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ORIGINAL ARTICLE

Responsiveness to therapy change of a global ultrasound assessment in spondyloarthritis patients

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Abstract The objective of this study is to evaluate the responsiveness to therapy change of a global ultrasound (US) assessment in the short-term monitoring of spondyloarthritis (SpA) patients with peripheral involvement. Consecutive SpA patients with both clinical peripheral involvement and active disease (initiating or changing therapy) were included. All patients underwent both clinical and US assessment in day entering the study and after 3 months of follow-up. Peripheral global US assessment included the recognition of abnormal inflammatory findings at joint, tendon, and entheseal level according tostandardized scanning methods. A total of 34 patients completed both basal and 3-month follow-up assessments. Acute phase reactants, both erythrocyte sedimentation rate and C-reactive protein, tenderness (68) and swollen (66) joint counts, Bath Ankylosing Spondylitis Disease Activity Index and Health Assessment Questionnaire decreased significantly at 3-month follow-up. Total score for the global US assessment also decreased significantly between basal and 3-month follow-up assessment [mean difference, 12.33 (IC 95 %, 9.23–15.42); $p<0.0001$]. All individual component, joint, tendon, and enthesis scores, also showed a significant decrease during the follow-up period. A high degree of intra-observer reliability was found for the global US assessment (ICC [95 % CI]: 0.977 [0.961–0.993]). This global US assessment, including joints, tendons, and entheses, showed a good responsiveness to clinical changes and might be useful for monitoring SpA patients with peripheral involvement.

Keywords Arthritis · Dactylitis · Enthesitis · Spondyloarthritis · Ultrasonography · Ultrasound

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Introduction

Spondyloarthritis (SpA) may present with diverse number of musculoskeletal manifestations during their clinical course, such as sacroiliitis, spondylitis, synovitis, tenosynovitis, dactylitis, and enthesitis. Due to the heterogeneity of clinical manifestations, therapeutic monitoring has been a challenge for rheumatologists in the last decades [1–6].

Ultrasound (US) has shown to be a useful tool for therapeutic monitoring in other inflammatory arthritis such as rheumatoid arthritis [7–12]. US scores assessing the entheses in SpA have been developed mainly for diagnostic purposes [13–16] and although there are some reports about the ability of US for monitoring patients with SpA, these have been mainly based in the assessment of entheses [17, 18].

To the best of our knowledge, to date, there are no reports about any global US assessment, including joints, tendons, and entheses, for monitoring SpA patients with clinical peripheral involvement.

The aim of the present study was to evaluate the usefulness of a global US assessment in the short-term monitoring of SpA patients with peripheral involvement.

Patients and methods

The study was conducted according to the Declaration of Helsinki and local regulations. Ethical approval for the study was obtained from the Hospital Local Ethics Committee, and informed consent was obtained from all patients.

A prospective cohort study was carried out. Consecutive SpA patients fulfilling the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial SpA [19, 20] and/or peripheral SpA [21] and attending the outpatient Rheumatology Unit at the "Hospital Italiano de Buenos Aires" were recruited. Patients with psoriatic arthritis (PsA), in addition, had to fulfill CASPAR criteria for psoriatic arthritis [22].

Regardless of the classification in axial or peripheral SpA, all patients had to have clinical peripheral involvement (arthritis, enthesitis, and/or dactylitis) detected by their treating rheumatologist at the time to be included.

The following exclusion criteria were adopted: under 18 years of age, body mass index (BMI) higher than 30, peripheral neuropathy of lower and/or upper limbs, history of surgery, and/or presence of evident deformity at the anatomical structure site to be examined.

In order to ensure entry to the study of patients with active disease, only patients initiating or changing classic disease-modifying antirheumatic drugs (DMARDs) or biologic therapy according to the decision of their treating rheumatologists were included.

All patients underwent both clinical examination and US assessment on the same day at entry to the study and after 3 months of initiating or changing therapy. Treatment decisions throughout the follow-up period were made based on the patient's clinical course, without knowledge of the US findings.

Clinical and laboratory assessment

A careful physical examination was performed in all included patients before US examination by the same experienced rheumatologist (MA) according to standard procedures. At each visit, 68/66 joints were assessed for tenderness and swelling, respectively. Patients rated their pain and overall disease activity on a 100-mm visual analog scale (VAS) at each visit. Functional ability was evaluated with a self-assessment Argentinean version of the Health Assessment Questionnaire (HAQ) [23]. Data on acute phase reactants (C-reactive protein [CRP] level [normal, 0–5 mg/l] and erythrocyte sedimentation rate [ESR] [normal, 10–20 mm/h]) were obtained from laboratory tests performed within 48 h of each clinical visit. Disease Activity Score in 28 joints (DAS28) [24], Leeds Enthesitis Index (LEI) [25] and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [26] were calculated for each patient at each visit.

In addition, the following data were recorded on report sheets: age, sex, body mass index, onset of typical symptoms and disease duration, and current and future rheumatologic therapy including both DMARDs and biologic therapies.

Ultrasound assessment

All US examinations (baseline and after 3-month follow-up) were performed in a darkened room by a rheumatologist (SR) trained in this imaging technique blinded to all clinical data. Patients were asked not to talk with the operator about their clinical conditions. A MyLab 70 XV (Esaote Biomedica, Genoa, Italy) machine provided with two linear multifrequency probes (4–13 and 6–18 MHz, respectively) was used.

Global US assessment included the recognition of abnormal inflammatory findings at joint, tendon, and entheseal level according to standardized scanning methods [27].The presence and location of synovitis, tenosynovitis, and enthesopathy was recorded with reference to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) preliminary definitions of pathology [28].

Joints The following joint areas were bilaterally assessed: wrist, second and third metacarpophalangeals (MCP), second and third proximal interphalangeals (PIP), and knee and second and fifth metatarsophalangeals (MTP). The presence of joint cavity widening (JCW), due to joint effusion and/or synovial hypertrophy (according to OMERACT preliminary definitions) [28], in the grayscale US (GSUS) assessment was determine and graded on a semiquantitative scale from 0 to 3 (0, absence; 1, mild; 2, moderate; 3, marked). Synovial vascularization due to intraarticular abnormal blood flow was assessed using power Doppler US (PDUS). A proper amount of gel was placed on the skin in order to avoid compression on soft tissues under examination. PD variables were adjusted to the lowest permissible pulse repetition frequency (PRF) to maximize sensitivity (approximately between 500 and 1,000 Hz depending on the joint scanned). Low wall filters were used. The dynamic range was between 20 and 40 dB. Color gain was set just below the level at which color noise appeared underlying bone (no flow should be visualized at the bony surface). Flow was additionally demonstrated in two planes and confirmed by pulsed wave Doppler spectrum to exclude artifacts. PD signal was graded on a semiquantitative

scale from 0 to 3 (0=absence: no intraarticular flow; 1=mild: single vessel signal; 2=moderate: confluent vessels in less than half of the intraarticular area; 3=marked: vessel signals in more than half of the intraarticular area).

Tendons The following tendons were bilaterally assessed: second and third finger flexor tendons and fourth and sixth extensor carpal compartments. Finger flexor tendons were evaluated on the volar aspect of the hands at MCP head level. Both fourth and sixth extensor carpal compartments were examined on the dorsal and lateral aspects of the wrist, respectively. The presence or absence (dichotomist evaluation) of both tendon sheath distention (TSD) on GSUS assessment and abnormal vascularization due to abnormal blood flow into the TSD by PDUS were evaluated using the same PD setting that the joints.

Entheses The following entheseal areas were bilaterally assessed: proximal plantar fascia, distal Achilles tendon, both distal and proximal patellar tendon insertions, and distal quadriceps tendon. Examination of knee entheses was performed with the patient in the supine position and the knee flexed at 30° and in neutral position (for PDUS evaluation). Achilles tendon and the plantar aponeurosis were examined with the patient lying prone and the feet hanging over the edge of the examination table at 90° of flexion and in neutral position (for PDUS evaluation). The following elemental lesions of enthesis on GSUS assessment were recorded as dichotomous evaluation (presence/absence) at each entheseal area: thickening, structural changes (hypoanechogenicity), calcifications, bursitis, bone erosions, and enthesophytes. Entheseal vascularization due to abnormal blood flow was assessed using PDUS and was graded on a semiquantitative scale from 0 to 3 (0, absence; 1, mild; 2, moderate; 3, marked). For PDUS assessment of the entheses, we use the same settings that of the joints.

Global US assessment US abnormal findings in both GSUS and PDUS were summed to obtain an individual score for each of the assessed structures (joints, tendons, and entheses) and the sum of each one of these represented the total score. Table 1 shows a detailed description of the global US assessment score.

Intra-observer reliability In order to assess intra-observer agreement about US findings, baseline images of 20 SpA patients were stored and read (without knowledge of any information about the images) after 2 months by the same rheumatologist who previously obtained the images.

Statistical analysis

Descriptive statistics were used to describe independent variables. The comparison of findings at baseline and follow-up were evaluated using Wilcoxon matched-pairs signed-rank test. For the correlation between US and clinical variables, Spearman's rank test was used for nonparametric values and Pearson's correlation was used for normal distributed metric values. Agreement between parametric values was tested with intraclass correlation (ICC) analysis of variance.

Results

A total of 34 patients with SpA (19 psoriatic arthritis, 7 undifferentiated SpA, 6 ankylosing spondylitis, and 2 reactive arthritis) completed both basal and 3-month follow-up assessments.

Table 1 Detailed explanation of the global ultrasound assessment score

	Joints	Tendons	Entheses
Number	16 (wrist, second and third metacarpophalangeals, second and third proximal interphalangeals, knee and second and fifth metatarsophalangeals, bilaterally)	8 (second and third finger flexor tendons and fourth and sixth extensor carpal compartments, bilaterally)	10 (proximal plantar fascia, distal Achilles tendon, both distal and proximal patellar tendon insertions and distal quadriceps tendon, bilaterally)
Grayscale US abnormalities	Joint cavity widening: 0–3 semiquantitative scale	Tendon sheath distension; 0 (absence) or 1 (presence)	Thickening, structural changes (hypoanechogenicity), calcifications, bursitis*, bone erosions and enthesophytes; all of these: 0 (absence) or 1 (presence)
Abnormal vascularization by PDUS	0–3 semiquantitative scale	0 (absence) or 1 (presence)	0–3 semiquantitative scale
Range score	0–96	0–16	0–86
Range score for the "Global US assessment": 0–198			

*Bursitis was evaluated at 6 out of 10 possible sites of entheses due to anatomical reasons

Table 2 Clinical and laboratory dataobtained at baseline and after three months follow-up

	Basal assessment, mean (95 % CI)	3-month follow-up assessment, mean (95 % CI)	Mean difference, mean (95 % CI)	*p*
Tenderness joint count, 68	5.81 (3.88–7.75)	2.57 (1.59–3.55)	3.24 (1.55–4.92)	0.0002
Swollen joint count, 66	3.9 (2.47–5.34)	1.33 (0.41–2.25)	2.57 (1.69–3.45)	<0.0001
DAS28	4.15 (3.75–4.54)	3.13 (2.69–3.58)	1.01 (0.72–1.3)	<0.0001
BASDAI	5.31 (4.35–6.27)	3.06 (2.23–3.89)	2.25 (1.56–2.93)	<0.0001
HAQ	0.76 (0.51–1)	0.44 (0.24–0.64)	0.31 (0.19–0.43)	<0.0001
LEI	0.42 (0.1–0.74)	0.12 (0.003–0.23)	0.3 (−0.02–0.62)	0.0670
ESR	23.27 (16.34–30.2)	17.27 (12.84–21.70)	6 (2.82–9.17)	0.0005
CRP	8.408696 (3.19–13.62)	2.86 (1.49–4.22)	5.54 (0.52–10.57)	0.0320

Patient characteristics Twenty-four patients (71 %) were males, median age was 31 years (interquartile range, 25–75:38–62 years), and median disease duration was 1 year (interquartile range, 25–75:0.4–3.4 years).

Eighteen (53 %) patients had axial involvement according to clinical manifestations and imaging data.

At basal clinical examination, all patients had inflammatory articular involvement, 25 (73.5 %) patients had oligoarthritis (up to 4 involved joints) with a median swollen joint count of 2 (interquartile range, 25–75:1–4) and 9 (26.5 %) had polyarthritis with a median swollen joint count of 8 (interquartile range, 25–75:6–8.5). Fourteen (42.5 %) patients had dactylits and 26 (79 %) patients had enthesitis of at least one site according to LEI score.

Regarding therapeutic information, according to the decision of the treating rheumatologist and independently of this study protocol, 10 out of 34 patients initiated therapy with DMARDs, 9/34 changed DMARDs, 7/34 added a second DMARDs, and finally, 8/34 patients started biologic therapy with anti-tumor necrosis factor inhibitors.

Clinical and laboratory findings at baseline and three months follow-up Both ESR and CRP levels, tenderness joint count, 68; swollen joint count, 66; BASDAI, and HAQ decreased significantly ($p=0.0005$, $p=0.0320$, $p=0.0002$, $p<0.0001$, $p<0.0001$, and $p<0.0001$, respectively) during the follow-up period. Although there was a downward trend in the LEI, this difference was not statistically significant (Table 2).

Peripheral global US assessment at baseline and three months follow-up Total score for the global US assessment showed a significant decrease between basal and 3-month follow-up period ($p<0.0001$) (Table 3; Fig. 1). All the individual components of the total score, joint, tendon, and enthesis scores, also showed a significant decrease during

Table 3 Global ultrasound assessment data obtained at baseline and after 3 months of follow-up

			Basal assessment, mean (95 % CI)	Three months follow-up assessment, mean (95 % CI)	Mean difference, mean (95 % CI)	*p*
Joints score	GSUS		7.88 (5.56–10.19)	4.08 (2.2–5.97)	3.79 (2.39–5.19)	<0.0001
	PDUS		4.02 (2.28–5.77)	0.91 (0.32–1.5)	3.11 (1.55–4.68)	0.0003
	Total		11.91 (8–15.81)	5 (2.63–7.36)	6.91 (4.2–9.62)	<0.0001
Tendons score	GSUS		0.76 (0.32–1.2)	0.14 (−0.004–0.29)	0.61 (0.22–1.01)	0.0031
	PDUS		0.52 (0.09–0.96)	0	0.52 (0.09–0.96)	0.0177
	Total		1.29 (0.44–2.14)	0.14 (−0.004–0.29)	1.14 (0.35–1.93)	0.0059
Entheses score	GSUS	Soft tissues abnormalities[a]	3.88 (2.8–4.96)	1.14 (0.6–1.68)	2.73 (1.94–3.52)	<0.0001
		Cortical bone changes[b]	4.52 (3.33–5.72)	3.76 (2.73–4.79)	0.76 (−0.35–1.88)	0.1754
	PDUS		1.47 (0.84–2.09)	0.29 (−0.03–0.62)	1.17 (0.72–1.62)	<0.0001
	Total		9.88 (7.73–12.03)	5.2 (3.93–6.47)	4.67 (3.17–6.17)	<0.0001
Total score			23.51 (18.73–28.29)	11.18 (8.24–14.12)	12.33 (9.23–15.42)	<0.0001

GSUS grayscale ultrasound, *PDUS* power Doppler ultrasound

[a] Soft tissues abnormalities include: thickening, structural changes (hypoanechogenicity) and bursitis

[b] Cortical bone changes include: calcifications, bone erosions and enthesophytes

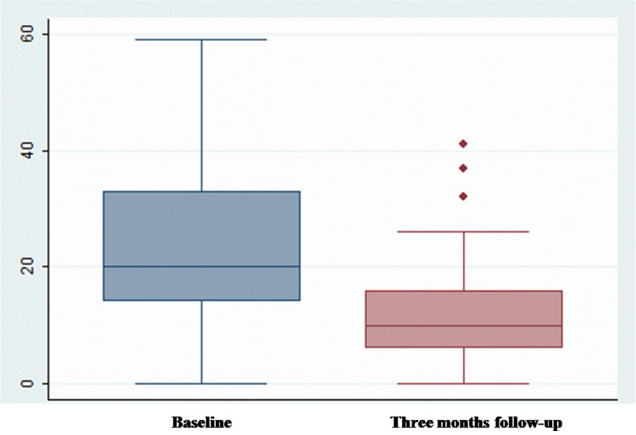

Fig. 1 Total score for the global US assessment at baseline and 3-month follow-up. The *box plots* provide information on the distribution symmetry, on the numerical measures of central tendency, and on the variability and spread of data in the distribution tails. The *box* contains the median values (represented by a *horizontal line* within the box), 25th and 75th percentiles, and whiskers representing the 10th and 90th percentiles

the follow-up period ($p<0.0001$, $p=0.0059$, and $p<0.0001$, respectively) (Table 3) (Fig. 2).There was no statistical difference in score change between different treatment groups. Fig. 3 shows some representative ultrasound images obtained during the study.

Intra-observer reliability for ultrasound findings A high degree of intra-observer reliability was found for the peripheral global US assessment (ICC [95 % confidence interval], 0.977 [0.961–0.993]). Each one of the components of the global US assessment, joint, tendon, and enthesis scores, also showed a high degree of intra-observer reliability (ICC [95 % confidence interval], 0.986 [0.976–0.996], 0.978 [0.948–1.009], and 0.980 [0.962–0.997], respectively).

Correlation between US findings with clinical and laboratory findings at baseline A moderate correlation was found between the global US assessment with DAS28 (Spearman's rho=0.4280). Correlation was fair with ESR and CRP (Spearman's rho=0.3126 and 0.3111, respectively) and was poor with HAQ, BASDAI, and LEI (Spearman's rho=0.1990, 0.0526, and 0.0413, respectively).

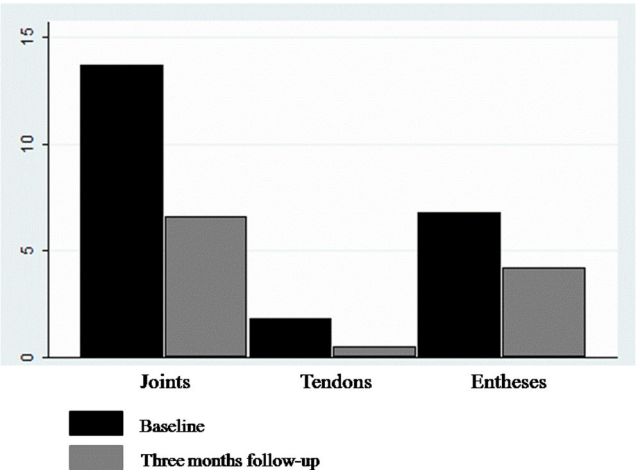

Fig. 2 Baseline and 3-month follow-up data for the different components of the global US assessment

Discussion

Enthesitis is one of the most important and distinctive features of SpA and has been widely investigated in recent years. US assessment has shown greater sensitivity compared with clinical examination for the detection of enthesitis [16, 29, 15, 13, 30] and good sensitivity to change during therapeutic monitoring [18, 17]. US scoring systems for entheses have been developed in patients with SpA [16, 13].

SpA represents a group of heterogeneous diseases which may also have inflammatory involvement of other anatomical structures such as joints and tendons. To date, a single study reported preliminary results of a PDUS composite score for monitoring therapeutic response in PsA [31] patients but not in all spectrum of SpA. So, to the best of our knowledge, this is the first study evaluating the value of a global US assessment including the evaluation of inflammatory changes at joint, tendon, and entheseal level in patients with SpA. This peripheral global US assessment showed a good sensitivity to change after 3 months of follow-up in accordance with the change in acute phase reactants and activity and functional clinical indices. US seems to be a valuable tool for the evaluation and monitoring of patients with SpA. The high level of intra-observer agreement minimizes the possibility that the variation of this peripheral global US assessment during the 3-month follow-up was due to the expected error for an operator-dependent imaging technique.

Although US findings at entheseal level showed a significant decrease after 3 months of follow-up, different elemental lesions showed dissimilar behaviors. Abnormal US findings at soft tissue level (thickening, structural changes, and bursitis) and PD signal were susceptible to change during the follow-up, while both abnormal US findings at cortical bone level and calcifications did not decrease significantly during follow-up. These results are in agreement with previous results reported by Naredo et al. [18].

There was no good correlation between global US assessment and activity and functional clinical indices and serum markers of inflammation at baseline. These results are consistent with previous studies that showed no correlation between US assessment of the entheses and clinical indices and laboratory findings [18, 31].This might reflect that both evaluations are

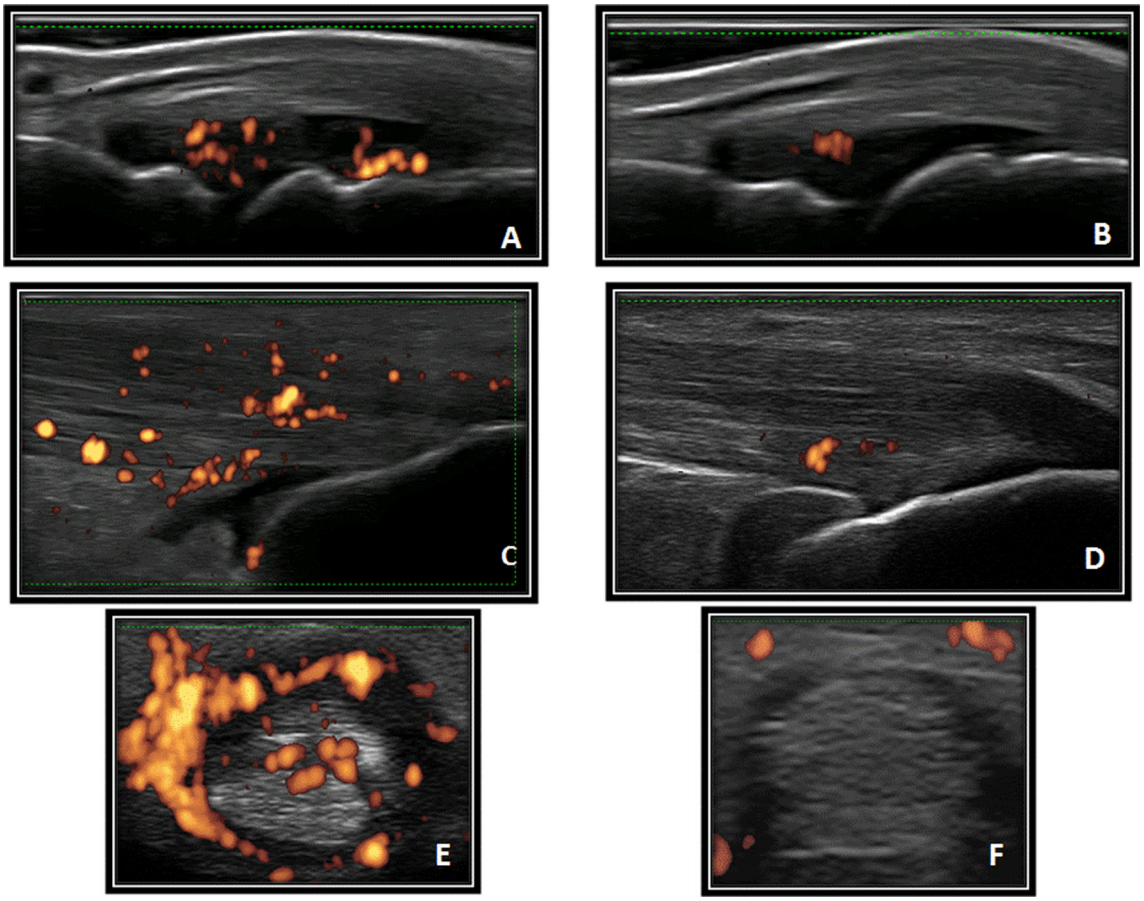

Fig. 3 Representative ultrasound images obtained during the study. **a**, **b** Basal and 3-month follow-up assessments, respectively, of a second metacarpophalangeal joint showing a reduction of the abnormal vascularization by power Doppler. **c**, **d.** Basal and 3-month follow-up assessments, respectively, of the Achiles tendon distal insertion at calcaneus bone demonstrating a reduction of the thickening, the size of the retrocalcaneal bursae and in the abnormal vascularization by power Doppler. **e**, **f** Basal and 3-month follow-up assessments, respectively, of the third finger flexor tendon with an important reduction of the abnormal vascularization by power Doppler

measuring different aspects of the disease and perhaps should be used jointly in the follow-up of these patients. As we describe above, both clinical indices, acute phase reactants and US abnormal findings, decreased significantly during the follow-up period.

A limitation of the present study was the fact that we only included joints and tendons usually assessed by US in patients with RA [9, 32, 8, 33, 7, 34–38] and PsA [39, 40]. This decision was mainly baseline of the limited number of previous reports on the use of US for evaluation of joints and tendons in SpA. It would be interesting, in future studies, to include the US assessment of the ankle joint and tendons, often involved in SpA. Nevertheless, both joint and tendon scores showed significant decrease during the 3 months follow-up. In a similar way, we only included lower limb entheses based on the fact that those are the entheses more often involved in SpA. Another limitation could be the fact that we only included patients with therapy changes (there was no control group), so we do not know the behavior of this score in patients with stable disease. Finally, another limitation was that we excluded obese patients that represent an important percentage of patients with PsA. It would be important to include this subgroup of patients in future studies.

One problem of this kind of US score is that it is time-consuming (each US assessment took around 25 min per patient) for use in clinical practice. However, knowing which components are responsive to therapy changes and the amount of responsiveness might help to build shorter scores useful on daily clinical practice.

In conclusion, this global US assessment, including joints, tendons, and entheses, showed a good responsiveness to clinical changes and might be useful for monitoring SpA patients with peripheral involvement after therapeutic changes in daily clinical practice. This results need to be confirmed in a large cohort of SpA patients.

Conflict of interest The authors declare that they have no any potential financial conflict of interest concerning this study.

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