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Original article

Clinical and ultrasonography assessment of peripheral enthesitis in ankylosing spondylitis

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Abstract

Objective. The aim of this study was to compare clinical examination with power Doppler US (PDUS) in the detection of entheseal abnormalities in patients with AS.

Methods. Thirty-six AS patients underwent clinical and PDUS examination of the following bilateral entheseal sites: common extensor tendon at its insertion at the lateral humeral epicondyle; gluteus tendons at their insertion at the greater trochanter; quadriceps tendon at its insertion at the superior pole of the patella; patellar tendon at its proximal insertion at the inferior pole of the patella; patellar tendon at its distal insertion at the tibial tuberosity; Achilles tendon at its insertion at the calcaneus; and plantar aponeuroses at its insertion at the calcaneus.

Results. Clinical and PDUS examination revealed at least one abnormal enthesis in 23 (63.9%) and 35 (97.2%) AS patients, respectively. Furthermore, of 432 entheses examined in our 36 AS patients, 64 (14.8%) were considered abnormal by clinical examination and 192 (44.4%) by PDUS. US abnormalities most commonly found were enthesophytes (31.7%), calcifications (33.7%), thickening (29.8%) and hypoechogenicity (26.6%). We found erosions and PD signals in 9.7 and 6% of examined entheseal sites, respectively. The evidence of entheseal abnormalities by clinical examination has a poor likelihood ratio (LR) for the presence of US abnormalities with vascularization (LR = 1.61), without vascularization (LR = 1.24) or erosions (LR = 1.51) at all sites.

Conclusions. PDUS permits detection of structural and inflammatory abnormalities of the enthesis in AS and may complement the physical examination in order to better evaluate enthesitis.

Key words: Power Doppler ultrasound, Enthesitis, Ankylosing spondylitis.

CLINICAL SCIENCE

Introduction

Enthesitis, defined as inflammation of the origin and insertion of ligaments, tendons, aponeuroses, annulus fibrosis and joint capsules, is a hallmark of AS. In primary AS, the frequency of peripheral enthesitis has been found to be within 25–58% [1], but the real prevalence of this feature depends on the type of assessment (i.e. clinical, imaging or histological). Peripheral enthesitis is usually revealed by clinical findings, such as localized pain, tenderness and swelling. Nevertheless, there are no definite clinical criteria for the diagnosis of this manifestation that may even be asymptomatic. Histological examination of the enthesis is the potential gold standard for evaluation of enthesitis, but is rarely obtained due to ethical and practical constraints. Imaging techniques include conventional radiography, bone scintigraphy, MRI or US [1]. Conventional radiography may show erosions and bone proliferation changes (ill-defined and finely speculated), but only in more advanced phases [1]. Technetium-99 m methylene diphosphonate scintigraphy has been shown to be a sensitive indicator of heel enthesitis, but its specificity has not been determined. MRI may show the swelling of the enthesis and the peritendinous soft tissue, the distension of adjacent bursae by fluid collection and oedema of the bone near the insertion. On the other hand, the study of entheses with MRI is limited because of its reduced availability and high costs [2], and also by

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the evidence that the normal features of the enthesis cannot be recognized with conventional sequences [3]. US has proved to be a highly sensitive and non-invasive tool to assess the presence of enthesitis, characterized by hypoechogenicity with loss of tendon fibrillar pattern, tendon thickening, local calcifications, enthesophytes and bony erosions. Moreover, the use of power Doppler US (PDUS) allows the detection of abnormal vascularization of soft tissues in inflammatory articular diseases [4].

Entheseal involvement in SpA is not always detected by clinical examination. US is better than clinical examination for detecting entheseal abnormalities, but there is a considerable discrepancy between clinical and US findings [5, 6]. It is unknown whether this discrepancy might be related to the different abnormalities of the enthesis or with the presence/absence of vascularization. The aim of this study was to compare clinical examination with PDUS in the detection of entheseal abnormalities in patients with AS.

Patients and methods

Thirty-six consecutive patients with AS (according to the modified New York criteria) [7] referred to the Rheumatology Unit at Sapienza University of Rome were studied. Patients with previous joint surgery of the knee or ankle, CS injection of the structures examined within the previous 6 weeks or peripheral neuropathy were excluded from the study. Informed consent was obtained from each patient before inclusion in the study. The study was approved by the ethics committee of the Università degli Studi di Roma 'La Sapienza' – Azienda Policlinico Umberto I.

All patients underwent clinical and US examinations of the following bilateral entheseal sites: common extensor tendon at its insertion at the lateral humeral epicondyle; gluteus tendons at their insertion at the greater trochanter; quadriceps tendon at its insertion at the superior pole of the patella; patellar tendon at its proximal insertion at the inferior pole of the patella; patellar tendon at its distal insertion at the tibial tuberosity; Achilles tendon at its insertion at the calcaneus; and plantar aponeuroses at its insertion at the calcaneus. Thus, a total of 432 entheses were examined. Our study was conducted in compliance with good clinical practice, following the routine monitoring procedures performed in our unit for patients with SpA.

Patients were initially assessed by a single rheumatologist who developed the clinical history (including potential traumatic factors and professional activity) and performed the physical examination, including clinical evaluation of the enthesis. Clinical enthesopathy was defined by the presence of at least one of the following findings: (i) spontaneous pain, (ii) tenderness elicited by pressure, mobilization and contraction against resistance of the corresponding tendons and (iii) local swelling of the enthesis [6]. All patients underwent evaluation using the BASMI [8], BASDAI [9], BASFI [10], HAQ [11], patient's and physician's visual analogue scale (VAS) on global disease activity (0–100 mm), ESR and CRP.

US assessment

Using a MyLab 70 XVG machine equipped with a broadband 6–18 linear probe, sonographic examination was performed at the same entheseal sites clinically evaluated by a rheumatologist experienced in musculoskeletal sonography (A.I.), who was unaware of the clinical findings. In all cases the following settings were used: grey-scale frequency 12–15 MHz; Doppler frequency 6.7–7.5 MHz; PD pulse repetition frequency 750 Hz; and low wall filters. At the beginning of each scanning session at different entheseal sites, the focus was positioned at the level of the region of interest and the colour box that was enlarged to the upper part of the image. Colour gain was adjusted just below the level that caused the appearance of noise artefacts [12].

Patients were asked to adopt the most appropriate position that produced an optimal sonographic scan of the various entheses. After having applied gel to the skin to provide an acoustic interface, PDUS examinations were carried out, paying attention not to apply probe pressure on the anatomical structures under examination. In all cases, both longitudinal and transverse scans were performed, keeping the probe parallel and perpendicular, respectively, to the tendon's fibres.

During the same scanning session, PDUS was initially performed in grey-scale modality with the aim of detecting morphological changes, and immediately afterwards using PD techniques to search for local abnormal vascularization [6]. According to OMERACT [13] definitions of enthesopathy, the following changes were registered: tendon hypoechogenicity at the level of its bony insertion; tendon thickening at the level of its bony insertion; intratendinous calcifications; enthesophytes; bony erosions at the level of the enthesis; bony cortex irregularities at the level of the enthesis; and the presence of Doppler signal at the level of the bony insertion. Where present, intratendinous Doppler signal, bursitis and both partial and full-thickness tendon lesions were registered. All findings had to be confirmed by two perpendicular planes. Elementary US and PD findings were recorded as being present, in accordance with the reported definitions in the literature [5, 6, 14, 15], as follows: hypoechogenicity: loss of the typical fibrillar pattern with appearance of local extended hypoechoic areas; thickening: tendon swelling at the level of its bony insertion; calcification: hyperechoic spot or linear formation; enthesophyte: step-up bony prominence at the enthesis–bone junction; bony erosion: discontinuity of the bony surface visible in two perpendicular planes; bony irregularity: change in the cortical profile not including definite enthesophyte or bone erosion; bursitis: abnormal hypoechoic–anechoic intra-bursal material that is displaceable and compressible; and tendon lesions: interruption of the tendon fibres with or without hypoechoic material filling the defect. All changes were recorded according to an absent–present criterion.

According to D'Agostino *et al*. [6], US enthesitis was classified considering the different combinations of abnormal grey-scale and/or PD features into the following five distinctive patterns: Stage 1: vascularization at the cortical

junction without abnormal findings in B mode; Stage 2a: vascularization associated with swelling and/or decreased echogenicity at the cortical junction in B mode; Stage 3a: same as Stage 2a, plus erosions of cortical bone and/or calcification of the enthesis, and optional surrounding bursitis; Stage 2b: abnormal findings in B mode as in Stage 2a, but without vascularization; and Stage 3b: abnormal findings in B mode as in Stage 3a, but without vascularization. We considered Stages 2a and 2b suggestive of inactive lesions [6].

Statistical analysis

Categorical variables were analysed by χ^2 test or Fisher's exact test. The results were presented as the median (25th–75th percentile) and the significance of the differences was determined using the Mann–Whitney test for unpaired samples and Wilcoxon's test for paired samples. Sensitivity, specificity, likelihood ratio (LR), false-negative (FNR) and false-positive rates (FPR) have been calculated with 95% CI. Agreement was assessed using the weighted κ-statistic ($\kappa = 0$, no concordance; $0 < \kappa < 0.20$, slight concordance; $0.21 < \kappa < 0.40$, fair concordance; $0.41 < \kappa < 0.60$, moderate concordance; $0.61 < \kappa < 0.80$, substantial concordance; and $0.81 < \kappa < 1.00$, perfect concordance. Statistical significance was accepted at $P < 0.05$.

Table 1 Main clinical and demographic features of 36 patients with AS

Male/female, *n*	28/8
Age, mean (range), years	51.3 (23–75)
Disease onset, mean (range), years	35.4 (15–65)
Disease duration, mean (range), years	15.8 (2–43)
BASDAI	4.5 (2.4–6.1)[a]
Peripheral involvement, *n* (%)	14 (38.9)
Extra-articular involvement, *n* (%)	15 (41.7)
BASMI	4 (1–6)[a]
BASFI	35 (15.5–49.6)[a]
HAQ	0.8125 (0.34–1.03)[a]
VAS patient, mm	45 (22–61)[a]
VAS physician, mm	47.5 (23–60)[a]
ESR, mm/h	12 (7–27)[a]
CRP, mg/l	0.6 (0.21–2.87)[a]
Treatment, *n*/%	
CSs	6/16.6
NSAIDs	22/61.1
DMARDs	4/11.1
Anti-TNF drugs	21/58.3

[a]Median (25th–75th percentile).

Results

The main clinical and demographic features are shown in Table 1. These features are not significantly different between patients treated with or without anti-TNF-α drugs. In particular, patients treated with or without anti-TNF-α drugs showed similar values (median/25th–75th percentile) of BASDAI (4.6/2.5–6.2 *vs* 4.5/2.7–5.8; P = n.s.), BASMI (4/1–4 *vs* 5/3.5–7; P = n.s.) and BASFI (32/14–49 *vs* 42/24–49; P = n.s.). Nineteen of 21 patients of the anti-TNF-α group were treated for at least 12 weeks. The extra-articular involvement included anterior uveitis ($n = 10$), psoriasis ($n = 2$), psoriasis plus uveitis and IBD ($n = 1$). Clinical and PDUS examination revealed at least one abnormal enthesis in 23 (63.9%) and 35 (97.2%) AS patients, respectively. Furthermore, of 432 entheses examined in our 36 AS patients, 64 (14.8%) were considered abnormal by clinical examination and 192 (44.4%) by PDUS. PDUS abnormalities of 432 examined entheseal sites are shown in Table 2.

Classification of abnormal peripheral enthesis features by B-mode US combined with PD in AS patients is shown in Table 3. The age (median/25th–75th percentile) of patients showing PDUS abnormalities with vascularization was significantly higher (57/50–65 *vs* 46/40.5–54 years; $P < 0.005$) than the age of patients showing PDUS abnormalities without vascularization. These groups of patients did not have any other differences in clinical or laboratory findings. Comparison of clinical findings with PDUS abnormalities (with or without vascularization) in 432 entheses of 36 AS patients is shown in Table 4.

Sensitivity, specificity, LR, FPR and FNR for the clinical examination *vs* PDUS abnormalities as the gold standard are shown in Table 5 (clinical examination *vs* PDUS abnormalities with vascularization) and Table 6 (clinical examination *vs* PDUS abnormalities without vascularization). The sensitivity, specificity and LR of the clinical examination for the presence of US erosions at all sites were 0.21 (95% CI 0.10, 0.37), 0.85 (95% CI 0.81, 0.89) and 1.51 (95% CI 0.81, 2.84), respectively. Values of κ (95% CI) between clinical examination and US abnormalities with vascularization, PDUS abnormalities without vascularization and US erosion were 0.05 (0, 0.24), 0.03 (0, 0.14) and 0.05 (0, 0.23), respectively. PDUS abnormalities (with or without vascularization) were not significantly different between patients treated with or without anti-TNF-α drugs.

Discussion

The concept of entheses prone to pathological changes in SpA is well recognized [3]. The relevant role of peripheral enthesitis is supported by the evidence that this feature, by clinical examination, has been included in the classification criteria of Amor (heel pain or other well-defined enthesopathic pain) [16], the ESSG [17] and the Assessment in SpondyloArthritis International Society (ASAS) for axial SpA [18].

Among imaging techniques, musculoskeletal US, by using both grey-scale and PD modalities, has an increasing and relevant role in the assessment of SpA, mainly for its capacity to detect enthesitis that may be clinically asymptomatic [5, 6, 19]. In the assessment of entheseal involvement, PDUS has shown to provide the visualization of abnormal vascularization and hyperaemia of soft

Table 2 PDUS abnormalities of 432 examined entheseal sites

Abnormalities	Sites						
	Lateral epicondyle	Great trochanter	Quadriceps tendon	Tibial tuberosity	Achilles tendon	Plantar fascia	All sites
Enthesophytes, *n* (%)	20 (27.7)	11 (1.,3)	43 (59.7)	23 (31.9)	35 (48.6)	5 (6.9)	137 (31.7)
Calcifications, *n* (%)	30 (41.6)	54 (75.0)	32 (44.4)	18 (25.0)	5 (6.9)	7 (9.7)	146 (33.7)
Tendon lesion, *n* (%)	1 (1.4)	0 (0)	2 (2.7)	0 (0)	0 (0)	1 (1.4)	4 (0.9)
Erosions, *n* (%)	26 (36.1)	6 (8.3)	1 (1.4)	6 (8.3)	3 (4.2)	0 (0)	42 (9.7)
Bone irregularity, *n* (%)	12 (16.6	19 (26.4)	4 (5.6)	17 (23.6)	2 (2.7)	1 (1.4)	55 (12.7)
Hypoechogenicity, *n* (%)	37 (51.4)	22 (30.5)	37 (51.4)	16 (22.2)	10 (13.9)	7 (9.7)	129 (29.8)
Thickening, *n* (%)	12 (16.6)	12 (16.6)	21 (29.1)	23 (31.9)	20 (27.7)	10 (13.9)	98 (22.6)
Bursitis, *n* (%)	0 (0)	0 (0)	1 (1.4)	21 (29.1	10 (13.9)	0 (0)	32 (7.4)
PD at the level of bony insertion, *n* (%)	10 (13.9)	1 (1.4)	5 (6.9)	4 (5.6)	6 (8.3)	0 (0)	26 (6.0)
At least one PDUS abnormality, *n* (%)	42 (58.3)	34 (47.2)	46 (63.8)	31 (43.0)	26 (36.1)	13 (18.0)	192 (44.4)
At least one clinical abnormality, *n* (%)	13 (18.0)	16 (22.2)	3 (4.16)	8 (11.1)	19 (26.4)	5 (6.9)	64 (14.8)

Table 3 Classification, according to D'Agostino *et al*. [6], of entheseal peripheral abnormalities (*n* = 192) by PDUS in AS patients

Entheseal site	Abnormalities with vascularization				Abnormalities without vascularization		
	Stage 1, *n* (%)	Stage 2a, *n* (%)	Stage 3a, *n* (%)	Total (1+2a+3a), *n* (%)	Stage 2b, *n* (%)	Stage 3b, *n* (%)	Total (2b+3b), *n* (%)
Lateral epicondyle	1 (1.4)	1 (1.4)	8 (11.1)	10 (13.9)	15 (20.1)	17 (23.6)	32 (44.4)
Great trochanter	1 (1.4)	0 (0)	0 (0)	1 (1.4)	23 (31.9)	10 (13.9)	33 (45.8)
Quadriceps tendon	2 (2.7)	0 (0)	3 (4.2)	5 (6.9)	14 (19.4)	27 (37.5)	41 (56.9)
Tibial tuberosity	0 (0)	0 (0)	4 (5.6)	4 (5.6)	10 (13.9)	17 (23.6)	27 (37.5)
Achilles tendon	1 (1.4)	1 (1.4)	4 (5.6)	6 (8.3)	5 (6.9)	15 (20.1)	20 (27.7)
Plantar fascia	0 (0)	0 (0)	0 (0)	0 (0)	11 (15.3)	2 (2.7)	13 (18.0)
All sites	5 (1.6)	2 (0.4)	19 (4.4)	26 (6.0)	78 (18.0)	88 (20.3)	166 (38.4)

Table 4 Comparison of clinical findings *vs* PDUS abnormalities with or without vascularization in 432 entheses of 36 AS patients

Entheseal site	Clinically positive enthesis (*n* = 64)			Clinically negative enthesis (*n* = 368)		
	Normal by US, *n* (%)[a]	US abnormalities with vascularization, *n* (%)[a]	US abnormalities without vascularization, *n* (%)[a]	Normal by US, *n* (%)[b]	US abnormalities with vascularization, *n* (%)[b]	US abnormalities without vascularization, *n* (%)[b]
Lateral epicondyle	3 (23.1)	3 (23.1)	7 (53.8)	27 (45.8)	7 (11.9)	25 (42.4)
Great trochanter	9 (56.2)	1 (6.2)	6 (37.5)	29 (51.8)	0 (0)	27 (48.2)
Quadriceps tendon	0 (0)	1 (33.3)	2 (66.6)	26 (37.7)	4 (5.8)	39 (56.5)
Tibial tuberosity	3 (37.5)	0 (0)	5 (62.5)	38 (59.4)	4 (6.2)	22 (34.4)
Achilles tendon	12 (63.1)	1 (5.3)	6 (31.6)	34 (64.1)	5 (9.4)	14 (26.4)
Plantar fascia	3 (60.0)	0 (0)	2 (40.0)	56 (83.6)	0 (0)	11 (16.4)
All sites	30 (46.8)	6 (9.3)	28 (43.7)	210 (57.1)	20 (5.4)	138 (37.5)

[a]The percentage (%) value is calculated on the number of total positive entheseal sites by clinical examination. [b]The percentage (%) value is calculated on the number of total negative entheseal sites by clinical examination.

Table 5 The sensitivity, specificity, LR, FPR and FNR of clinical examination for the presence of PDUS abnormalities with vascularization

Entheseal site	Sensitivity (95% CI)	Specificity (95% CI)	LR^+ (95% CI)	FPR (95% CI)	FNR (95% CI)
Lateral epicondyle	0.3 (0.08, 0.64)	0.83 (0.71, 0.91)	1.86 (0.61, 5.6)	0.76 (0.45, 0.93)	0.11 (0.05, 0.23)
Great trochanter	1 (0.05, 1)	0.78 (0,67, 0,87)	4.73 (3,01, 7,41)	0.93 (0.67, 0.99)	0 (0, 0.07)
Quadriceps tendon	0.2 (0.01, 0.70)	0.97 (0.88, 0.99)	6.7 (0.72, 61.8)	0.66 (0.12, 0.98)	0.05 (0.01, 0.14)
Tibial tuberosity	0 (0, 0.60)	0.88 (0.77, 0.94)	0 (0, NaN)	1 (0.59, 1)	0.06 (0.02, 0.16)
Achilles tendon	0.16 (0, 0.63)	0.72 (0.60, 0.82)	0.61 (0.09, 3.81)	0.94 (0.71, 0.99)	0.09 (0.03, 0.21)
Plantar fascia	NaN (NaN, NaN)	0.93 (0.83, 0.97)	NaN (NaN, NaN)	1 (0.46, 1)	0 (0, 0.06)
All sites	0.23 (0.09, 0.44)	0.85 (0.81, 0.88)	1.61 (0.76, 3.38)	0.9 (0.8, 0.96)	0.05 (0.03, 0.08)

Table 6 The sensitivity, specificity, LR, FPR and FNR of clinical examination for the presence of PDUS abnormalities without vascularization

Entheseal site	Sensitivity (95% CI)	Specificity (95% CI)	LR^+ (95% CI)	FPR (95% CI)	FNR (95% CI)
Lateral epicondyle	0.21 (0.09, 0.40)	0.85 (0.69, 0.93)	1.45 (0.54, 3.91)	0.46 (0.20, 0.73)	0.42 (0.29, 0.55)
Great trochanter	0.18 (0.07, 0.36)	0.74 (0.57, 0.86)	0.7 (0.28, 1.74)	0.62 (0.35, 0.83)	0.48 (0.34, 0.61)
Quadriceps tendon	0.04 (0, 0.17)	0.96 (0.81, 0.99)	1.51 (0.14, 15.9)	0.33 (0.01, 0.87)	0.56 (0.44, 0.68)
Tibial tuberosity	0.18 (0.07, 0.38)	0.93 (0.80, 0.98)	2.77 (0.72, 10.7)	0.37 (0.10, 0.74)	0.34 (0.23, 0.47)
Achilles tendon	0.3 (0.12, 0.54)	0.75 (0.60, 0.85)	1.2 (0.52, 2.72)	0.68 (0.43, 0.86)	0.26 (0.15, 0.40)
Plantar fascia	0.15 (0.02, 0.46)	0.94 (0.84, 0.98)	3.02 (0.56, 16.32)	0.6 (0.17, 0.92)	0.16 (0.08, 0.27)
All sites	0.16 (0.11, 0.23)	0.86 (0.81, 0.90)	1.24 (0.79, 1.96)	0.56 (0.43, 0.68)	0.37 (0.32, 0.42)

tissues [6, 19]. In particular, abnormal vascularization was present only in the SpA patients, while this finding was not observed in the healthy controls [6]. Moreover, PDUS has been demonstrated to be more sensitive than physical examination in the detection of enthesitis in AS, even though there is a discrepancy between clinical and US examinations [5, 6, 20]. In our study, the evidence of at least one abnormality by PDUS in 97.2% of AS patients and in 44% of all examined sites confirms previous results [5, 6, 19, 20]. In fact, Balint *et al.* [5] found US abnormalities in 56% of five entheseal sites of the lower limbs (superior pole and inferior pole of patella, tibial tuberosity, Achilles tendon and plantar aponeurosis) in 35 SpA patients (27 with AS). Lehtinen *et al.* [21] reported that enthesopathic abnormalities were more frequently (66%) found at the distal part of lower limbs (i.e. as patella insertion, Achilles tendon and plantar fascia insertions) with respect to the proximal part of lower limbs (i.e. ischial tuberosity, great trochanter and insertion of adductor muscles) in 31 patients with SpA. Kiris *et al.* [22] showed that changes in the grey scale combined with PD were more prevalent in lower extremity entheses in a group of 30 AS patients. Borman *et al.* [23] reported pathological US abnormalities at insertions of the Achilles tendon and plantar fascia on the calcaneum in 56.8% of 44 SpA patients, whereas 37% showed signs of entheseal involvement by clinical examinations. D'Agostino *et al.* [6] reported that 161 (98%) of 164 patients with SpA (104 patients with AS) had at least one abnormal enthesis by grey scale combined with PD. The sites most commonly affected were the distal portions of the lower limbs (i.e. Achilles tendon, plantar fascia and patellar tendon origin were abnormal in 79, 74 and 59%, respectively, of AS patients).

Why there is a predilection for the distal part of lower limbs by the enthesitic process is unknown, but anatomic and physiological factors, such as the major length of the tendon, might play a role. In fact, the major length of the Achilles tendon or its movement on the adjacent bursa may be responsible of a more relevant mechanical injury at this entheseal site [3, 6, 21]. Nevertheless, we frequently found PDUS abnormalities both in upper and lower limbs (Table 3). In particular, we found US abnormalities in 58% of lateral epicondyle sites. Thus, in our study, the evidence of frequent involvement of entheseal sites localized in upper and lower limbs suggests that the mechanical hypothesis should be applied at each different site, considering its anatomic and physiologic features. The role of stress or trauma in the pathogenesis of enthesitis in SpA patients has been reviewed by Olivieri *et al*. [24]. In fact, physical injury may trigger peripheral manifestations of SpA such as enthesitis [25] and dactylitis [26], as well as arthritis [24]. The damage and repair at the enthesis level in SpA could trigger an inflammatory reaction and may regulate immune activation [27]. Thus biomechanical stress factors can play a role in the pathogenesis of both inflammatory and mechanical enthesopathies, but the effects of mechanical load can be amplified in SpA, especially in HLA-B27-positive patients

[28]. Our study showed that the US abnormalities most commonly found were enthesophytes (31.7%), calcifications (33.7%), thickening (29.8%) and hypoechogenicity (26.6%), but these findings are not specific for AS. On the other hand, we found erosions at the level of the entheseal organ complex, strongly suggestive of AS, in 9.7% of examined entheseal sites. This result agrees with the prevalence (6.3%) reported previously [5]. Furthermore, we found that the prevalence (6%) of the PD signal at the level of examined entheseal sites was lower than that of a previous study, reporting a PD signal in 81% of abnormal enthesis [6]. In our study, the high percentage of patients treated with anti-TNF-α drugs could explain this discrepancy.

Finally, the age of our AS patients showing PDUS abnormalities with vascularization was significantly higher than the age of patients showing PDUS abnormalities without vascularization. This observation agrees with Peers *et al*. [29], showing a positive correlation between PDUS and age in patients with chronic Achilles tendinopathy, suggesting a possible role of repeated microtrauma in the development of entheseal neo-vascularization. Although it is well demonstrated that anti-TNF-α treatments reduce enthesitis in SpA, we found that PDUS abnormalities were not significantly different between patients treated with or without anti-TNF-α drugs. Nevertheless, these results do not permit us to assess the efficacy of anti-TNF drugs on enthesitis, because this cross-sectional study was not designed to assess their efficacy.

Another interesting aspect of our study is the discrepancy between entheseal abnormalities evaluated clinically and by US. In fact, this aspect is not surprising because enthesopathies could be asymptomatic [20] and US detects more entheseal abnormalities than clinical examination [5, 6]. On the other hand, 46.8% of positive entheseal sites by clinical examination did not show any PDUS changes. These results agree with previous results showing a considerable discrepancy between clinical and US findings [5, 6]. Moreover, Alcalde *et al*. [20] found normal US images in symptomatic entheses with a remarkable dissociation between sensitivity to local pressure and US findings. For explaining this dissociation, it has been suggested that structures in proximity, such as bone marrow, rather than the enthesis itself, could account for the pain [30].

In our study, taking PDUS as the gold standard, clinical examination showed a low sensibility for the PDUS presence of entheseal abnormalities with vascularization (23%), entheseal abnormalities without vascularization (16%) and entheseal erosions (21%) in all examination sites. Instead, the specificity of clinical examination was high for the PDUS presence of abnormalities with vascularization (85%), abnormalities without vascularization (86%) and erosions (85%). This low sensitivity and high specificity of clinical examination agree with results of Balint *et al.* [5], despite the fact that they used only grey-scale US. Furthermore, the evidence of entheseal abnormalities by clinical examination has a poor LR for the presence of US abnormalities with vascularization (LR = 1.61), without vascularization (LR = 1.24) and without erosions (LR = 1.51) at all sites. Nevertheless, at single sites, such as the patellar insertion of the quadriceps tendon and tendon insertion at the great trochanter, the evidence of entheseal abnormalities by clinical examination had a high LR for the presence of PDUS abnormalities with vascularization (6.7 and 4.73, respectively), suggesting the importance of the anatomy of a single enthesis.

In our study, the discrepancy between clinical and PDUS examinations has been further confirmed by slight concordance using the weighted κ-statistic. In fact, κ-values between clinical examination and US abnormalities with vascularization, PDUS abnormalities without vascularization and US erosion were 0.05, 0.03 and 0.05, respectively.

In conclusion, musculoskeletal US, a fast and relatively inexpensive imaging tool, has an increasing and relevant role in the assessment of peripheral entheseal involvement in AS. In fact, PDUS permits detection of structural and inflammatory abnormalities of the enthesis and may complement physical examination in order to better evaluate enthesitis.

Rheumatology key messages

- There is a discrepancy between AS peripheral entheseal involvement evaluated clinically and by US.
- PDUS detects structural and inflammatory abnormalities of the enthesis and may complement physical examination.

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