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Clinical Study

Clinical and Ultrasound Examination of the Leeds Enthesitis Index in Psoriatic Arthritis and Rheumatoid Arthritis

G. Ibrahim,[1] C. Groves,[1] M. Chandramohan,[1] A. Beltran,[2] R. Valle,[2] B. Reyes,[3] P. Healy,[4] A. Harrison,[4] and P. S. Helliwell[1,5]

[1] *St. Luke's Hospital, Bradford Teaching NHS Foundation Trust, Bradford BD5 0NA, UK*
[2] *Rheumatology Unit, Central Military Hospital, Bogotá, Colombia*
[3] *Rheumatology Unit, Central Police Hospital, Bogotá, Colombia*
[4] *Department of Rheumatology, Hutt Hospital, Lower Hutt, Wellington 5011, New Zealand*
[5] *Academic Unit of Musculoskeletal Disease, University of Leeds, Leeds LS7 4SA, UK*

Correspondence should be addressed to P. S. Helliwell, p.helliwell@leeds.ac.uk

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Objective. To compare scores for the Leeds enthesitis index in psoriatic arthritis and rheumatoid arthritis using clinical assessment and ultrasonography (US). *Design*. Swelling and tenderness of the enthesis was assessed at six sites: lateral epicondyles of humerus (LE), medial condyles of femur (MC), and the insertion of the Achilles tendon (AT). US assessed "inflammatory activity" (power Doppler signal, oedema, tendon thickening, and bursal swelling) and "damage" (erosions and enthesophytes). *Results*. 94 patients were included, 71 with PsA and 23 with RA. The patients with RA were significantly older (PsA 47.6 years; RA 62.6 years; (mean difference in ages =15.0 years, 95% CI 9.3–20.7 years)). US scores were higher in RA at the LE, significantly so for the "damage" scores. No differences between RA and PsA were seen at the other sites. As a result, the odds ratio for PsA, given an US score above the median, was 0.41 (0.13–1.03). However, using the clinical score, the odds ratio for PsA was 2.16 (0.81–5.70). *Conclusions*. Although clinical scores of enthesitis are greater in PsA compared to RA, US enthesitis scores did not distinguish between RA and PsA. This may in part be due to more frequent juxta-articular involvement in RA and in part due to the older age of the subjects with RA.

1. Introduction

It is recognised that certain clinical features help differentiate PsA from rheumatoid and other forms of arthritis [1]. Included among these distinguishing clinical features is the presence of enthesitis. Entheses, the point of attachment of ligaments and tendons to bone, are widely distributed in the body, but the major entheses of the lower limb around the calcaneum provide the hallmark features of enthesitis in PsA and other spondyloarthropathies and form part of the newly developed CASPAR classification criteria for psoriatic arthritis [1, 2]. Enthesitis may underlie most of the changes found in the spine in spondyloarthropathy, and it has even been suggested that enthesitis is the primary pathological lesion in the peripheral joints in PsA [3]. Further, enthesitis has been proposed as an important domain of assessment, and outcome, in PsA [4, 5].

If clinical enthesitis is a classification criterion and hallmark feature of spondyloarthropathy, and if clinical enthesitis is to be measured as an indicator of disease activity, then it should be anticipated that both clinical and US enthesitis should not be prominent in other rheumatic diseases, such as rheumatoid arthritis. Generally, that is the case [6]. However, there is also evidence that the "blind" assessment of both radiographs and US images fails to distinguish between the two diseases [7, 8]. Recently, an enthesis index specific to PsA has been developed. This index examines tenderness at six sites: lateral epicondyles of the humerus, medial condyles of

the femur, and the insertion of the Achilles tendon [9]. The current study examined clinical and US evidence of enthesis at these six sites in both psoriatic arthritis and rheumatoid arthritis.

2. Methods

This study was carried out at 3 centres: Bradford, UK, Bogota, Colombia, and Wellington, New Zealand. At each centre full ethical committee approval was given for this study and all patients gave their signed, informed consent to take part. Subjects were seen in rheumatology outpatient clinics and, after consent procedures, examined using a standard clinical protocol. Patients with a physician diagnosis of PsA and RA were included in an approximate ratio of 2 : 1 PsA : RA. The protocol gathered clinical information sufficient to assess the CASPAR criteria [2], an acute phase marker and a swollen joint count. The protocol included an assessment of the entheses of the Leeds Enthesitis Index (LEI). These include bilaterally the lateral epicondyle of the humerus at the common extensor origin, the medial condyle of the femur, superior to the joint line, at the origin of the medical collateral ligament, and the posterior prominence of the calcaneum at the insertion of the Achilles tendon)—pressure was exerted at the enthesis sufficient to blanch the finger nail of the examiner (approximately 4 Kg). In addition, the examiner assessed the presence of soft-tissue swelling at the enthesis. For each entheseal site, an assessment was made of the adjacent joint in terms of tenderness and soft-tissue swelling. Careful attention was devoted to try and distinguish, swelling and tenderness separately at the joint and the juxta-articular enthesis.

3. Ultrasound Examination

The following US protocol was applied. US was performed by experienced radiologists (CG, MC both with over 10 years experience in musculoskeletal US) or rheumatologists (AH, 2 years experience in musculoskeletal US, and BR, over 3 years in musculoskeletal US). The sonographers were blinded to the patient's condition, and patients were asked not to communicate with the radiologist during the procedure. When possible the scans were performed on the same day as the clinical examination. The scans were performed on the following machines: Bradford, Philips HDI 5000 machine using a 10–15 MHz linear probe; Bogota, General Electric Logic P-5 using a 10–13 MHz linear probe; Wellington, GE Healthcare Logiqe machine using a 5–13 MHz linear probe. The sonographic assessments were made at each of the Leeds enthesis sites (lateral epicondyles of the humerus, medial condyles of the femur, and Achilles tendon insertions). The common extensor origin of the humerus was evaluated with the patient seated, and the hand resting on the knee with the elbow slightly flexed and the wrist in gentle internal rotation. The medial collateral ligament insertion into the femur was examined with the patient supine and the knee extended. The tendo-Achilles insertion was examined with the patient prone, with the feet hanging over the edge of the couch with the ankle in neutral position.

Grey scale imaging in the longitudinal and transverse planes was used to assess the enthesis for the presence of erosions, enthesophytes, bursitis, entheseal thickening, and perientheseal soft tissue oedema. Care was taken to negate the effect of anisotropy, and lesions were only scored if seen in both planes. Lesions were scored as present (score 1) or absent (score 0). An erosion was defined as a step-down cortical contour defect seen in two planes and measuring greater than or equal to 2mm in diameter. An enthesophyte was defined as step-up bony prominence at the end of a normal bone contour and forming a bony spur seen within the tendinous portion of the enthesis. Bursitis was taken to be present if there was a localised, well-delineated hypoechoic area at the site of an anatomical bursa which was compressible, indicating that it was due to fluid. Entheseal thickening was scored as present if there was a discrepancy in the thickness at the contralateral enthesis or if the normally smooth entheseal contour appeared bulky. No attempt was made to measure the thickness of the enthesis due to perceived difficulties in standardising the measurement site. Perientheseal soft tissue oedema was scored as present if there was compressible fluid within the soft tissues on the outer margin of the enthesis. The assessment of entheseal vascularisation was performed using power Doppler. Individual optimisation of Doppler gain and gate for detecting low velocity flow was done and a specific preset of power Doppler settings was used for each machine. All entheses were assessed for the presence of neovascularity in the longitudinal and transverse plains just adjacent to the entheseal insertion. Entheseal vascularity was scored as present (score 1) or absent (score 0).

Interobserver agreement between centres was obtained by agreeing definitions of lesions (as indicated above) and distributing a library (created in Bradford) of standardised images. No formal evaluation of interobserver agreement was undertaken.

4. Statistics

All statistics were carried out using SPSS v15.0. The US assessments were combined as follows, as an approximation of "inflammation" and "damage" at the enthesis:

(i) the four items of vascularisation, soft-tissue oedema, bursitis and thickening as an "inflammation" score (score range 0–4),

(ii) the two items of erosion and enthesophyte as a "damage" score (score range 0–2).

Aggregate LEI and US scores across all sites were used to compare between disease categories. Sensitivity and specificity of the LEI and US indices in PsA (using RA as a comparator) were calculated by taking the median score of each index in the PsA group as the cutoff for positivity. In this way it was also possible to calculate the odds ratios for PsA, given a positive clinical or US score.

Table 1: "Inflammation" and "damage" scores by US at each enthesis. Scores are mean (median and IQR).

	Psoriatic arthritis		Rheumatoid arthritis	
	Inflammation	Damage	Inflammation	Damage
LER	1.0 (0, 2)	0.5 (0, 1)	1.4 (1, 3)	1.0 (1, 2)*
LEL	0.7 (0, 1.3)	0.4 (0, 1)	1.0 (1, 2)	0.8 (1, 2)*
MCR	1.4 (1, 3)	0.5 (0, 1)	1.3 (1, 2)	0.7 (1, 1)
MCL	1.7 (2, 3)	0.7 (1, 1)	1.6 (2, 3)	0.8 (1, 0.75)
ATR	0.9 (0, 2)	0.6 (0, 1)	0.9 (0, 2)	0.4 (0, 1)
ATL	1.0 (0, 2)	0.5 (0, 1)	0.6 (0, 1)	0.3 (0, 0.75)

* Comparison of PsA and RA denotes $P = .02$ using Mann-Whitney U-test.
LER: right lateral epicondyle, LEL: left lateral epicondyle, MCR: right medial condyle, MCL: left medial condyle, ATR: right Achilles tendon insertion, and ATL: left Achilles tendon insertion.

Table 2: "Inflammation" and "damage" US scores for each enthesis according to the presence or absence of juxta-articular joint tenderness. Scores are the mean (median, IQR).

	Inflammation index at associated enthesis		Damage index at associated enthesis	
	Tender	Nontender	Tender	Nontender
EJR	1.9 (2, 2.8)	0.8 (0, 2.0)*	0.9 (1, 2.0)	0.5 (0, 1.0)*
EJL	1.0 (1, 2.0)	0.7 (0, 1.3)	0.7 (1, 1.0)	0.5 (0, 1.0)
KJR	2.3 (3, 2.5)	1.3 (1, 2.0)*	0.8 (1, 0.8)	0.5 (1, 1.0)
KJL	1.5 (2, 3.0)	1.7 (2, 3.0)	0.7 (1, 1.0)	0.8 (1, 0.3)
AJR	1.0 (1, 2.0)	0.8 (0, 2.0)	0.4 (0, 0.8)	0.5 (0, 1.0)
AJL	1.0 (0, 2.0)	0.8 (0, 1.5)	0.5 (0, 1.5)	0.4 (0, 1.0)

* Comparison of tender versus nontender: denotes $P < .05$ using Mann-Whitney U-test.
EJR: right elbow joint, EJL: left elbow joint, KJR: right knee joint, KJL: left knee joint, AJR: right ankle joint, AJL: left ankle joint.

5. Results

The study included 94 patients, 71 with PsA (36 male, 35 female, mean age 47.6 years, mean duration of disease 5.5 years, mean CRP 15.7 mg/dL, mean swollen joint count 2.5) and 23 with RA (10 male, 13 female, mean age 62.6 years, mean duration of disease 12.6 years, mean CRP 8.9 mg/dL, mean swollen joint count 3.9). The difference in age between the two groups was significant (mean difference in ages =15.0 years, 95% CI 9.3–20.7 years).

US scores were generally higher for RA at the epicondyles, significantly so for the "damage" scores (Table 1). The sensitivity and specificity of the US scores for "diagnosing" PsA (with RA as the comparator) were 0.41 and 0.37, respectively. For the clinical score (the LEI) these figures were 0.54 and 0.65, respectively. The odds ratio (OR) for having PsA, given an aggregate US score above the median was 0.41 (95% confidence intervals: 0.13–1.03), for the clinical score (LEI) and, the OR was 2.16 (0.81–5.70).

Given that four of the LEI points are adjacent to joints, the relationship between entheseal tenderness, US scores and tenderness and swelling in the adjacent joint as examined and the results given in Table 2. Only a few joints were clinically swollen so only the results for articular tenderness are presented, but the results for joint swelling were qualitatively similar. A significant relationship between articular tenderness and US scores was found for the right elbow and right knee only. However, scores were generally higher when the adjacent joint was tender, with the exception of the ankle joints. There was proportionally more articular involvement in the cases with RA, with overall figures for articular swelling and tenderness in RA of 16% and 18%, respectively; the same figures for PsA were 3% and 15%, respectively.

6. Discussion

This study was done as part of the ongoing validation of the LEI. In particular the aim was to examine the specificity of the instrument both based on clinical and US assessment comparing two differing types of rheumatic disease. Although clinical assessment appeared to confirm the specificity of the LEI, the results suggest that an US index, employing a recognised framework for recording both grey-scale and power Doppler features of enthesitis, cannot readily distinguish between rheumatoid arthritis and psoriatic arthritis. Indeed, US scores were higher in RA compared to PsA at the lateral epicondyles of the elbow. The discrepancy between clinical and US enthesitis in spondyloarthropathy is not a novel finding [10, 11]. This may in part be due to the fact that clinical examination and US are measuring different things. For example, US cannot visualise osteitis yet, osteitis may cause tenderness at the enthesis. Osteitis, or bone oedema, can be visualised at the enthesis in spondyloarthropathy using MRI and this has been interpreted as indicating enthesitis [12]. In this way, tenderness at the enthesis may have a different meaning to US appearances and may in fact be a more sensitive sign of enthesitis, but further studies are required to resolve this issue.

Previous studies comparing US enthesitis in spondyloarthropathy and "controls" have been conflicting. An Italian group found abnormalities around the heel equally in PsA and RA [8] but other studies, including one from the same group, have not been able to confirm this result [10, 13]. Certain entheseal sites have a closer relationship with joints than others, this being one reason why the MASES index favoured sites that were not adjacent to joints [14]. One possible explanation for the results of the current study is that articular inflammation, particularly at the elbow and radiohumeral joint, may extend to the enthesis at the lateral epicondyle. A similar argument could be used for the medial condyle of the femur and the knee joint. However, this argument could not apply to the ankle and the Achilles tendon and the results from Table 2 would support this.

In this way, enthesitis and entheseal new bone formation may be seen in RA. However, studies using plain radiographic images have indicated that entheseal new bone formation may also occur at sites remote from joints, such as the Achilles insertion and around the pelvic bones [7]. In the CASPAR study, a large international study to develop new classification criteria for psoriatic arthritis, images of 588 patients with psoriatic arthritis were compared to images from 395 patients with rheumatoid arthritis and 97 patients

with ankylosing spondylitis [7]. Entheses examined were at the calcaneus, the knee and the pelvis. No differences in entheseal new bone formation between psoriatic arthritis and rheumatoid arthritis were found. A further consideration of the results from Table 1 is the difference in the average ages of the patients from the two groups. The patients with rheumatoid arthritis were significantly older than the patients with PsA. Given that degenerative changes, represented by enthesophytes, in articular and juxta-articular structures are likely to increase with age this may explain the significant differences in Table 1. The higher "inflammation" scores in rheumatoid arthritis would not be explained by this mechanism, particularly since these were mainly seen at the elbow. An argument could have been made for more frequent inflammatory changes in the retrocalcaneal bursa in rheumatoid arthritis, yet this was not observed in this study.

Interobserver differences in the measurement of US enthesitis have been previously noted. In this study a three-step process to improve reliability of these features, as previously described by D'Agostino et al. [15], was not adopted. Instead, we aimed to obtain some form of standardisation by the use of a CD of standard images. However, given that the main finding of this paper was the difference between the two disease groups, PsA and RA, and that this contrast was replicated across the centres, absolute agreement on the presence or absence of features is less important: in this sense centres acted as their own controls.

The hypothesis that PsA is largely an entheseal-based disease, and RA is one largely synovial based, is not supported by this study [3]. However, it should be noted that most of the cases in this study had established disease and contiguous spread of inflammation might have obfuscated the initial sites of inflammation. Such a mechanism might have explained the findings of Marzo-Ortega et al. who could not differentiate RA and PsA on the basis of MRI studies of the hand in relatively early disease [16].

In summary, the results of this study suggest that US evidence of enthesitis cannot distinguish between RA and PsA, possibly because of the more frequent juxta-articular inflammation in RA. Further studies are needed with alternative clinical ways of assessing enthesitis and using MRI and US for imaging comparison.

Authors' Contribution

Dr. Helliwell conceived the study, collected data, and undertook the analysis. Drs. Groves, Chandramohan, Harrison, and B Reyes performed the ultrasound examinations. Drs. Ibrahim, A. Beltran, Valle and Healy collected clinical study data. All authors have reviewed the paper. None of the authors have a conflict of interest.

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