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Greater magnitude of entheseal microdamage and repair in psoriatic arthritis compared with ankylosing spondylitis on ultrasound

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Abstract

Objectives. AS and PsA share clinical and immunological features centred on enthesitis. However, a strong association between PsA and preceding injury has been recognized. The aim of this study was to test the hypothesis that the entheseal damage seen by US is commoner in PsA patients than in AS patients.

Methods. Seventy-nine AS and 85 PsA patients had US scans of 1640 entheses to calculate entheseal inflammation (hypoechogenicity, thickening and Doppler) and damage scores (calcifications, enthesophytes and erosions). Regression modelling was done to evaluate the effect of diagnoses on outcomes, controlling for age, gender, BMI, clinical enthesitis, HLA-B27, and anti-TNF use.

Results. Both inflammation and damage scores on US were correlated with BMI ($r = 0.392$; $r = 0.320$) and age ($r = 0.308$; $r = 0.538$) ($P < 0.001$), and men had higher inflammation scores than women [12.3 (7.5) *vs* 8.9 (7.3), $P = 0.001$]. In multivariate analysis, despite similar (anti-TNF–treated patients) or slightly less inflammation (anti-TNF–naïve patients) in the PsA group, they had 4.22 times more US damage than their counterparts with AS. The difference was even higher in the anti-TNF–naïve patients (5.6 times).

Conclusion. On US assessment, PsA patients have greater entheseal insertion damage scores compared with AS, suggesting potential differences in tissue repair, immunobiology or response to injury at insertions.

Key words: enthesitis, ultrasound, spondyloarthritis, ankylosing spondylitis, psoriatic arthritis

Rheumatology key messages

- PsA has more entheseal damage and tissue repair than AS on US.
- The exaggerated entheseal injury seen in PsA may have similarities with Koebner phenomenon in the skin.
- BMI, age and gender contribute to entheseal scores on US in PsA and AS.

Introduction

AS and PsA share many clinical and genetic similarities, however there are also well-known differences between these two forms of arthritis [1–3]: PsA affects men and women equally, whereas AS is observed three times more in men; peripheral arthritis and dactylitis are more common in PsA; and spondylitis, sacroiliitis and the presence of syndesmophytes, a characteristic entheseal pathology, are more severe in patients with AS and more symmetrical [3, 4].

Enthesitis is the inflammation of the insertion of tendons, ligaments and capsules into the bone and is frequently observed in both AS and PsA [5, 6]. Ultrasonography is a sensitive tool for visualizing enthesitis, and is suitable for detecting both inflammatory changes and damage [7]. Since Koebner's reaction is a

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CLINICAL SCIENCE

well-known phenomenon in psoriasis, whereby patients respond to trauma to the skin by forming new skin lesions, we hypothesized that, mimicking the skin, PsA patients may be responding differently to biomechanical stress in other structures, for example, in the form of entheses. Here, we report a study investigating the similarities and differences in enthesitis between AS and PsA, and possible associations with factors that are known to be related to the severity of the inflammation and the damage seen on US in both groups.

Methods

Patients and clinical assessment

One hundred and sixty-four consecutive adult patients with PsA ($n = 85$) and AS ($n = 79$) were recruited, fulfilling the Classification for Psoriatic Arthritis (CASPAR) and Modified New York criteria, respectively [8, 9], regardless of their disease activity status. However, PsA patients with psoriatic skin lesions around the entheseal sites included in the US protocol were excluded so that the sonographer was blind to the group to which each patient belonged. The study was approved by the local Ethics Committee at Marmara University, and all patients gave informed consent before enrolment. The disease characteristics, therapies and clinical assessment on 66/68 joint counts and 10 entheses (same sites of US) were collected on the day of the US assessment.

Ultrasonography scanning and blinding

All patients underwent an US scan (MyLab 70 XVG, Esaote Biomedica, Genoa – Italy) equipped with a broadband 6–18 MHz linear probe, performed by the same rheumatologist (SZA), experienced in musculoskeletal US and blinded to the clinical examination findings. Bilateral Achilles tendons, plantar fascia, quadriceps tendon insertions, and patellar tendon origins and insertions were scanned, using a protocol as described before [10].

US image interpretation

Hypoechogenicity, thickness of the tendon insertion, calcification, enthesophytes, erosion and Doppler activity within 2 mm of the insertion were included as elementary lesions of enthesitis [11]. The US findings were scored on a scale between 0 and 3, as described before [10]. US findings were categorized as inflammation score (sum of hypoechogenicity, thickening, and entheseal Doppler scores) and damage score (sum of calcification, erosions and enthesophytes).

Statistical analyses

All analyses were performed using SPSS V24 (SPSS Inc., Chicago, IL, USA) and R statistical software V3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous data were expressed as means (S.D.), and categorical variables were expressed as percentages. Continuous variables were compared by using a Mann–Whitney *U* test. The correlation analysis was performed using the Spearman's rank correlation coefficient.

As there were differences in demographics that might have influenced the results, we fitted a regression model to see the effect of diagnosis on each outcome (inflammation and damage), controlling for demographics and treatment (age, gender, BMI, clinical enthesitis, HLA-B27 and anti-TNF use) (details in supplementary data, section Statistical modelling, available at *Rheumatology* online). Depending on the analysis, the regression models were interpreted in a multiplicative manner, that is, one unit increase in a quantitative predictor leads to a multiplicative change in the outcome variable. All the results are presented as two-tailed values.

Results

PsA patients were older ($P < 0.005$), had higher BMI ($P = 0.021$), were more frequently female ($P < 0.001$), had a lower frequency of HLA-B27 positivity ($P < 0.001$) and were less frequently treated with anti-TNFs ($P < 0.001$) (Table 1). For disease activity assessment, PsA patients had more clinical enthesitis, and higher tender and swollen joint counts than AS ($P < 0.001$ for all).

Factors affecting the US scores

The PsA patients had significantly higher damage scores than the AS patients ($P = 0.008$), and numerically higher inflammation scores ($P = 0.077$) (Table 1 and Fig. 1). Men had higher inflammation scores than women [12.3 (7.5) *vs* 8.9 (7.3), $P = 0.001$]. HLA-B27–positive patients ($n = 50$, including 44 patients with AS and 6 patients with PsA) had lower US scores than HLA-B27–negative patients ($n = 81$) [inflammation: mean (S.D.) scores 6.5 (5.3) *vs* 10.8 (7.8), $P < 0.001$); damage: 8 (6.7) *vs* 9.8 (5.9), $P = 0.03$]

Neither clinical enthesitis nor anti-TNF treatment influenced the US scores for either inflammation or damage (data not given). Inflammation scores were positively correlated to BMI ($r = 0.392$; $P < 0.001$), disease duration ($r = 0.223$; $P = 0.017$) and age ($r = 0.308$; $P < 0.001$), whereas damage scores were only correlated to BMI ($r = 0.320$; $P < 0.001$) and age ($r = 0.538$; $P < 0.001$). When the elementary lesions were analysed separately, hypoechogenicity and entheseal Doppler were more frequent in the PsA group (Table 1).

Multivariate analysis

With respect to inflammation scores, the effect of anti-TNF therapies was found significant at the level of $P = 0.083$. Among patients receiving anti-TNF treatment, diagnosis was not found to be significant ($P = 0.738$), and no significant differences between inflammation scores in the PsA versus the AS groups were observed when adjusting for factors such as BMI, age, gender, clinical enthesitis or HLA-B27 status, which likely reflected the benefit of anti-TNF therapy in both disease groups (Supplementary Table S1, available at *Rheumatology* online). In the group of patients not receiving anti-TNF treatment, a difference in

Table 1 Patient demographics, US scores and elementary lesions

	AS	PsA	*P*-value
Number of patients	79 (48.1)	85 (51.9)	
Male/female	50 (63.3)/29 (36.7)	19 (22)/66 (77)	$P < \mathbf{0.001}$
Age, mean (S.D.), years	44.4 (11)	49.9 (13.7)	$P < \mathbf{0.005}$
BMI, mean (S.D.), kg/m^2	27.1 (4.7)	29.3 (5.5)	$P = \mathbf{0.021}$
Percentage of patients on of anti-TNF	40 (50.6)	9 (10.6)	$P < \mathbf{0.001}$
Disease duration, mean (S.D.), years	12.7 (9)	9.5 (8.4)	$P = \mathbf{0.02}$
Enthesitis on physical examination	18 (22.8)	48 (56.5)	$P < \mathbf{0.001}$
HLA-B27 *n*/total *n* (%)	44/65 (67.7)	6/66 (9.1)	$P < \mathbf{0.001}$
RF *n*/total *n* (%)	1/66 (1.5)	4/73 (5.5)	
BASDAI, mean (S.D.)	4.1 (2.3)	4.4 (2.3)	$P = 0.5$
BASFI, mean (S.D.)	3.3 (2.5)	2.9 (2.4)	$P = 0.3$
Tender joint count, mean (S.D.)	1 (1.5)	3.7 (7.2)	$P = \mathbf{0.001}$
Swollen joint count, mean (S.D.)	0.1 (0.5)	1.3 (3.2)	$P < \mathbf{0.001}$
US scores			
Inflammation scores, mean (S.D.)	9.2 (6.9)	11.3 (8)	$P = 0.077$
Damage scores, mean (S.D.)	8.4 (6)	10.4 (5.5)	$P = \mathbf{0.008}$
Total scores, mean (S.D.)	17.7 (11.2)	21.7 (12)	$P = \mathbf{0.013}$
Elementary lesions			
Hypoechogenicity	46 (58.2)	65 (76.5)	$P = \mathbf{0.019}$
Thickening	77 (97.5)	80 (94.1)	$P = 0.45$
Power Doppler	12 (15.2)	30 (35.3)	$P = \mathbf{0.004}$
Calcifications	16 (20.3)	14 (16.5)	$P = 0.6$
Erosions	10 (12.7)	13 (15.3)	$P = 0.7$
Enthesophytes	79 (100)	85 (100)	NA

Statistically significant *P*-values highlighted in bold. Values are *n* (%) unless otherwise stated. NA: not available.

inflammation levels was observed between PsA and AS patients: women with PsA had 5% (e^(−0.519 + 0.466)) less inflammation than women with AS (Supplementary data, section Inflammation scores, and Supplementary Table S2, available at *Rheumatology* online). A similar trend was observed in men, though that trend was not significant.

With respect to damage scores, the association between diagnosis and age was found to be significant ($P < 0.001$). After adjusting for age, PsA patients had 4.22 times more US damage than their counterparts of similar age in the AS group. The aged-adjusted US damage was 3.05 and 5.60 times higher for PsA patients who did, and did not, receive anti-TNF treatment, respectively, compared with AS patients (Supplementary data, section Damage scores, available at *Rheumatology* online).

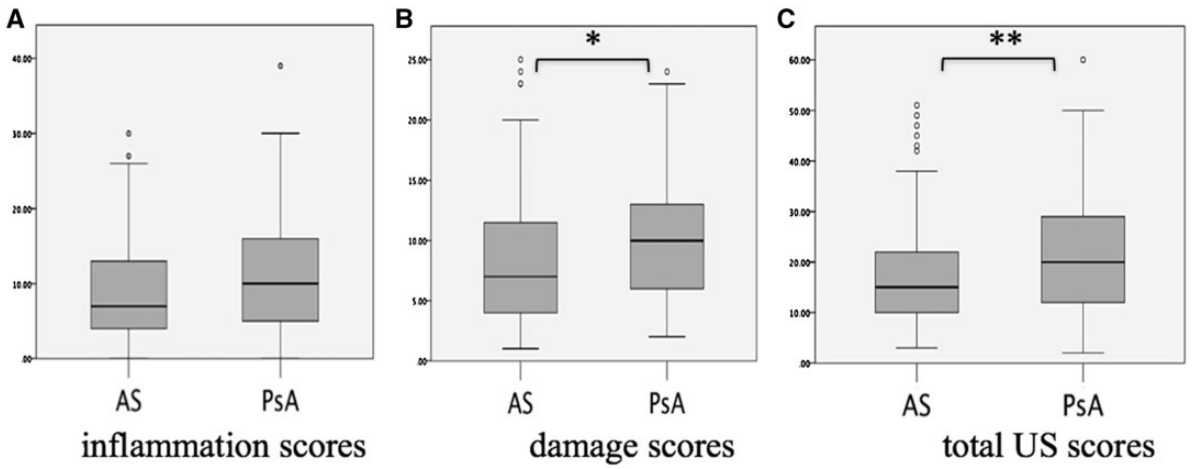
Discussion

The limited previous imaging studies of axial involvement in AS and PsA have reported some differences [3, 4], but there have been no studies comparing peripheral entheseal changes in these two types of arthritis. To the best of our knowledge, this is the first study to explore the similarities and differences in entheseal abnormalities in AS and PsA using US, and factors that might be related to the severity of the entheseal inflammation and damage. In this study, PsA patients were found to have more damage on US at the entheseal insertions than AS, and BMI, age and gender related to the entheseal scores.

Biomechanical stress is thought to play an important role in SpA, especially in PsA. Koebner's response in the skin for psoriasis and deep Koebner responses in the joint for PsA are well recognized [12]. Psoriatic skin lesions commonly occur around the sacral area, knees and elbows, within areas that have more tension due to relatively higher range of motion and/or pressure compared with the flexor surfaces [13]. Also, obesity is more frequent in PsA compared with in psoriasis without arthritis, supporting the hypothesis that biomechanical stress in the joints plays a role in the development of entheses [14]. Both inflammation and damage scores on US within the enthesis were correlated with BMI in the present study in both AS and PsA. Since patients with PsA are usually more overweight than those with AS, we performed a regression analysis to control for BMI. This analysis indicated that having PsA meant that a patient had four times the risk of having damage at the enthesis, than a patient with AS. Thus, not only was high BMI a risk factor for entheses for patients with PsA, but the response to the same BMI was different and exaggerated in PsA, with more damage. Together, our findings raise the possibility of the immunobiology and tissue repair response in PsA being different from those in AS, and this needs to be assessed in future studies.

Our study has some limitations. There were differences in the demographics between the groups, but this result

Fig. 1 The comparison of ultrasonography scores in AS and PsA



(**A**) Inflammation; (**B**) damage; (**C**) total US. *P=0.008, **P=0.013.

for the comparison between AS and PsA was expected, and we performed a regression analysis to control for those demographic parameters. HLA-B27 status was positive in a small group of PsA patients, which may have impacted on the outcomes; however, we would expect this to be the case in any population of PsA patients. With respect to treatments, our analysis was restricted to anti-TNF medication and did not investigate other medications. Another study design on an inception cohort and on patients without any treatment might produce different results. However, an inception cohort without any treatments would end up with a bias to include very early and mild disease only.

In conclusion, this is the first study to show sonographically determined differences in entheses when comparing PsA patients and AS patients. In particular, PsA patients had more damage on US at the entheseal insertions than AS patients, suggesting various possibilities, including the effect of Koebner's phenomenon on entheses, better repair in AS, and different immunobiological mechanisms for each disease. The implications of the greater magnitude of the damage-related changes in PsA require further investigation to ascertain whether it is relevant to various factors, including PsA epidemiology, diagnosis and response to biologic therapy.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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