (C.C.G.), using a Logiq E9 machine (General Electric, Wauwatosa, Wisc., USA) and a linear probe at 9–14 MHz. The US assessment was performed in a darkened room and the sonographer was blinded as far as possible to the presence or absence of arthritis and nail disease. Patients were asked not to communicate with the sonographer. All US assessments were performed using a multiplanar technique, scanning the nail from the medial to the lateral side and from the lunula to the distal nail in order to provide as complete coverage as possible. The nail plate, nail matrix and nail bed of all fingers of the hands were scanned. A thick gel layer allowed for appropriate transmission of US without any additional device.

The nail plate is seen in normal nails as two hyperechogenic bands with a hypoechogenic band in the middle, which is thus called a trilaminar appearance. The loss of this trilaminar appearance of the nail plate and the presence of pits or irregularities in the nail surface were noted using grey-scale US.

OCT Assessment

All patients and controls were scanned using OCT by a different investigator (S.Z.A.) blinded to the clinical details using a VivoSight Topical OCT Probe (Michelson Diagnostics, Orpington, UK) which is a multibeam frequency-domain type OCT with a central laser wavelength of 1,305 nm and a sweep range of 150 nm.

The nail plates were assessed longitudinally from the lunula to the distal nail and from the lateral to the medial side. The OCT probe was applied directly to the nail without intermediate gel. The scanning of each nail lasted less than 1 min and did not cause dis-

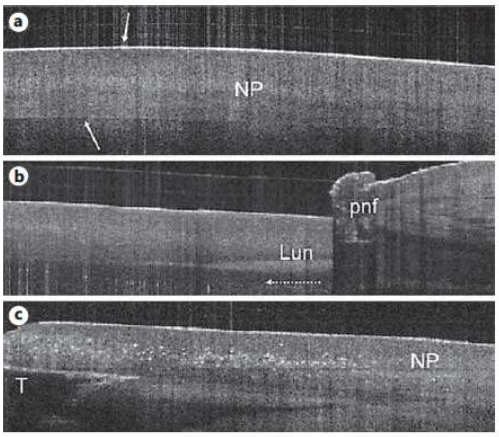

Fig. 1. a Typical appearance of the healthy nail by OCT. The superficial and the deeper layers of the nail plate (NP) are clearly marked (arrows). **b** The lunula (Lun) has a bright triangle shape with the apex showing the tip of the finger (dashed arrow showing the direction). **c** Highly reflective spots within the tip (T) of the nail. PNF = Proximal nail fold.

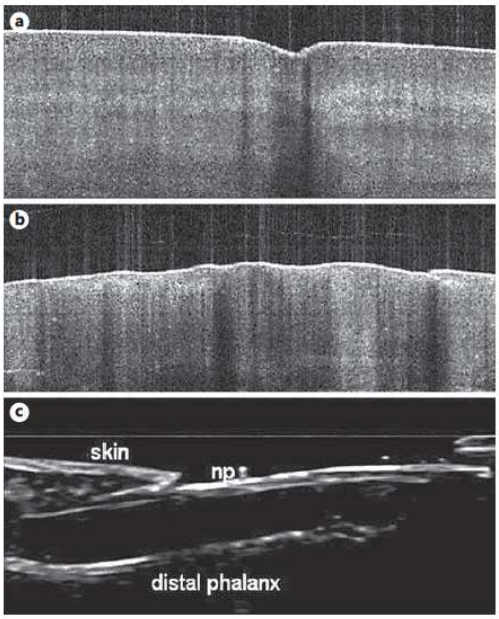

Fig. 2. OCT of the nails in psoriasis and PsA. Pitting is seen as an irregularity of the superficial nail plate, sometimes associated with an underlying shadow. **a** Focal pitting. **b** A more diffuse lesion seen as waving of the superficial nail plate. **c** Corresponding US image of the nail seen in **a**. NP = Nail plate.

comfort to the subjects studied. OCT provided images of the nail plate, the nail bed and the matrix up to a depth of 2 mm and a width of 4 mm. The multislice mode was used, recording 100 slices per nail with interslice spacing of 4 μm to provide densely sampled 3D 'bread slice' image volumes.

In standard OCT the nail plate appeared as a layered structure containing a number of horizontal homogeneous bands of varying intensity and thickness. At the lunula and at sites of leuconychia, distinct horizontal white bands were seen at the deep end of the nail plate and within the nail plate, respectively. We assessed these lesions as well as other findings within the nail plate and surface abnormalities that have not been described previously.

Statistics

Data are expressed either as frequencies or means (± standard deviation). The concordance between OCT, US and physical examination was evaluated using absolute agreements and kappa analysis and the prevalence of findings was compared by χ^2 test. The sensitivities, specificities and likelihood ratios of different OCT findings to differentiate psoriasis were calculated. Statistical analysis was performed using SPSS version 11.5.

Results

Clinical Assessment

None of the HCs had any abnormal nail findings by physical examination whereas all psoriasis patients (including patients with or without arthritis) had at least one abnormal nail. Clinical abnormalities were seen in 122/180 (67.8%) nails of patients with psoriasis. The mean (standard deviation) number of abnormal nails per patient within the psoriasis group [6.7 (3.3)] was significantly higher than in HCs [0 (0); $p < 0.0001$], as was the mean mNAPSI score [14 (11.4) vs. 0 (0); $p < 0.0001$].

Ultrasound Findings

Fourteen of the 18 (77.8%) psoriasis patients had at least one abnormality detected on US. Within 180 assessed nails, 61 (33.9%) had either loss of trilaminar appearance or pitting (50 had loss of trilaminar appearance, 25 had pitting and 14 had both). Of the 58 nails in the psoriatic subjects that were scored clinically as normal, 11 had loss of trilaminar appearance on US, 7 had pitting and 5 had both.

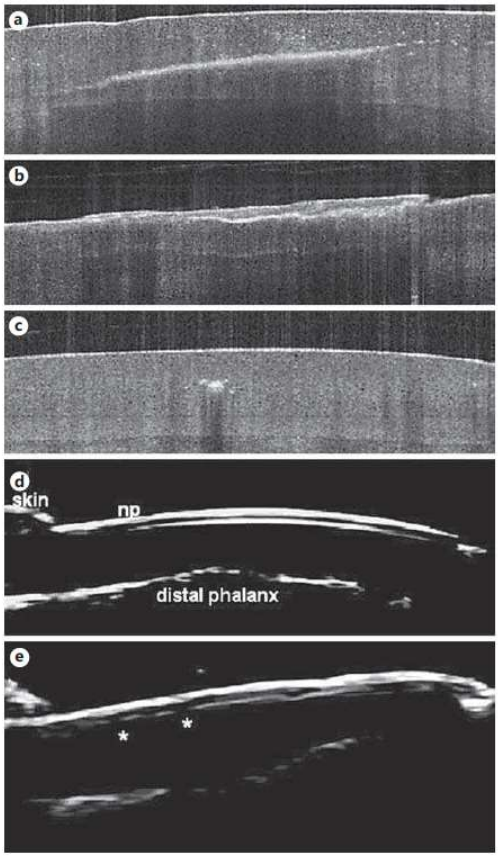

Fig. 3. a–c Appearance of hyperreflective lesions on OCT. **a** Linear regular stripes (seen clinically as leuconychia) located in between the two borders of the nail plate. **b** Thickening and irregularity of the superficial layer. **c** Hyperreflective spots, sometimes with an underlying shadow, depending on the density of the calcification. **d**, **e** Corresponding US images. **d** US image corresponding to **a**, demonstrating the well-depicted trilaminar appearance [nail plates seen as two white (hyperechoic) lines with a black line (anechoic) in between. **e** US image corresponding to **c**, with local losses of trilaminar appearance, but no focal lesions are seen in between the nail plates. Asterisks indicate loss of the trilaminar appearance.

OCT of Normal Nail Matrix and Plate

The typical appearance of the nail by OCT is demonstrated in figure 1a. The skin underneath the lunula appeared brighter than that more distally. This may be due to better light penetration of the lunula region where nail keratinisation is less pronounced (fig. 1b). The tips of the nails in normal subjects had areas of high reflective spots, which was also very common in patients (fig. 1c). Therefore this finding was not considered as an abnormality.

OCT of Nails in Psoriasis and Psoriatic Arthritis

Because of the depth of the tissues and the attenuation of signal in depth, the imaging capabilities of OCT for visualisation of the nail matrix and extensor tendon enthesis region were poor compared to US, so the nail matrix region was not evaluated. On OCT, pitting could be seen to be remarkably superficial and it was often associated with small areas of sclerosis in the superficial nail plate, which, on occasion, attenuated the incident light to a critical degree, causing a shadow under the pit (fig. 2a). Milder lesions could be observed as wavy irregularity of the superficial nail plate (fig. 2b).

Leuconychia had a very characteristic OCT appearance: it could be visualized as linear regular white stripes which were evident in the mid third of the nail plate and were always angled downwards from proximal to distal (fig. 3a). Other hyperechoic lesions of the nail plate could be seen, including thickening and irregularity of the superficial layer (fig. 3b) and hyperreflective spots (fig. 3c). Hyperreflective spots were sometimes seen as multiple lesions and sometimes as one lesion per nail. Depending on the density of the hyperreflective lesion, a post-lesion shadow could be seen, again hiding the structure of the nail plate.

Two of the 12 HCs (16.7%) had at least one abnormal nail by OCT. One HC had 4 abnormal nails by OCT, all having hyperreflective spots. The other HC had one nail with linear hyperreflective lesions on OCT. None of the HCs had pitting/waving. Within patients, 15/18 (83.3%) had at least one abnormal nail by OCT. As expected, the number of involved nails by OCT per patient was significantly higher in patients compared to HCs [4.4 (3.4) vs. 0.4 (1.2); $p < 0.0001$]. When analysed per nail, patients had a significantly higher number of involved nails by OCT compared to HCs [80/180 (44.4%) vs. 5/120 (4.2%); $p < 0.0001$].

OCT detected abnormalities in 12/58 clinically normal nails in psoriatic patients (6 with linear stripes, 3 with thickening of the superficial layer, 5 with pitting and 2 with multiple lesions) compared to 5/120 nails in HCs ($p = 0.001$). The absolute agreement between OCT and

Table 1. Sensitivity, specificity as well as positive and negative likelihood ratios (LR+, LR–) of the OCT findings

	Sensitivity	Specificity	LR+ (CI)	LR– (CI)
Hyperreflective lesions on OCT	41.1	95.8	9.9 (4.1–23.7)	0.6 (0.5–0.7)
Punctate hyperreflective lesion	8.9	96.7	2.7 (0.9–7.8)	0.9 (0.9–1)
Diffuse linear hyperreflective lesion	18.9	99.2	22.7 (3.2–163.4)	0.8 (0.8–0.9)
Hyperkeratinisation of the superficial layer	13.3	100	nc	0.9 (infinite)
Pitting/waving of the superficial layer	13.9	100	nc	0.9 (infinite)
Any OCT finding	44.4	95.8	10.7 (4.5–25.6)	0.6 (0.5–0.7)
Combination of OCT findings	10.6	100	nc	0.9 (0.85–0.94)

CI = Confidence interval; nc = not calculable.

clinical assessment was 76.3%. There was a moderate agreement with a kappa value of 0.49 ($p < 0.0001$).

Comparison of US and OCT was made on 180 nails of the psoriatic group (with or without arthritis) where both assessments were available. The absolute agreement between OCT and US was 65%. There was a fair agreement between the two modalities with a kappa value of 0.27 ($p < 0.0001$). Within the psoriasis and PsA patient groups, OCT detected abnormalities in 41 nails where US assessment was normal. On the contrary, there were 22 nails that were abnormal by US and 54 clinically involved nails despite having a normal OCT.

Predictive Value of OCT for Psoriasis

Having a positive OCT (either signal changes or contour abnormalities) had a sensitivity and specificity of 44.4 and 95.8%, respectively, with a positive likelihood ratio of 10.7 for a diagnosis of psoriasis (with or without arthritis). When different findings of OCT were compared, diffuse intra-nail plate linear hyperreflective lesions and superficial thickening of the nail had the highest positive likelihood ratios (table 1).

When data were analysed per patient, having at least one abnormal nail by OCT had an 83.3% sensitivity and an 83.3% specificity for a diagnosis of psoriasis, with a positive likelihood ratio of 5 (1.4–18) and a negative likelihood ratio of 0.2 (0.07–0.6).

Psoriasis versus Psoriatic Arthritis

This study was underpowered to assess the differences between psoriasis patients with or without arthritis as there were only 5 patients without arthritis. Within psoriasis patients 26/50 nails were OCT-positive (52%), similar to PsA patients (54/130 nails, 41.5%; $p = 0.2$). The number of OCT-positive nails was also similar in both groups [4 (1–10) in psoriasis versus 5 (0–8) in PsA; $p = 0.5$].

Discussion

The purpose of this work was to evaluate OCT in comparison to US with respect to nail disease in psoriasis and PsA. Based on our findings, we suggest that OCT has the potential to become the modality of choice for imaging the nail in subjects with psoriasis-related nail disease. It seems likely that OCT could permit a more objective imaging assessment of nail disease and may be helpful in diagnosis and assessment of treatment responses.

The OCT technique allows a more detailed assessment of the nail structure than has previously been possible. We have shown that pitting was remarkably superficial but that leuconychia was in the middle layer of the nail. We also describe a number of additional features that are readily appreciated on OCT. Our preliminary findings herein showed no obvious differences between PsA and psoriasis.

Little data were available previously on the use of OCT in assessing nail disease. Two small OCT studies in HCs described the appearance of the nail using OCT; these mentioned leuconychia with a similar pattern to that which we have noted [22, 29]. One other study assessed patients with a variety of nail disorders [30]. This included two patients with psoriatic nail disease, with the first description of the appearance of nail pitting.

Our results also indicate that OCT is capable of detecting subclinical nail involvement in some psoriasis and PsA cases compared to healthy subjects. This raises the possibility that it could be used clinically in the rheumatology setting to look for nail changes in patients without obvious psoriasis in the presence of an undifferentiated seronegative arthritis. On the other hand clinical assessment was more positive than OCT, and whether OCT detects more severe lesions that may progress needs fur-

ther follow-up. It is possible that OCT could have a diagnostic role and serve as an objective and potentially quantifiable tool to assess nail disease in psoriasis, which will be addressed in prospective, larger studies.

A potential technical limitation of this work was that the mNAPSI score was performed independently by a clinical assessor and that quite often multiple lesions were encountered in the same nail, including pitting, onycholysis and leuconychia. These nails were invariably reported as abnormal on OCT but it was therefore not possible to correlate individual lesions between the OCT and the mNAPSI. Another relevant issue to consider is that the resolution of US is improving all the time and that with higher-resolution probes, it may be that the sonography will also prove to be useful for the visualisation of the nail. Further work in this regard is planned.

Research into the potential uses of OCT in this field is ongoing in several centres. Recent studies have shown some potential for the use of OCT in the diagnostic assessment of fungal nail disease, with good sensitivity but lower specificity than other methods [30, 31]. In a separate study, a change in nail thickness has been demonstrated using OCT after exposure to water [29]. Clearly, the use of OCT in the differential diagnosis between psoriatic and other types of nail disease merits further assessment.

In conclusion, this work shows that OCT may become the imaging modality of choice for the assessment of nail disease in psoriasis, including use as an objective measure to assess response to therapy.

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Disclosure Statement

The authors declare no conflict of interest.

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5.4. Predictive factors in Psoriatic Arthritis and Spondyloarthritis

5.4.1. ARTICLE 7

TITLE: "The link between enthesitis and arthritis in psoriatic: a switch to a vascular phenotype at insertions may play a role in arthritis development"

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5.4.1.1. PATIENTS AND METHODS

This part of the Thesis work was carried out at two European centres, at the Leeds Teaching Hospitals (UK) and the University Hospital Department of Verona (Italy). Ethics approval for the study was obtained at both sites.

5.4.1.1.1. Patient groups and clinical assessment

One hundred consecutive patients (42 with psoriasis and 58 with PsA) and 23 HC were recruited. PsA patients were included if they fulfilled the CASPAR criteria.14 Psoriasis patients were excluded if they had a current or previous history of arthralgia, arthritis or enthesitis. The clinical assessment was performed by one rheumatologist at each centre, who was blinded to the US data. This assessment included the psoriasis area and severity index (PASI), tender and swollen joint counts (TJC, SJC) and the Leeds and SPARCC enthesitis indices in the patients with PsA. Patients receiving

glucocorticoids and anti-tumour necrosis factor therapies were excluded from the study, those receiving disease-modifying antirheumatic drug therapy were recruited if they had active skin or joint disease (inad- equate responders).

5.4.1.1.2. Ultrasonography

US was performed by three rheumatologists fully trained in musculoskeletal ultrasound and with a special interest in scanning enthesitis (SZA and CCG in UK, IT in Italy). US was performed using a Logiq E9 machine (General Electric, Wauwatosa, Wisconsin, USA) in the UK and a Logiq 5 machine (General Electric) in Italy, both with a linear probe at 6–15 MHz. The lower limb entheses that have previously been described in the GUESS scoring system (including Achilles, plantar fascia, quadriceps, patellar tendon origins and insertions) were scanned. To enable blinding, patients were asked not to com- municate with the sonographer about their disease during the US assessment. The sonographer did not perform a physical examination, therefore sites other than those involved in the US scan were not seen by the sonographer. The room was completely darkened starting from the beginning of the US assessment. The light from the US machine alone is not enough for the sonographer to see the skin clearly. The patients were placed in a supine position to assess the entheses around the knee. The knee was extended to assess the presence of Doppler signal and semiflexed to 30° to assess the grey-scale (GS) changes. They were then asked to take a prone position with the feet over the end of the examination Table in a neutral position for visualisation of the entheses around the heel. The PD settings were standardised with a pulse repetition frequency of 800 Hz, a colour-mode frequency of 9.1 MHz and low wall filters. The colour gain was increased to the maximum level not generating PD signals under the bony cortex. All US assessments were performed using a multiplanar

scanning technique.

5.4.1.1.3. Ultrasound images interpretation

The GUESS scoring system was modified and the outcome measures in rheumatology clinical trials definition of enthesopathy was used to interpret ultrasound images: ‘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 two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity’(5). Bursal enlargement was also scored. The thickness of the enthesis was measured at the level of insertions and was evaluated on a quantitative basis. Normal values for each insertion were accepted as reported in the literature (2) and less than 1 mm of increase exceeding the threshold was scored as grade 1, 1 mm or greater but less than 2 mm of increase was scored as grade 2 and 2 mm or greater was scored as grade 3. Erosions were also scored quantitatively by the máximum diameter of the erosion (grade 1, >0 mm but <2 mm; grade 2, ≥2 mm and <3 mm; grade 3, ≥3 mm). The rest of the assessments were scored on a semiquantitative basis (mild changes grade 1, moderate grade 2 and severe grade 3).

It is now recognised that the enthesis represents an integrated organ comprising the insertion (which is avascular in health) and adjacent tendon, fibrocartilages and the immediately adjacent synovium when present.15 For the PD assessment we therefore looked for PD signal in all the components of the enthesis organ, including signals at the insertion and inside the adjacent bursa, wherever these were present. It is not possible to define the margins of the enthesis by US; however, the entheseal vascularity

was assessed when the Doppler signal was close to the cortical bone.

US findings were categorised according to the following: GS changes related to inflammation (entheseal hypoechogenicity, thickening and bursal enlargement) were added up to calculate a 'GS inflammation score'. PD scores were added up to calculate a 'Doppler inflammation score'. These two scores created a 'total inflammation score'. The GS changes related to chronic findings (calcifications, erosions and enthesophytes) were added up to calculate a 'chronicity score'. These scores were summated to give a total US enthesopathy score.

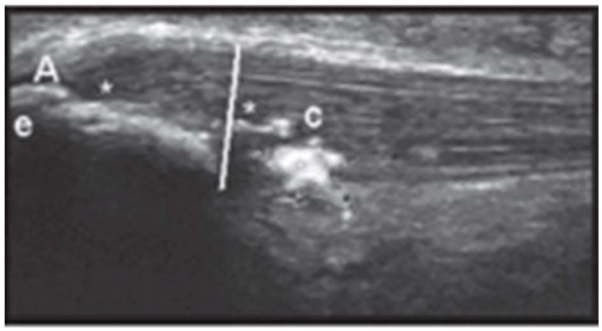

Figure 21 US findings on enthesis in psoriatic arthritis: The origin of patellar tendon with moderate thickening (white line); hypoecogenicity (*); small enthesophyte (e); calcifications (c)

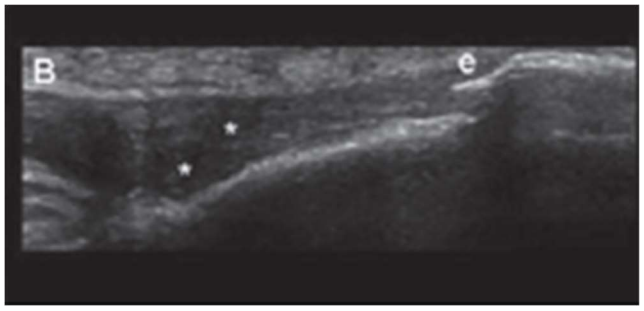

Figure 22 US findings on enthesis in psoriasis: hypoecogenicity (*); small enthesophyte (e)

5.4.1.1.4. Statistics

Data are expressed either as frequencies, means (SD) or medians (range) according to the variability. The prevalence of each individual lesion by ultrasound in patients with or without arthritis was compared by using a χ^2 test. The Mann–Whitney U test was used to compare ultrasound scores between groups. Correlations between clinical parameters (TJC, SJC, PASI and disease duration) and ultrasound scores (separately for ultrasound scores related to inflammation, damage and total) were analysed using the Pearson correlation test.

Statistical analysis was performed using SPSS V.11.5. To provide agreement between sonographers, all investigators agreed on definitions and the scoring system before the study both on saved images and while acquiring sample images. Stored images from the first 21 patients included in the study (total 1020 images) were scored by all three sonographers for GS and PD for all entheses. Intraclass correlation coefficient values were calculated for each pair of investigators and for all types of ultrasound scores used for the purpose of this study.

EXTENDED REPORT

The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development

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ABSTRACT

Objective Subclinical enthesopathy is recognised in both psoriasis and psoriatic arthritis (PsA). This study used ultrasonography with power Doppler (PD) to test the hypothesis that subclinical enthesopathy in PsA was associated with an 'inflammatory' or vascular phenotype compared to that seen in psoriasis.

Methods 100 patients with a mean age of 46.3 years (SD 15) (42 with psoriasis and 58 with PsA) and 23 matched healthy controls (HC) from two centres were included. 1230 lower limb entheses were scanned by ultrasonographers blinded to clinical details. Both inflammatory and chronic features of enthesopathy were scored.

Results Psoriasis patients (with or without arthritis) were more likely to express a vascular phenotype, with higher inflammation-related enthesopathy scores than HC (for inflammation $p<0.0001$, for chronicity $p=0.02$, for total ultrasound scores $p<0.0001$). The PsA patients had higher ultrasound enthesopathy scores than psoriasis patients (inflammation $p=0.04$, chronicity $p=0.02$) and HC (inflammation $p<0.0001$, chronicity $p=0.003$). When symptomatic entheses were excluded, PsA patients still had higher PD scores than psoriasis patients ($p=0.003$). Doppler positivity in at least one entheseal site was observed more frequently in PsA (21/58, 36.2%) versus psoriasis (4/42, 9.5%; $p=0.002$).

Conclusions This study shows that the ultrasound appearances of subclinical enthesitis in psoriasis differ from the subclinical enthesitis in PsA, with PsA patients having more PD. This is suggestive of a more inflammatory or vascular process in PsA, and offers potentially novel insights into the progression from skin to joint disease in psoriasis.

INTRODUCTION

During the past decade it has emerged that enthesitis and associated osteitis are the common denominators underlying the multifaceted skeletal manifestations of psoriatic arthritis (PsA) that include axial and appendicular disease.[1] In keeping with the importance of enthesitis as the key pathological lesion in PsA, some studies have shown enthesopathy in asymptomatic large insertions of the lower limbs in patients with spondyloarthropathies including PsA.[2] This is reminiscent of studies in inflammatory oligoarthritis, in which ultrasound detected synovitis in joints that were clinically uninvolved.[3] Of even greater importance is that several studies have shown subclinical enthesopathy or osteitis in up to 50% of psoriasis patients with no skeletal symptoms.[4]

Ultrasonography is well suited to the assessment of entheses and is able to depict soft tissue thickening and oedema in addition to new bone formation and erosions.[5] In recent years, power Doppler (PD) ultrasonography has been increasingly used in rheumatology as it identifies vascular abnormalities known to be associated with inflammation. PD ultrasound to some extent provides a reflection of the degree of angiogenesis, which is critically related to joint damage and therapeutic responses to drugs.[6–9] An extra-articular PD signal has been demonstrated in both PsA and psoriasis patients.[10–13] However, there is limited work directly comparing PD changes at the insertions between patients with PsA and psoriasis.

The purpose of this study was to undertake ultrasonography of symptomatic and asymptomatic insertions in cases with PsA and cases with psoriasis, the latter having no clinical arthritis. The hypothesis tested was that the imaging phenotypes might differ between PsA patients and psoriasis cases without clinical arthritis. In particular, we hypothesised that the enthesopathy associated with PsA would have a greater degree of vascularisation compared to that seen in psoriasis without arthritis. We also postulated that subclinical vascular changes at the entheses might be associated with more widespread disease activity in PsA. Such an imaging biomarker could be helpful in understanding and predicting the disease evolution from psoriasis to PsA, which at the present time is not fully understood.

METHODS

The study was carried out at two European centres—at the Leeds Teaching Hospitals (UK) and the University Hospital Department of Verona (Italy). Ethics approval for the study was obtained at both sites.

Patient groups and clinical assessment

One hundred consecutive patients (42 with psoriasis and 58 with PsA) and 23 healthy controls (HC) were recruited. PsA patients were included if they fulfilled the CASPAR criteria.[14] Psoriasis patients

were excluded if they had a current or previous history of arthralgia, arthritis or enthesitis. The clinical assessment was performed by one rheumatologist at each centre, who was blinded to the ultrasound data. This assessment included the psoriasis area and severity index (PASI), tender and swollen joint counts (TJC, SJC) and the Leeds and SPARCC enthesitis indices in the patients with PsA. Patients receiving glucocorticoids and anti-tumour necrosis factor therapies were excluded from the study, those receiving disease-modifying antirheumatic drug therapy were recruited if they had active skin or joint disease (inadequate responders).

Ultrasonography

Ultrasonography was performed by three rheumatologists fully trained in musculoskeletal ultrasound and with a special interest in scanning enthesitis (SZA and CCG in UK, IT in Italy). Ultrasound was performed using a Logiq E9 machine (General Electric, Wauwatosa, Wisconsin, USA) in the UK and a Logiq 5 machine (General Electric) in Italy, both with a linear probe at 6–15 MHz.

The lower limb entheses that have previously been described in the GUESS scoring system (including Achilles, plantar fascia, quadriceps, patellar tendon origins and insertions) were scanned.[2] To enable blinding, patients were asked not to communicate with the sonographer about their disease during the ultrasound assessment. The sonographer did not perform a physical examination, therefore sites other than those involved in the ultrasound scan were not seen by the sonographer. The room was completely darkened starting from the beginning of the ultrasound assessment. The light from the ultrasound machine alone is not enough for the sonographer to see the skin clearly. The patients were placed in a supine position to assess the entheses around the knee. The knee was extended to assess the presence of Doppler signal and semiflexed to 30° to assess the grey-scale (GS) changes. They were then asked to take a prone position with the feet over the end of the examination Table in a neutral position for visualisation of the entheses around the heel.

The PD settings were standardised with a pulse repetition frequency of 800 Hz, a colour-mode frequency of 9.1 MHz and low wall filters. The colour gain was increased to the maximum level not generating PD signals under the bony cortex. All ultrasound assessments were performed using a multiplanar scanning technique.

Ultrasound images interpretation

The GUESS scoring system was modified and the outcome measures in rheumatology clinical trials definition of enthesopathy was used to interpret ultrasound images: '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 two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity'.[5] Bursal enlargement was also scored. The thickness of the enthesis was measured at the level of insertions and was evaluated on a quantitative basis. Normal values for each insertion were accepted as reported in the literature[2] and less than 1 mm of increase exceeding the threshold was scored as grade 1, 1 mm or greater but less than 2 mm of increase was scored as grade 2 and 2 mm or greater was scored as grade 3. Erosions were also scored quantitatively by the maximum diameter of the erosion (grade 1, >0 mm but <2 mm; grade 2, ≥2 mm and <3 mm; grade 3, ≥3 mm). The rest of the assessments were scored on a semiquantitative basis (mild changes grade 1, moderate grade 2 and severe grade 3).

It is now recognised that the enthesis represents an integrated organ comprising the insertion (which is avascular in health) and adjacent tendon, fibrocartilages and the immediately adjacent synovium when present.[15] For the PD assessment we therefore looked for PD signal in all the components of the enthesis organ, including signals at the insertion and inside the adjacent bursa, wherever these were present. It is not possible to define the margins of the enthesis by ultrasound; however, the entheseal vascularity was assessed when the Doppler signal was close to the cortical bone.

Ultrasound findings were categorised according to the following: GS changes related to inflammation (entheseal hypoechogenicity, thickening and bursal enlargement) were added up to calculate a 'GS inflammation score'. PD scores were added up to calculate a 'Doppler inflammation score'. These two scores created a 'total inflammation score'.

The GS changes related to chronic findings (calcifications, erosions and enthesophytes) were added up to calculate a 'chronicity score'. These scores were summated to give a total ultrasound enthesopathy score.

Statistics

Data are expressed either as frequencies, means (SD) or medians (range) according to the variability. The prevalence of each individual lesion by ultrasound in patients with or without arthritis was compared by using a χ^2 test. The Mann–Whitney U test was used to compare ultrasound scores between groups.

Correlations between clinical parameters (TJC, SJC, PASI and disease duration) and ultrasound scores (separately for ultrasound scores related to inflammation, damage and total) were analysed using the Pearson correlation test. Statistical analysis was performed using SPSS V.11.5.

To provide agreement between sonographers, all investigators agreed on definitions and the scoring system before the study both on saved images and while acquiring sample images. Stored images from the first 21 patients included in the study (total 1020 images) were scored by all three sonographers for GS and PD for all entheses. Intraclass correlation coefficient values were calculated for each pair of investigators and for all types of ultrasound scores used for the purpose of this study.

RESULTS

Interobserver agreement on sonography scoring

A moderate to excellent agreement between both investigator pairs was found for different scores: for GS inflammation the intraclass correlation coefficient values were in the range 0.91–0.93 (95% CI 0.79 to 0.97), for PD inflammation 0.74–0.95 (95% CI 0.45 to 0.98), for chronicity scores 0.89–0.93 (95% CI 0.76 to 0.98) and for total ultrasound scores 0.92–0.95 (95% CI 0.81 to 0.98).

Patient characteristics

Patients and HC were of similar age (46.3 years (15) vs 52.2 years (11), respectively; p=NS) and body mass index (26.7 (19.3–42.4) vs 24.2 (21–31.3); p=0.08). The gender distribution was also similar in both groups (43% female in the psoriasis group and 52% in the HC). None of the patients with psoriasis had clinical enthesitis compared to 51.7% of the patients with PsA (30/58). In the PsA patients, the median TJC was 4 (0–20) and the SJC was 4 (0–19). PASI scores were slightly lower in the patients with PsA (3.3 (0–18)) compared to those with

Table 1 Total number of ultrasound findings at all sites

	HC (230 entheses) n (%)	Psoriasis (420 entheses) n (%)	PsA (580 entheses) n (%)	p Value*
Hypoechogenicity	29 (12.6)	105 (25)	208 (35.9)	0.0003
Thickening	69 (30)	162 (38.6)	250 (43.1)	0.15
PD	0 (0)	2 (0.4)	12 (2.1)	0.05
Calcifications	22 (9.6)	17 (4.1)	57 (9.8)	0.0005
Bursal enlargement	3 (1.3)	35 (8.3)	77 (13.3)	0.02
PD inside the bursa	0 (0)	3 (0.7)	16 (2.8)	0.02
Enthesophytes	90 (39.1)	180 (42.9)	297 (51.2)	0.01
Erosions	1 (0.4)	12 (2.9)	29 (5)	0.1

*p Values are given for comparisons between groups with PsA and psoriasis.
HC, healthy control; PD, power Doppler; PsA, psoriatic arthritis.

psoriasis (4.3 (0–22); p=0.02). The groups had similar disease durations (19.1 years (12.5) for PsA and 17.5 years (11) for psoriasis). In general, hypoechogenicity, thickening and enthesophytes were the most frequent ultrasound findings for each site, whereas PD and erosions were relatively rare (table 1) (figure 1). These findings are described in more detail below.

Soft tissue changes at insertions

As expected, patients with psoriasis (with or without arthritis) had higher enthesitis scores related to inflammation than HC (for inflammation p<0.0001, for total ultrasound scores p<0.0001). The PsA patients had higher ultrasound scores than both psoriasis patients without arthritis (for inflammation p=0.04, for total ultrasound scores p=0.02) and HC (for inflammation p<0.0001, for total ultrasound scores p<0.0001) (table 2). Certain findings including hypoechogenicity and bursal enlargement were more frequent in PsA compared to psoriasis (table 1).

PD evaluation

Doppler positivity in at least one entheseal site was observed more frequently in PsA (21/58, 36.2%) than in psoriasis (4/42, 9.5%; p=0.002). A Doppler signal was not seen in any HC. The presence of Doppler positivity had a sensitivity of 36% (95% CI 24% to 50%) and a specificity of 91% (95% CI 77% to 97%) with a positive likelihood ratio of 3.8 to discriminate PsA and psoriasis. The most discriminative site for PD positivity was the retrocalcaneal bursa (seven PsA vs one psoriasis patient). Furthermore, six patients had a PD signal at more than one site and five of these patients had PsA.

Bone erosion and spur formation

Psoriasis patients (with or without arthritis) had more chronic changes compared with HC (p=0.02). The PsA patients had higher chronicity scores than both patients with psoriasis (p=0.02) and HC (p=0.003) (table 2). This may reflect previous episodes of inflammation. Calcification and enthesophytes were also more frequent in the entheses of patients with PsA compared to the psoriasis group, which may be in keeping with previous inflammatory episodes with subsequent tissue remodelling (table 1).

Clinical assessments and their association with ultrasound findings

When patients with clinical enthesitis were excluded from the PsA group, patients with arthritis still had higher PD enthesopathy scores than patients with psoriasis (p=0.003), as well as higher chronicity scores (p=0.01) (table 2).

The TJC (r^2=0.21; p=0.03) and SJC (r^2=0.29; p=0.003) correlated to entheseal Doppler scores. Furthermore, the SJC correlated to total ultrasound scores (r^2=0.21; p=0.03). No link between PASI and disease duration and ultrasound scores was evident (data not given).

DISCUSSION

This study showed that the frequency of enthesis-related PD change was significantly higher in PsA compared to psoriasis even when only sites of asymptomatic enthesopathy were evaluated in PsA. Moreover, the frequency of subclinical enthesopathy was significantly higher in PsA compared to psoriasis. The results of this cross-sectional study suggest that there may be a trend towards increased entheseal thickening with subsequent vascular changes representing a step in the progression towards PsA in psoriasis cases. This will require confirmation in a longitudinal study.

It is noteworthy that abnormal patterns of vascularity have been reported in psoriatic arthritis synovium both by arthroscopic inspection and by histological assessment.[16 17] Likewise, prominent vascular changes have been reported in skin disease and at the nail matrix in psoriasis.[18 19] Furthermore, normal entheseal insertions are sites prone to microdamage and in the course of physiological tissue repair at such sites prominent histological evidence of vascular changes is seen even in healthy individuals.[20] In this study we found a high prevalence of enthesophytes in the HC. Enthesophytes are not specific to enthesitis and may be related to mechanical forces. This finding also reflects the high sensitivity of ultrasound to detect these changes.

In this study, we found no entheseal PD signals in the HC group. The majority of the literature supports the absence of

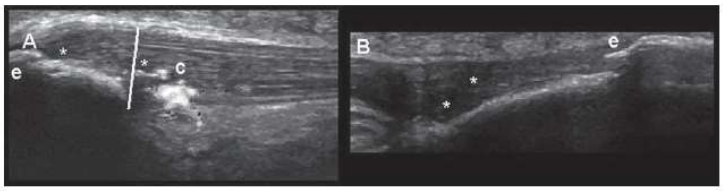

Figure 1 Examples of ultrasound findings on enthesitis in psoriatic arthritis (A) and psoriasis (B). (A) The origin of patellar tendon with moderate thickening (white line), hypoechogenicity (*), a small enthesophyte (e), calcifications (c) and power Doppler signals inside the enthesis B. The insertion of patellar tendon with moderate hypoechogenicity (*) and a large enthesophyte (e). This figure is only reproduced in colour in the online version.

Table 2 Ultrasound scores for enthesitis

	Ultrasound findings related to inflammation				
	GS score	PD score	Total inflammation score	Chronicity score	Total ultrasound score
HC (n=23)	4 (0–15)	0 (0–0)	4 (0–15)	6 (1–22)	10 (3–36)
Psoriasis (n=42)	9.5 (0–30)	0 (0–3)	9.5 (0–30)	8 (0–25)	16 (0–55)
PsA (n=58)	11.5 (1–44)	0 (0–7)	13 (1–46)	10 (2–29)	21.5 (4–69)
PsA (symptomatic enthesitis excluded) (n=28)	12 (2–44)	0 (0–4)	12.5 (2–46)	10 (2–24)	23 (4–69)

Numbers are given as median (range).
GS, grey-scale; HC, healthy control; PD, power Doppler; PsA, psoriatic arthritis.

ultrasound-detectable blood flow in normal individuals,[21] PD changes have been reported in a few cases.[22] This raises the possibility of using Doppler signals for early diagnosis, although this would need to be demonstrated in prospective trials.

This study was performed in two different European populations by different sonographers, which raises issues about its reliability and general applicability. However, both study populations exhibited identical trends in patterns of disease. Likewise, the sonographers met and agreed on standard sonographic criteria for enthesitis and the interobserver agreement was quite high.

Taken together, these findings now need to be applied in a large inception cohort of psoriasis patients to ascertain whether they define the subgroup that will be likely to evolve into PsA in the following months and years. In that regard, we have previously used ultrasound to show a high frequency of subclinical entheseal involvement in patients presenting with psoriasis but without clinically evident arthritis.[23] After following this cohort for 3.5 years we have seen a link between subclinical enthesopathy in patients with psoriasis and the future development of PsA.[24]

In conclusion, this study shows that the degree of systemic subclinical enthesopathy is much greater in PsA compared to psoriasis. Of particular note, the difference in vascular changes in PsA compared to psoriasis might have implications for determining the likelihood of a given patient progressing to PsA. This will form the basis for future studies.

Contributors DGM conceived the study, supervised its conduct and takes responsibility for the integrity of the work as a whole, from inception to finish. ZRA, IT and SZA were involved in the design of the study. Ultrasound scans were performed by SZA, CCG and IT. All authors contributed to data acquisition and were involved in the critical revision of the final manuscript.

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Competing interest None.

Ethics approval Ethics approval for the study was obtained at Leeds Teaching Hospitals (UK) and the University Hospital Department of Verona (Italy).

Provenance and peer review Not commissioned; externally peer reviewed.

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5.4.2. ARTICLE 8

TITLE: "Long Term follow up of an early Oligoarthritis cohort shows that early aggressive intervention leads to drug free remission after 10 years: results from the LoTO study"

JOURNAL: Accepted in International Journal of Clinical Rheumatology (14th March2017)

AUTHORS: Castillo-Gallego C, Green MJ, Aydin SZ, Nizam S, Emery P, Marzo-Ortega H.

5.4.2.1. PATIENTS AND METHODS

This part of the Thesis work is a single-centre, single time-point observational study of long term follow up of patients presenting with an early oligoarthritis (disease duration <12 months) from two historical cohorts of the Leeds Early Arthritis Clinic EAC. In the first study, subjects were treated with a protocol of intra-articular steroid injections into all clinically involved joints. In the second, subjects were randomized into an early intervention group with intra-articular steroid injections into all synovitic followed by DMARDs therapy with sulfasalazine or initial treatment with NSAIDs followed by intensive treatment on the second group.

For the present report, subjects were identified through clinical records and were invited through letter to either attend for a single study visit or a telephone consult. Patients who did not respond to this first invitation were then contacted by telephone

and invited to answer a short questionnaire. Data collected included demographic variables. Investigations such as CRP or radiography (sacro-iliac joints/lumbar spine or any relevant joints) were only performed in attenders in case of clinical need or to clarify the diagnosis when applying the ASAS criteria for classification of axial spondyloarthritis, modified New York criteria for AS, CASPAR criteria for PsA or the new ACR RA criteria. All patients signed informed consent and the study had the approval of the local ethics committee.

5.4.2.1.1. Outcome measures and statistics

Predictors of outcome recorded include the HLA-B27 status (positive or negative), early intervention therapy with steroid injections and/or SSZ, number of swollen joints at the onset of the disease, disease duration from symptom onset and baseline RF. Anti-CCP status was recorded at follow-up as this test was not available at time of study design. Variables were analysed in a descriptive manner.

Research Article

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Long term follow up of an early oligoarthritis cohort shows that early aggressive intervention leads to drug free remission after 10 years: results from the LoTO study

Objective: To report the long-term outcome in the long-term follow up of the Leeds Early Oligoarthritis Cohort.
Methods: Cross-sectional follow up of patients who participated in two previous interventional studies. Subjects were invited to either attend for a single study visit or a telephone consults. Presence/absence of any musculoskeletal symptoms and current diagnosis was recorded. Blood tests for inflammatory markers and radiographs of SIJs or any relevant joints were performed only if clinically indicated to establish a diagnosis if persistent clinical symptoms.
Results: Follow up data were available from 63.3% (n=74 patients) of the initial cohort (n=117 patients) [mean SD disease duration at presentation 11.8 ± 1.8 months; disease duration at follow up: 13 ± 3 years]. Of these 74 patients, 63.51% (n=47) had persistent arthritis since the end of the previous studies (19.5% were RF positive; 33.3% anti-CCP positive and 32.4% HLA-B27 positive). The majority (75%) had received joint steroid injections sulfasalazine on the original study protocols. Oligoarthritis was still the predominant articular pattern in 68% of the patients at follow up and over a third of patients (36.5%) were in clinical remission (4% and 17.4% RF and HLA-B27 positive respectively).
Conclusion: Ten-year follow up of an early oligoarthritis cohort shows that over a third of patients attending for review are in drug free clinical remission.

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Keywords: long-term • follow-up • early spondyloarthritis • intervention

Introduction

Oligoarthritis is an inflammatory arthritis affecting ≤4 joints [1,2]. It represents either an early clinical presentation or a unique disease phenotype within the conditions collectively termed the seronegative spondyloarthropathies (SpA). Oligoarthritis typically affects young people causing high morbidity [3-5] and it may have a variable outcome although long term follow up data are sparse [5-8].

The majority of published studies have only reported on short/middle term outcomes. Some reports have described as many as 75% of patients with ReA having persistent disease at 6 months [6], whereas other cohort studies have suggested rates of persistence as low as 15% [5]. In our first study, at 12 months of follow up, 51% of patients satisfied criteria for complete response (absence of synovitis) [1]. In the second study, at 12 months, up to 81% of the patients in the early intervention group had no clinical evidence of synovitis compared with 57% of the patients in the conservative group [2]. Both reports indicated a significant benefit from an early intervention protocol in the short term, with better results in the second study, suggesting that this may have been due to the early use of sulphasalazine (SSZ) as a DMARD.

In the current report we aim to assess the long term follow up of these patients, we were interested in particular, to assess the prognostic role of biomarkers such as HLA-B27 and RF.

Methods

Study design

This is a single-centre, single time-point observational study of long term follow up of patients presenting with an early oligoarthritis (disease duration <12 months) from two historical cohorts of the Leeds Early Arthritis

Clinic EAC [1,2]. In the first study, subjects were treated with a protocol of intra-articular steroid injections into all clinically involved joints [1]. In the second, subjects were randomized into an early intervention group with intra-articular steroid injections into all synovitic followed by DMARDs therapy with sulfasalazine or initial treatment with NSAIDs followed by intensive treatment on the second group [2].

For the present report, subjects were identified through clinical records and were invited through letter to either attend for a single study visit or a telephone consults. Patients who did not respond to this first invitation were then contacted by telephone and invited to answer a short questionnaire. Data collected included demographic variables. Investigations such as CRP or radiography (sacro-iliac joints/lumbar spine or any relevant joints) were only performed in attenders in case of clinical need or to clarify the diagnosis when applying the ASAS criteria for classification of axial spondyloarthritis [9], modified New York criteria for AS [10], CASPAR criteria for Psoriatic Arthritis [11] or the new ACR RA criteria [12]. All patients signed informed consent and the study had the approval of the local ethics committee.

Outcome measures and statistics

Predictors of outcome recorded include the HLA-B27 status (positive or negative), early intervention therapy with steroid injections and/or SSZ, number of swollen joints at the onset of the disease, disease duration from symptom onset and baseline RF. Anti-CCP status was recorded at follow-up as this test was not available at time of study design. Variables were analyzed in a descriptive manner.

Results

The original cohort comprised of a total of 117 patients, of whom 5 were deceased. A total of 112 patients were contacted, of whom 63.3% (n=74) [56.76% (n=42) male: 43.24% (n=32) female; mean ± SD disease duration at presentation was 11.8 ± 1.8 months; with a disease duration of 13 ± 3 years at follow up] consented to for follow up. Of these 112 patients contacted, 19.64% (n=22) attended for a hospital review visit; 25% (n=28) were assessed via telephone consult and 21.45% (n=24) had data extracted from the clinical notes. A total of 37 patients could not be reached either by letter or by telephone. Only one of the patients contacted declined consent to participate in the study. Analysis of the 74 attenders showed that 63.51% (n=47) of the patients had had persistent arthritis since the end of the initial studies (19.5% RF positive; 33.3% anti-CCP positive and 32.4% HLA-B27 positive at follow up). The majority (75%) had received joint steroid injections ± SSZ on the initial study protocols. Only 19% had a mono-articular presentation. The majority of patients (82%) had an oligo-articular pattern at disease presentation and this was maintained over time in 68%. Fifteen percent (15%) had evolved into a mixed phenotype with axial and peripheral joint involvement. Total resolution of symptoms was documented in 36.5% of patients (4% and 17.4% RF and HLA-B27 positive respectively) who had remained asymptomatic in this time with no hospital follow up. The majority of these (57.7%) had an oligo-articular pattern at initial presentation and 42.3% presented with a mono-arthritis. Sixty five percent and 5.40% had received joint steroid injections or SSZ respectively in the previous studies. Eight out of ten who was RF positive at baseline evolved into polyarthritis (**TABLE 1**). The distribution of diagnosis continued to change from the time of the first evaluation at the two previous studies throughout the observation period (**FIGURE 1**). Regression analysis to evaluate predictors of outcome was not possible due to the low patient numbers.

Discussion

Oligoarthritis is a common condition with a variable outcome that typically affects young people and can lead to high morbidity. However long term follow up data are sparse [13-15]. Our original reports [1,2] showed that prompt intervention in early oligoarthritis led to significant improvements in clinical outcomes when compared to a more conservative approach using NSAIDs. The aim of the current project was to report on the long-term outcome of an inception cohort of patients, with early onset of oligoarthritis to identify prognostic factors.

Our results show that up to 65.4% and 5.40% of the patients that remained asymptomatic at follow up had received joint steroid injections or SSZ respectively in the previous studies, but when we compare this to patients who had persistent arthritis over the years there is no statistically significant difference. One explanation for this could be the small numbers of patients followed up. We believe that the real percentage of patients in remission among this group could be much higher than the 36% found, and that

Table 1. Previous and current diagnosis of the 74 attenders. *IBD: Inflammatory bowel disease; **OA: Osteoarthrtitis; ***LE: Lupus erythematosus.

Previous diagnosis	No. of patients	Current diagnosis	No. of patients
Undiferentiatied Oligoarthritis (monoarthritis)	37 (20)	Persistent Oligoarthritis	17
Reactive arthritis	12	Reactive arthritis	10
Psoriatic arthritis	7	Psoriatic arthritis	13
Sarcoid arthritis	1	Sarcoid arthritis	2
Gout	3	Gout	4
Peripheral and axial Spondyloarthritis	0	Peripheral and axial Spondyloarthritis	2
Rheumatoid Arthritis	8	Rheumatoid Arthritis	13
*IBD associated to arthritis	1	IBD associated to arthritis	1
Fibromyalgia	1	Fibromyalgia	1
**OA	2	**OA	5
Mechanical problem	2	-	-
-	-	***LE	1
-	-	No Rheumatology Diagnosis at follow up	5

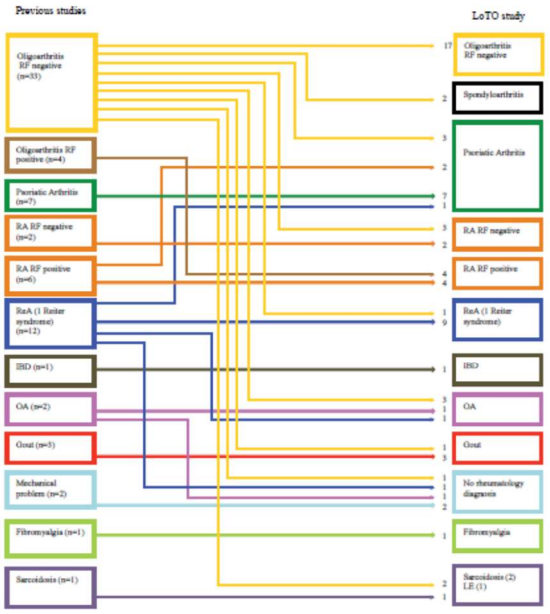

Figure 1. Distribution of diagnosis at the end of original studies and at the final follow up visit. RF: Rheumatoid factor; RA: Rheumatoid arthritis; ReA: Reactive arthritis; IBD: Inflammatory bowell disease related to arthritis; OA: Osteoarthritis; LE: Lupus erythematosus.

this may be the reason why subjects have not remained under follow up. This is an important limitation of our study but common with follow up of longitudinal cohorts. A substantial number of subjects from our initial cohort were young adults attending university who represent a highly mobile group and we were unable to track them down after the years.

Only a few studies have reported long-term outcome in uSpA or oligoarthritis for prognostic factors. Sampaio-Barros et al. [13], published data on 5 to 10 years follow up for 105 and 42 uSpA patients respectively with a mean disease duration at onset of 5 years. Huerta-Sil, et al. [14] reported the findings in 50 patients with peripheral arthritis and inflammatory back pain

with disease duration of 5.4 years after 3-5 years. In Kumar's long term follow up (11 years) study [15], 22 patients, all of them with inflammatory back pain and a high proportion of peripheral arthritis, had mean disease duration at onset of 8 months. In a recent multicentre cohort study [16] 440 children with juvenile idiopathic arthritis were followed for up to 7 years after disease onset. By comparison, the Leeds Cohort represents a unique inception group by virtue of its very short symptom duration at the time of clinical presentation which was of 10 weeks (median) on the first study [1] and 16 weeks in the second study [2]. In addition, follow up averaged 14 years in some cases, which makes this the largest long term study of patients presenting with oligoarthritis.

Another limitation of our study comes from the fact that only 29.73% of the 74 patients attended for a hospital visit with the majority feeling there was no need for it as they were completely asymptomatic. Indeed, 27 patients (36.49%) were assessed via telephone consult and in the remaining (32.43%) data were collected from clinical notes as these were still regular hospital attenders.

In conclusion, ten-year follow up of an early oligoarthritis cohort shows that over a third of patients attending for review are in drug free clinical remission. The majority had received joint steroid injections ± SSZ early on in their disease onset. These results can throw important insights into the pathogenesis of this condition and provide useful guidance for clinicians managing these patients.

Conflict of interest statement

No, there is no conflict of interest.

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6. GLOBAL RESULTS

6.1. MRI in the assessment of axial Psoriatic Arthritis and Spondyloarthritis

In this part of the Thesis work we performed a cross-sectional audit of MRI scans of lumbar spine (L-spine) and sacroiliac (SI) joints. Using the semiquantitative Leeds Scoring System in which bone marrow oedema is graded from 0 to 3 according to severity of the lesions, MRI scans were scored independently by 2 expert readers who were blinded to the clinical characteristics of the patients. Concordant data from the 2 readers were used to report on definite lesions.

- Results:

MRIs from 76 patients with comparable age ranges were categorized into 3 groups: those from PsA patients, those from patients with non-radiographic axial SpA, and those from AS patients. HLA–B27 positivity was similar in PsA patients (10 of 33) and patients with non-radiographic axial SpA (10 of 24) and higher in AS patients (18 of 19). Total MRI scores (L-spine plus SI joints) were higher in AS patients than in PsA patients ($P = 0.025$) or in patients with non-radiographic axial SpA ($P = 0.007$). A relationship was seen between the severity and extent of disease and HLA–B27 positivity in PsA patients, which was comparable to that in AS patients. HLA–B27 negative PsA patients had lower MRI scores than HLA–B27 positive PsA patients ($P = 0.03$) and AS patients ($P = 0.006$), whereas scores were similar in HLA–B27–positive PsA patients and AS patients. Similarly, MRI scores of HLA–B27–negative patients with non-radiographic axial SpA were lower than those of AS patients ($P = 0.01$).

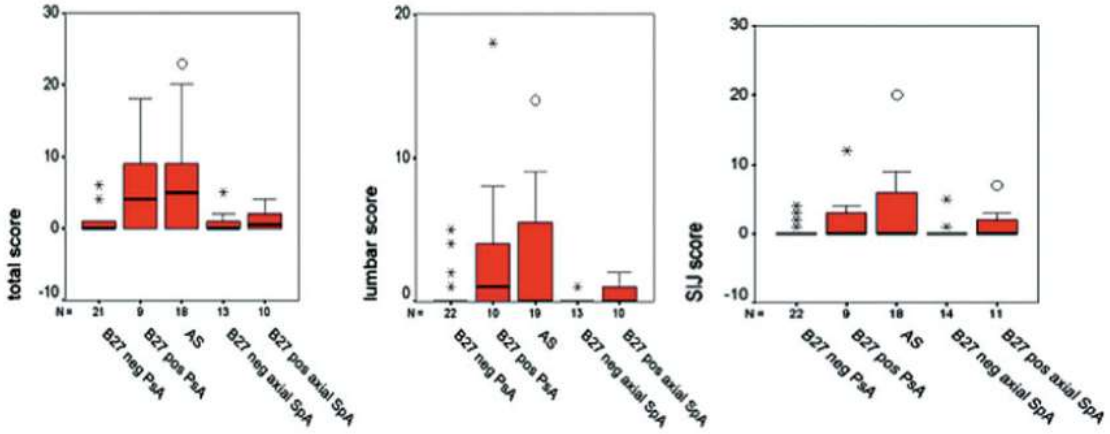

Figure 23 Comparison of total numbers of inflammatory (bone marrow oedema) lesions on MRI of the lumbar spine and sacroiliac joint (SIJ) between patients with PsA, patients with AS, and patients with non-radiographic axial Sp) in relation with HLA.B27 status (negative or positive):

Data are shown as box plots
Each box represents the 25th to 75th percentiles
Lines inside the boxes represent the median
Lines outside the boxes represents the 10th and the 90th percentiles
Circles and asterisks indicates outliers

6.2. US in Spondyloarthritis and Psoriatic Arthritis

6.2.1. Ultrasonography of the Achilles enthesis bursa in early Spondyloarthritis

6.2.1.1. The importance of the bursa in spondyloarthritis: Achilles enthesis US in early Spondyloarthritis

This part of the Thesis work is a transversal blind and controlled two-dimensional (2D) and three-dimensional (3D) US study of Achilles enthesis bursa in

early SpA. Clinical outcome measures were collected.

- 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-spine 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 enthesis (67.4%) vs. 27/46 enthesis (58.7%) of healthy controls ($p<0.01$), and 10/46 enthesis (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 enthesis 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 ($p<0.01$).

6.2.1.2. Achilles enthesis US as an outcome measure of disease activity in early Spondyloarthritis

This part of the Thesis work is a longitudinal Achilles enthesis US study in

patients with early SpA. 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 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 = 0.03) 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.

6.2.2. Ultrasonography of the Sacroiliac joints in Spondyloarthritis

This was a cross-sectional, blinded, case-control study of 108 cases divided into three groups: a) 53 SpA patients with inflammatory back pain (IBP); b) 28 SpA patients with no IBP; and c) 27 healthy mechanical lumbar pain subjects. Physical examinations of the SIJs were assessed as positive or negative in each SIJ and were used as the gold standard. SIJs were examined with CDUS and spectral Doppler, and the SIJs were

assessed as positive when both colour Doppler and the RI were less than the cut-off point within the SIJs area.

- Results:

A total of 108 cases (53 female; mean age 36 10 years old) were studied. The physical examination of the SIJs was positive in 38 patients (59 SIJs). Ultrasound detected Doppler signal within the SIJs in 37 cases (58 SIJs): 33 of them had symptomatic SpA (52 SIJs), 3 of them had asymptomatic SpA (5 SIJs), and 1 was a healthy control (1 SIJ). The accuracy of CDUS, when compared to physical SIJ examination, at the patient level in the overall group had a sensitivity of 70.3%, a specificity of 85.7%, a positive likelihood ratio of 4.9 and a negative likelihood ratio of 0.36. For the spectral Doppler RI, with an optimal cut-off point ≤ 0.75, the sensitivity was 76.2%, and the specificity was 77.8%.

6.2.3. Ultrasonography of the Nail and extensor tendon enthesis

In this part of the Thesis work 86 psoriatic patients (169 nails) and 20 HC (40 nails) were assessed with both the mNAPSI and US. The thickness of the nail plate, nail matrix region and adjacent extensor tendon were assessed and compared with physical examination findings.

- Results:

A good agreement between clinical and sonographic nail findings was noted (kappa value = 0.52, $p<0.0001$). Entheseal thickening of the extensor tendon on US was more frequent in patients with clinical nail disease compared to patients without clinical

nail disease in both psoriasis and psoriatic arthritis (38 vs. 16%, p = 0.03, and 47 vs. 19%, p = 0.008, respectively). Nail thickness, nail matrix and adjacent skin thickness were higher in psoriatic patients compared to HC.

6.3. OCT and US in the assessment of nail disease in Psoriasis and Psoriatic Arthritis

In this part of the Thesis work we compared OCT and US for nail disease assessment in 18 patients with psoriatic disease, with at least one involved nail and 12 healthy controls were scanned using OCT; psoriatic patients also had an US scan (using a linear probe at 9–14 MHz). Nail and contour abnormalities were documented. Clinical onychopathy was scored independently using the modified Nail Psoriasis Severity Index.

- Results:

Among 180 nails, 67.8% had clinical findings whereas 33.9% were abnormal by US and 44.4% had abnormalities on OCT. A positive OCT had a sensitivity and specificity of 44.4 and 95.8%, respectively, with a positive likelihood ratio of 10.7 for nail disease. OCT demonstrated 76.3% absolute agreement compared with clinical assessment and 65% with US. OCT detected subtle abnormalities in 12 clinically normal nails and in 41 nails with normal US findings. Conclusion: These findings show that OCT has a potential for the systematic characterisation of psoriatic nail changes and could be useful in diagnosis and more objective assessment of treatment response.

6.4. Predictive factors in Psoriatic Arthritis and Spondyloarthritis

6.4.1. The link between enthesitis and arthritis in psoriatic: a switch to a vascular phenotype at insertions may play a role in arthritis development

In this part of the Thesis work US with PD was used to test the hypothesis that subclinical enthesopathy in PsA was associated with an 'inflammatory' or vascular phenotype compared to that seen in psoriasis. 100 patients with a mean age of 46.3 years (SD 15) (42 with psoriasis and 58 with PsA) and 23 matched healthy controls (HC) from two centres were included. 1230 lower limb entheses were scanned by ultrasonographers blinded to clinical details. Both inflammatory and chronic features of enthesopathy were scored.

- Results:

Psoriasis patients (with or without arthritis) were more likely to express a vascular phenotype, with higher inflammation-related enthesopathy scores than HC (for inflammation $p<0.0001$, for chronicity $p=0.02$, for total US scores $p<0.0001$). The PsA patients had higher ultrasound enthesopathy scores than psoriasis patients (inflammation $p=0.04$, chronicity $p=0.02$) and HC (inflammation $p<0.0001$, chronicity $p=0.003$). When symptomatic entheses were excluded, PsA patients still had higher PD scores than psoriasis patients ($p=0.003$). Doppler positivity in at least one entheseal site was observed more frequently in PsA (21/58, 36.2%) versus psoriasis (4/42, 9.5%;

p=0.002).

6.4.2. Long Term follow up of an early oligoarthritis cohort shows that early aggressive intervention leads to drug free remission after 10 years: results from the LoTO study

This part of the Thesis work is a cross-sectional follow up of patients who participated in two previous interventional studies. Subjects were invited to either attend for a single study visit or a telephone consult. Presence/absence of any musculoskeletal symptoms and current diagnosis was recorded. Blood tests for inflammatory markers and radiographs of SIJs or any relevant joints were performed only if clinically indicated to establish a diagnosis
if persistent clinical symptoms.

- Results:

Follow up data were available from 63.3% (n=74 patients) of the initial cohort (n=117 patients) [mean ± SD disease duration at presentation 11.8 ± 1.8 months; disease duration at follow up: 13 ± 3 years]. Of these 74 patients, 63.51 % (n=47) had persistent arthritis since the end of the previous studies (19.5 % were RF positive; 33.3 % anti-CCP positive and 32.4% HLA-B27 positive). The majority (75%) had received joint steroid injections ± sulfasalazine on the original study protocols. Oligoarthritis was still the predominant articular pattern in 68% of the patients at follow up and over a third of patients (36.5 %) were in clinical remission (4 % and 17.4 % RF and HLA-B27 positive respectively).

7. DISCUSSION

7.1. Relation of HLA B27 status with extent of disease in MRI assessment of axial Psoriatic Arthritis

In this part of the Thesis work we investigated the role of the HLA–B27 gene on the MRI phenotypes in PsA and axial SpA including AS. Our findings confirm that the HLA–B27 gene has a major effect on both the severity of axial lesions and the number of different distinct lesions. In accordance with previous studies, we have shown that the majority of patients with axial PsA and non-radiographic axial SpA are HLA–B27 negative (99). In addition, we show that HLA–B27–positive axial PsA and AS have the same pattern of bone marrow oedema. Conversely, HLA–B27–negative axial disease including PsA has a much lower extent of bone marrow oedema. Collectively, these findings support the concept of the key role of the HLA–B27 gene as a determinant of the extent of osteitis in SpA.

These findings have important implications for understanding SpA. There is now a link established between MRI-determined bone marrow oedema and subsequent disease progression at diseased segments. Given that symptomatic PsA has less bone marrow oedema, it might be expected that there is less diffuse spinal disease. Indeed, historical radiographic imaging studies have shown asymmetric, less severe disease in PsA compared to classic AS, but the studies in question did not note the HLA–B27 status (2). It is interesting to note that AS, psoriasis, and PsA are all class I major histocompatibility complex–associated diseases. In the case of psoriasis, the HLA–

Cw0602 gene is a severity factor for the extent of skin disease but does not appear to be linked to the joint disease. It seems that HLA–B27 is a marker for the extent of bone marrow oedema in SpA irrespective of the presence of skin psoriasis. Just as T cells appear to be associated with the dissemination of disease in HLA–Cw0602–positive skin psoriasis, T cells may be associated with the development of disease at different bony sites. This hypothesis has never been tested, and the role of the affected bone in SpA and the basis for disease in relation to HLA–B27 have not been evaluated at this site.

These findings also have a practical aspect for consideration. The majority of PsA patients who were HLA–B27 negative were reported as having a normal MRI scan. This may reflect the fact that MRI may be insensitive at picking up subtle soft tissue changes at entheses (100). Our study has some limitations. First, this is a retrospective audit of MRI scans requested in daily clinical practice, and data on clinical outcomes such as the Bath Ankylosing Spondylitis Disease Activity Index (101) or Ankylosing Spondylitis Disease Activity Score (102) were not systematically collected to allow for a correlation with clinical symptoms. Previous studies on early inflammatory back pain have shown a higher level of disease activity as shown by clinical outcomes in patients with psoriasis (99), suggesting a possible role of psoriasis as an independent contributor to disease activity.

Taken together, these results suggest a role for HLA–B27 and psoriasis as partly independent contributors to inflammation and disease activity in axial PsA. Second, the sample size was small, which represents an important limitation to conducting a multivariate analysis of the data. Third, only the lumbar portion of the spine in addition

to the SI joints was imaged as opposed to the whole spine. Ideally, the whole spine should have been imaged to allow for the assessment of cervical and thoracic sites where a significant proportion of lesions may have been missed. Further, we have looked at inflammatory bone lesions only as represented by bone marrow oedema, but a "positive" MRI result reflecting disease may need to incorporate other features of structural change such as fatty degeneration, sclerosis, or erosions.

The presence of structural lesions in the absence of inflammation would help us to understand why axial PsA is indeed more asymptomatic than AS and can go largely undiagnosed. Larger, prospective MRI studies of the whole spine with associated genotypes are needed to confirm these results.

7.2. US in Spondyloarthritis and Psoriatic Arthritis

7.2.1. Ultrasonography of the Achilles bursa in patients with early Spondyloarthritis

7.2.1.1. US of the bursa-synovial of the Achilles enthesis in early SpA

The purpose of this part of the Thesis work was to determine whether the US recognition of bursa affectation on enthesis could be relevant as elemental lesion in the concept of entheseal 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 enthesis with the neighbouring bone (11), the connection between enthesitis and bursal-synovitis remains a subject of debate (12). OMERACT's enthesopathy definition does not include bursa affectation 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.

Our study tries to assess the prevalence and relevance of the bursa-synovial lesión in SpA using the Achilles enthesis as a model. In this sense, similar to previous data, our findings demonstrate that retrocalcaneal bursa can be detectable by US in normal subjects (30, 103). 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 ≥2mm 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 (14, 24, 35, 36). 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. (12, 27, 28). In this sense, and supporting the idea of the importance of the participation of the synovial bursal tissue in enthesis damage, previous reported data have demonstrated that erosions typically occur in the bursal proximal portion of the enthesis in SpA patients, possibly establishing a link between these lesions (13, 104).

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 (88, 105). 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 this 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 enthesis US examination, but

this is not different from other elemental lesions included in enthesopathy definition such as thickness that had less contribution (36). Probably no one lesion, as bursa presence, but the combination of entheseal lesions improve the knowledge of the SpA enthesis 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 enthesis. Even in other published data by expert groups a similar low prevalence of Doppler signal was found (36, 88, 105) (31,34, 35). In this sense, it is remarkable that the analysis of Doppler presence taking into account clinical variables achieved statistical significance.

7.2.1.2. US examination for the assessment of disease activity in early SpA

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 (e.g. 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 (106). 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

(102, 107).

The enthesis, which is one of the more important targets in the pathogenesis of SpA, is undervalued in the assessment of disease activity. The inclusion of enthesitis 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 (108). 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 entheseal alterations in SpA diseases in recent years (14, 24, 35, 36).

Disease activity in SpA patients is most likely related to at least three aspects: axial, synovial and entheseal 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 enthesis 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 enthesis 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 enthesis 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 entheseal disease activity than does the BASDAI.

One limitation of this study is the exploration of a single peripheral enthesis. The challenge will be to verify if another single enthesis or a composite US entheseal index has better validity than the Achilles tendon by itself. Even so, the consistency of our results using just one enthesis 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.

7.2.2. Ultrasonography of the Sacroiliac joints in Spondyloarthritis

Currently, there is little available knowledge on the use of ultrasound on the SIJs or the applicability of US in the diagnosis and monitoring of SpA. In this sense, conducting new studies in this field is important. Previous studies have provided initial evidence of the validity of SIJ US (37-43). Analyses of these data showed that US could provide an opportunity to assess the SIJs. There have been different research end points used in these studies, using grayscale mode, colour Doppler, ultrasound-enhanced media and RI. Contrast-enhanced studies have shown very good results in terms of validity, but it is an invasive technique that increases the time and cost of examinations and can lead to adverse events in patients.

To determine the real possibilities for the use of US SIJ examinations in clinical practice, it is interesting to note that an LR greater than 10 or less than 0.1 is considered to be sufficiently strong evidence to confirm or disprove, respectively, a diagnosis in most circumstances. LRs of 5-10 and 0.1-0.2 generate moderate shifts in pre-test and post-test probabilities, respectively, and LRs of 2-5 and 0.5-0.2 generate smaller (but sometimes important) changes in these probabilities. In our study, the positive LR achieved by US in the SIJs was 4.9, meaning that US could be a useful test to assess active sacroiliitis in clinical practice. This result was better than the previously reported data of 4.25 (38) and 2.67 (40) but was lower than the results when enhanced ultrasound media were used, for which the positive LR was 6.71 (38).

Zhu et al, (43) studied the complex appearance of vascularity of the SIJs in AS and commented that most of the colour flow signs corresponded to venous flow in active AS patients. In our study, spectral Doppler tracing was obtained to confirm that each CDUS signal represented a true arterial or venous flow pattern, and the inflammatory patterns were also checked using the RI to improve the accuracy. In the evaluation of the RI, our study had similar RI results to those achieved by previous publications (38, 40, 43), demonstrating statistically significant differences between SpA patients and controls. However, we went one step further with the calculation of the better cut-off for the RI (≤0.75) to differentiate clinical activity from normality using flow pattern assessment.

Furthermore, the presence of IBP is a key symptom of axial involvement in SpA, and it is present in the majority of patients (34). Therefore, we studied whether CDUS assessment could answer a relevant question in clinical practice, i.e., whether IBP is related to the diagnosis of SpA. In our study, the presence of Doppler signals in the SIJs resulted in a high positive LR value when compared to patients with or without IBP. The combination with IBP increased the post-test probability of SI joint US examination to a positive LR of 8.4; thus, CDUS of the SIJs could be of relevance in the detection of active sacroiliitis and in the diagnosis of SpA, but these data need to be confirmed in further studies.

There were some limitations to our study. First, an increased body mass index can reduce the sensitivity of CDUS. It was difficult to detect CDUS signals with our US equipment when the SIJs were deeper than 4 cm. This fact could have resulted in some false negatives cases. Second, we compared US results to physical examination as the

gold standard. There are many physical examination tests for the SIJs, and all of them have been advocated as useful tools in identifying patients with SIJ pain; however, none of the available SIJ tests appears to be clearly superior to the others (109). To reduce this limitation, we used several of these tests. Moreover, physical examination has been accepted as the gold standard in previous studies (40, 43), although it is probably not the actual gold standard. Histopathology is the most accurate gold standard, but it is difficult to perform. MRI is accepted as a good technique to assess sacroiliitis, but its correlation with histopathology has a relative lack of sensitivity (110). CDUS can also be used to perform US-guided sacroiliac joint injection in the treatment of sacroiliitis (111) and to detect the changes of sacroiliitis and peripheral enthesitis in AS patients under biologic therapy (112).

7.2.3. Ultrasonography of the Nail and the extensor tendon enthesis in psoriasis and Psoriatic Arthritis

This is the first study using US to assess the entire nail apparatus including the nail plate and nail matrix region, where it is now known that the nail is integrated with the skeleton (49). Both US and clinical examination were broadly similar for the assessment of the nail plate region. In the evaluation of the nail matrix region we noted an association between extensor tendon enthesopathy and nail disease. This enthesopathy was specifically associated with nail disease but not clinical PsA. These findings are relevant for the development of US for the assessment of the nail disease and also point towards the importance of the enthesis in nail involvement.

These findings have implications for a better understanding of nail disease in psoriasis. The link between enthesopathy on US and clinical nail disease was not

confined

to pitting, a recognised matrix-specific abnormality, but was also seen with onycholysis (thought to be a nail plate lesion) which therefore would not be expected to be related to extensor tendon disease. These findings raise the possibility that nail pain and loss of function seen in the dermatological setting may in part be related to microenthesopathy-related pain. The relevance of these changes for the development of PsA and their relevance for the prognosis of nail disease awaits further study.

Another noteworthy finding of the present study was that the DIP enthesopathy was associated with both epidermal thickening and dermal oedema. This is interesting since it suggests a very close link between the pathology in the skin and the adjacent enthesis and to the best of our knowledge has not being recognised before. Perhaps the skin changes may be secondary to extension of the inflammatory processes to the adjacent dermis with secondary epidermal changes, or they may reflect common mechanical stretching responses to the skin and enthesis during finger flexion.

There are some potential limitations to this study. As with all US studies on psoriasis, it is not technically possible to be completely blinded to the skin findings if the patient has very severe disease. We tried to avoid this situation by avoiding conversation between the patient and the ultrasonographer about their disease and by having the room completely darkened from the beginning of the assessment.

In conclusion, this study confirms that US is helpful to objectively assess psoriatic nail disease and compares favourably with clinical assessment. Given that only superficial changes can be detected by physical examination, US proved to be

informative in the nail matrix and adjacent extensor tendon region. In particular the US findings in this study showed a link between extensor tendón enthesopathy and nail disease. This supports the concept that nail disease in psoriasis is more than skin deep, and is linked to enthesopathy. This has broad implications for further studies into nail disease in psoriasis.

7.3. OCT and US in the assessment of nail disease in Psoriasis and Psoriatic Arthritis

The purpose of this part of the Thesis work was to evaluate OCT in comparison to US with respect to nail disease in psoriasis and PsA. Based on our findings, we suggest that OCT has the potential to become the modality of choice for imaging the nail in subjects with psoriasis-related nail disease. It seems likely that OCT could permit a more objective imaging assessment of nail disease and may be helpful in diagnosis and assessment of treatment responses.

The OCT technique allows a more detailed assessment of the nail structure than has previously been possible. We have shown that pitting was remarkably superficial but that leuconychia was in the middle layer of the nail. We also describe a number of additional features that are readily appreciated on OCT. Our preliminary findings herein showed no obvious differences between PsA and psoriasis.

Little data were available previously on the use of OCT in assessing nail disease. Two small OCT studies in HCs described the appearance of the nail using OCT; these mentioned leuconychia with a similar pattern to that which we have noted (57, 113).

One other study assessed patients with a variety of nail disorders (114). This included two patients with psoriatic nail disease, with the first description of the appearance of nail pitting.

Our results also indicate that OCT is capable of detecting subclinical nail involvement in some psoriasis and PsA cases compared to healthy subjects. This raises the possibility that it could be used clinically in the rheumatology setting to look for nail changes in patients without obvious psoriasis in the presence of an undifferentiated seronegative arthritis. On the other hand clinical assessment was more positive than OCT, and whether OCT detects more severe lesions that may progress needs fur ther follow-up. It is possible that OCT could have a diagnostic role and serve as an objective and potentially quantifiable tool to assess nail disease in psoriasis, which will be addressed in prospective, larger studies.

A potential technical limitation of this work was that the mNAPSI score was performed independently by a clinical assessor and that quite often multiple lesions were encountered in the same nail, including pitting, onycholysis and leuconychia. These nails were invariably reported as abnormal on OCT but it was therefore not possible to correlate individual lesions between the OCT and the mNAPSI. Another relevant issue to consider is that the resolution of US is improving all the time and that with higher-resolution probes, it may be that the sonography will also prove to be useful for the visualisation of the nail. Further work in this regard is planned. Research into the potential uses of OCT in this field is ongoing in several centres.

Recent studies have shown some potential for the use of OCT in the diagnostic

assessment of fungal nail disease, with good sensitivity but lower specificity than other methods (114). In a separate study, a change in nail thickness has been demonstrated using OCT after exposure to water (115). Clearly, the use of OCT in the differential diagnosis between psoriatic and other types of nail disease merits further assessment.

In conclusion, this work shows that OCT may become the imaging modality of choice for the assessment of nail disease in psoriasis, including use as an objective measure to assess response to therapy.

7.4. Predictive factors in Psoriatic Arthritis and Spondyloarthritis

7.4.1. Enthesis US as an imaging biomarker in psoriasis and psoriatic arthritis

This study showed that the frequency of enthesis-related PD change was significantly higher in PsA compared to psoriasis even when only sites of asymptomatic enthesopathy were evaluated in PsA. Moreover, the frequency of subclinical enthesopathy was significantly higher in PsA compared to psoriasis. The results of this cross-sectional study suggest that there may be a trend towards increased entheseal thickening with subsequent vascular changes representing a step in the progression towards PsA in psoriasis cases. This will require confirmation in a longi- tudinal study. It is noteworthy that abnormal patterns of vascularity have been reported in psoriatic arthritis synovium both by arthroscopic inspection and by histological assessment (116, 117). Likewise, prominent vascular changes have been reported in skin disease and at the nail matrix in psoriasis (118, 119). Furthermore, normal entheseal insertions are sites prone to microdamage and in the course of physiological tissue repair at such sites prominent

histological evidence of vascular changes is seen even in healthy individuals (29). In this study we found a high prevalence of enthesophytes in the HC. Enthesophytes are not specific to enthesitis and may be related to mechanical forces. This finding also reflects the high sensitivity of ultrasound to detect these changes.

In this study, we found no entheseal PD signals in the HC group. The majority of the literature supports the absence of ultrasound-detectable blood flow in normal individuals (120), PD changes have been reported in a few cases (36). This raises the possibility of using Doppler signals for early diagnosis, although this would need to be demonstrated in prospective trials.

This study was performed in two different European populations by different sonographers, which raises issues about its reliability and general applicability. However, both study populations exhibited identical trends in patterns of disease. Likewise, the sonographers met and agreed on standard sonographic criteria for enthesitis and the interobserver agreement was quite high.

Taken together, these findings now need to be applied in a large inception cohort of psoriasis patients to ascertain whether they define the subgroup that will be likely to evolve into PsA in the following months and years. In that regard, we have previously used US to show a high frequency of subclinical entheseal involvement in patients presenting with psoriasis but without clinically evident arthritis (83). After following this cohort for 3.5 years we have seen a link between subclinical enthesopathy in patients with psoriasis and the future development of PsA (121).

In conclusion, this study shows that the degree of systemic subclinical enthesopathy is much greater in PsA compared to psoriasis. Of particular note, the difference in vascular changes in PsA compared to psoriasis might have implications for determining the likelihood of a given patient progressing to PsA. This will form the basis for future studies.

7.4.2. Ten years follow-up of an Early Oligoartrhitis Cohort

Oligoarthritis is a common condition with a variable outcome that typically affects young people and can lead to high morbidity. However long term follow up data are sparse (122, 123). Our original reports (92, 93) showed that prompt intervention in early oligoarthritis led to significant improvements in clinical outcomes when compared to a more conservative approach using NSAIDs. The aim of the current project was to report on the long-term outcome of an inception cohort of patients, with early onset of oligoarthritis to identify prognostic factors.

Our results show that up to 65.4 % and 5,40% of the patients that remained asymptomatic at follow up had received joint steroid injections or SSZ respectively in the previous studies, but when we compare this to patients who had persistent arthritis over the years there is no statistically significant difference. One explanation for this could be the small numbers of patients followed up. We believe that the real percentage of patients in remission among this group could be much higher than the 36% found, and that this may be the reason why subjects have not remained under follow up. This is an important limitation of our study but common with follow up of longitudinal cohorts. A substantial number of subjects from our initial cohort were young adults attending university who represent a highly mobile group and we were unable to track them down after the years.

Only a few studies have reported long-term outcome in uSpA or oligoarthritis for prognostic factors. Sampaio-Barros, *et al* (122) published data on 5 to 10 years follow up for 105 and 42 uSpA patients respectively with a mean disease duration at onset of 5 years. Huerta-Sil, *et al* (123) reported the findings in 50 patients with peripheral arthritis and inflammatory back pain with disease duration of 5.4 years after 3-5 years. In Kumar's long term follow up (11 years) study (124), 22 patients, all of them with inflammatory back pain and a high proportion of peripheral arthritis, had a mean disease duration at onset of 8 months. In a recent multicentre cohort study (125) 440 children with juvenile idiopathic arthritis were followed for up to 7 years after disease onset. By comparison, the Leeds Cohort represents a unique inception group by virtue of its very short symptom duration at the time of clinical presentation which was of 10 weeks (median) on the first study (92) and 16 weeks in the second study (93). In addition, follow up averaged 14 years in some cases, which makes this the largest long term study of patients presenting with oligoarthritis.

Another limitation of our study comes from the fact that only 29.73% of the 74 patients attended for a hospital visit with the majority feeling there was no need for it as they were completely asymptomatic. Indeed, 27 patients (36.49%) were assessed via telephone consult and in the remaining (32.43%) data were collected from clinical notes as these were still regular hospital attenders.

In conclusion, ten-year follow up of an early oligoartritis cohort shows that over a third of patients attending for review are in drug free clinical remission. The majority had received joint steroid injections ± SSZ early on in their disease onset. These results can throw important insights into the pathogenesis of this condition and provide useful guidance for clinicians managing these patients.

8. CONCLUSIONS

8.1. English

1. HLA–B27–related active axial PsA shows an extent of inflammation on MRI comparable to that of AS and superior to that of HLA–B27–negative PsA. The results suggest that this subgroup of PsA shares common etiopathogenic mechanisms of disease with AS and may carry a comparable disease burden.
2. US findings at retrocalcaneal bursa level have low sensitivity, but could have an important contribution in differentiating patients with early SpA (positive likelihood ratio of 4.6). Its inclusion in future new consensus definition of enthesitis should be evaluated.
3. Doppler US is significantly associated with other commonly used disease activity measures and seems to be a valid tool for assessing entheseal inflammation in SpA patients. As a disease status measure, it seems that, compared with the BASDAI, the ASDAS reflects entheseal inflammation better. This study supports the construct validity of enthesis US and supports its role in the assessment of disease activity in patients with early SpA.
4. CDUS is a promising imaging technique for the detection of active sacroiliitis and could be a less expensive and easier-to-apply alternative method to MRI for detecting inflammation secondary to increased SIJ vascularization. Our results showed good sensitivity and high specificity of CDUS combined with RI, especially when they were associated with IBP. CDUS might be as cost-effective a technique as an initial imaging assessment in the study of inflammatory lower back pain.
5. US and clinical findings show good correlation for the assessment of the nail in

psoriatic disease. The demonstration of extensor tendon enthesopathy in both psoriasis and PsA supports the importance of enthesopathy in nail disease pathogenesis whether or not clinical arthritis is present.

6. OCT has a potential for the systematic characterisation of psoriatic nail changes and could be useful in diagnosis and more objective assessment of treatment response.
7. Ultrasound appearances of subclinical enthesitis in psoriasis differ from the subclinical enthesitis in PsA, with PsA patients having more PD. This is suggestive of a more inflammatory or vascular process in PsA, and offers potentially novel insights into the progression from skin to joint disease in psoriasis.
8. Ten-year follow up of an early oligoarthritis cohort shows that over a third of patients attending for review are in drug free clinical remission following an initial early treatment.

8.2. Spanish

1. Los pacientes HLA-B27 positivo con artritis psoriásica axial activa presentan un grado de inflamación en la resonancia magnética comparable al de los pacientes con espondilitis anquilosante y superior al de los pacientes con artritis psoriásica HLA-B27 negativo. Los resultados sugieren que este subgrupo de artritis psoriásica comparte mecanismos etiopatogénicos de la enfermedad con la espondilitis anquilosante y que puede presentar una afectación de la enfermedad similar.
2. Los hallazgos ecográficos obtenidos del estudio de la bursa retrocalcánea tienen baja sensibilidad, pero podrían tener una importante papel en la diferenciación de los pacientes con espondiloartritis precoz (razón de verosimilitud positiva de 4.6). Debería considerarse la inclusión de la bursa en la futura definición de consenso de la entesitis.
3. La presencia de señal Doppler en la ecografía de entesis se asocia significativamente con otras medidas de actividad de la enfermedad usadas habitualmente en pacientes con espondiloartritis. Como medida de actividad de de la enfermedad, parece que, en comparación con el BASDAI, el ASDAS refleja mejor la inflamación entesítica. Este estudio apoya la validez de constructo de la ecografía de entesis y apoya su papel en la valoración de la actividad de la enfermedad en pacientes con espondiloartritis precoz.
4. La ecografía Doppler color es una técnica de imagen prometedora para la detección de sacroileítis activa y podría ser un método alternativo menos costoso y más fácil de aplicar a la resonancia magnética para detectar inflamación en las articulaciones sacroilíacas. Nuestros resultados muestran una buena sensibilidad

y alta especificidad de la ecografía Doppler color en combinación con el índice de resistividad, especialmente cuando se asocia con dolor lumbar inflamatorio. La ecografía Doppler color puede ser coste eficiente como técnica de imagen de valoración inicial en el estudio de los pacientes con dolor lumbar inflamatorio.

5. Los hallazgos clínicos y ecográficos muestran una buena correlación para la evaluación ungueal en la psoriasis. La demostración de la entesopatía del tendón extensor, tanto en la psoriasis como en la artritis psoriásica, apoya la importancia de la entesis en la patogénesis de la enfermedad ungueal, con o sin artritis clínica asociada.
6. La tomografía óptica de coherencia tiene un gran potencial para la caracterización sistemática de lesiones en las uñas de pacientes con psoriasis y podría ser útil en el diagnóstico y la valoración de respuesta al tratamiento.
7. Los hallazgos ecográficos de la entesitis subclínica en pacientes con psoriasis difieren de los encontrados en la entesitis subclínica de los pacientes con artritis psoriásica, encontrándose más señal PD en estos últimos. Esto es sugestivo de un proceso inflamatorio o vascular mayor en la artritis psoriásica, y ofrece perspectivas novedosas en el conocimiento de la progresión de la afectación cutánea a la afectación articular.
8. El seguimiento a diez años de una cohorte de oligoartritis temprana muestra que más de un tercio de los pacientes están en remisión clínica y sin tratamiento tras una intervención terapéutica precoz inicial.

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