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

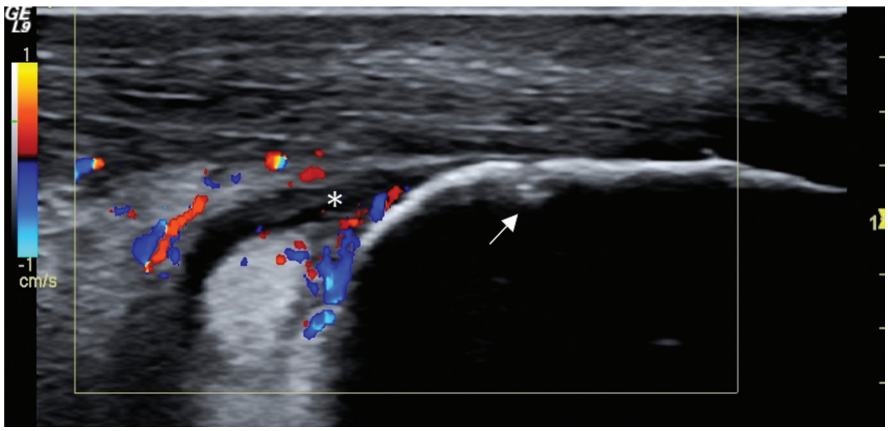

Fig. 1. Ultrasonographic appearance of entheseal Achilles insertion. Bursal enlargement with Doppler signal (*), and erosion (arrow) in a longitudinal view.

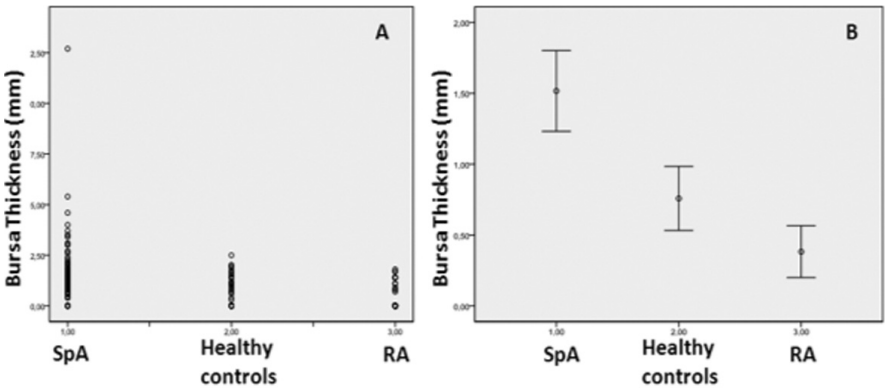

Fig. 2. Ultrasound bursa measures in spondyloarthritis (SpA) and controls. **A**. Scattergram dots distribution in SpA, healthy controls and rheumatoid arthritis (RA) control group. **B**. Mean and 95%CI of bursa thickness in SpA, healthy controls and RA controls.

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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