Development of ultrasound enthesitis score to identify patients with enthesitis having spondyloarthritis: prospective, double-blinded, controlled study

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Abstract

Objective

To distinguish patients (pts) with enthesitis having spondyloarthritis (SpA) from pts with enthesitis without SpA by ultrasound (US) enthesitis score.

Methods

The study sample included 127 pts with enthesitis (76 pts with SpA, 26 pts with rheumatoid arthritis, 25 pts with mechanically-related enthesitis). The entheses of plantar fascia, Achilles, patellar, quadriceps and common extensor tendon on lateral epicondyle were examined by US. Two operators, blinded to clinical diagnosis and enthesitis symptoms, assessed enthesis thickness, echogenicity, enthesophytes, power Doppler signal and erosions. Logistic regression and receiver operating characteristic (ROC) curve analysis were used to determine the predictive value of each enthesitis lesion for diagnosis of SpA. The best predictive value for SpA was accomplished when absence and presence of increased thickness, hypoechogenicity and enthesophytes were scored as 0 and 1; absence and presence of PD and erosions were scored as 0 and 4. Belgrade Ultrasound Enthesitis Score (BUSES) represents a cumulative score of derived enthesitis lesion scores at examined entheses. Independent-samples t-test was used for BUSES comparison between pts with and without SpA. Validity of BUSES for SpA diagnosis was evaluated by sensitivity and specificity. Cut-off point was chosen as the smallest value with specificity of at least 90%. The reliability was analysed by intra-class-correlation coefficient (ICC).

Results

BUSES was 9.9±12.4 (mean±SD) in SpA pts and 3.1±4.2 in pts without SpA ($p<0.001$). BUSES cut-off point ≥7 achieved excellent specificity (90.2%) and fair sensitivity (47.4%). ICC was 0.99.

Conclusion

BUSES is highly specific, valid and reliable to identify patients with SpA.

Key words

ultrasound score, enthesitis, spondyloarthritis

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Received on December 17, 2014; accepted in revised form on May 26, 2015.

Competing interests: none declared.

Introduction

Inflammation of the enthesis, site of the tendon, ligament, fascia and capsular insertion to bone is called enthesitis. Peripheral enthesitis is one of the fundamental features in all subtypes of spondyloarthritis (SpA) (1-4), but it can be observed in endocrine, metabolic, traumatic and degenerative diseases (5). Clinical evidence of Achilles and plantar enthesitis are included in the European Spondyloarthritis Study Group (ESSG) (6), Amor (7) and Assessment of SpondyloArthritis International Society (ASAS) classification criteria for SpA (8, 9). However, clinical manifestations of the enthesitis shows low sensitivity and specificity (10-12), even though there are difficulties with true positive clinical assessment of enthesitis (13). Therefore it is very important that musculoskeletal ultrasound (US) is proved to be a valuable diagnostic tool to detect the enthesitis a long while ago (11, 12, 14-16). The importance of US lies in the ability to identify morphostructural and inflammatory changes (17). The Outcome Measures in Rheumatology (OMERACT) consensus was proposed definition for ultrasonographic enthesopathy as "abnormally hypoechoic (lack of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions or irregularity" (18). However, because of the lack of consensus about US definition of enthesitis and its elementary lesions OMERACT Task Force subgroup was formed (19). As a result of their work it was obtained first consensus based US definition of enthesitis and its elementary lesions (20). Despite the numerous papers in the field of ultrasonographic assessment of entheses in patients with SpA (21), some questions still remain open in this field, so it is necessary that the development work continue (19, 22, 23).

The aim of this study was to distinguish patients with symptoms of the enthesitis having SpA from patients with enthesitis symptoms without SpA by ultrasound enthesitis score.

Methods

Patients

We performed a prospective study on a sample of 127 consecutive patients (pts) with enthesitis symptoms. Enthesitis symptom was diagnosed if there was tenderness and/or pain and/or swelling at the time of the clinical examination. Among them there were 76 pts with SpA according to the criteria of ESSG (6) or ASAS (8, 9), 26 pts with rheumatoid arthritis (RA) fulfilling the American College of Rheumatology (ACR) 1988. criteria (24) or The American College of Rheumatology/The European League Against Rheumatism (ACR/EULAR) classification criteria for RA (25) and 25 pts with mechanically-related enthesitis (MRE). In group patients with SpA there were 39 pts with ankylosing spondylitis (AS) fulfilling the modified New York criteria (26), 27 pts with psoriatic arthritis fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR) (27), 6 pts with reactive arthritis fulfilling the criteria of Wilkens *et al*. (28) and 4 pts with undifferentiated SpA.

The study had the following inclusion criteria: (1) age >18 years, (2) established clinical diagnosis and (3) presence of enthesitis symptoms whether at the heels, knees or elbows. Exclusion criteria were age ≤18 years, visceral manifestations of the rheumatic inflammatory diseases only in the acute phase (we wanted to avoid any possible inconvenience that the patients with acute visceral manifestations might have during the US examinations), peripheral neuropathy, recent trauma or surgery of the heels, knees or elbows. All patients signed the informed consent to participate in the study. The study was approved by the Ethics Committee of the Institute of Rheumatology, Belgrade, Serbia.

Ultrasound examination

Two experienced US operators performed examination consecutively and blindly to identity of patients, clinical diagnosis and enthesitis symptoms. The operators used a Logiq9 (GE Medical Systems, Waukesha, WI, USA) with a M12L Matrix Array 5-13MHz linear probe. The Doppler settings were opti-

mised to low flow, with a low wall filter. The pulse repetition frequency (PRF) was adjusted to provide maximal sensitivity at the lowest possible value for each site, resulting in PRF of 500-750 Hz. The color gain was adjusted to the level just below the noise floor.

The entheses of the plantar fascia, Achilles tendon, patellar tendon distal and patellar tendon proximal insertion, quadriceps tendon and common extensor tendon on lateral epicondyle, were explored always bilaterally, in longitudinal and transversal plane. These chosen entheses were in accordance with the latest recommendations about the optimal choice of US examined entheses in SpA (19). The patient's position depended on the depicted area, recommended by EULAR consensual acquisition protocol (29).

The following elementary lesion of US detected enthesitis were assessed: (1) increased thickness (measured at the point of maximal thickness at the bony insertion with a difference compared to the body of the tendon); (2) hypoechogenicity was combined with lack of the normal homogeneous fibrillar pattern); (3) enthesophytes (step up of bony prominence at the end of the bone contour, with/without acoustic shadow, seen in both planes) with/without calcifications at the area of the insertion (hyperechoic foci consistent with calcific deposits, seen in both planes); (4) Doppler signal at the enthesis (up to 2mm near the bony cortex) and (5) erosions (cortical breakage with a step down contour defect, seen in both planes). US findings of the tendon body and corresponding bursa, as perientheseal features, were not examined. The agreement on US definitions of elementary enthesitis lesions was reached before interobserver assessment (Fig- 1).

The next step of the study required determining does the presence of each elementary lesion have the same predicting value for diagnosis of SpA. For this purpose logistic regression was used. The best discriminatory performance (*e.g.* the largest area under the ROC curve) was accomplished when absence and presence of the increased thickness, of the normal fibrillar echogenicity and enthesophytes with/without calcifications were scored as 0 and 1 points, and when absence and presence of power Doppler signal and erosions were scored as 0 and 4 points. Belgrade Ultrasound Enthesitis Score (BUSES) was created as a cumulative score of derived elementary lesion scores at all examined entheses.

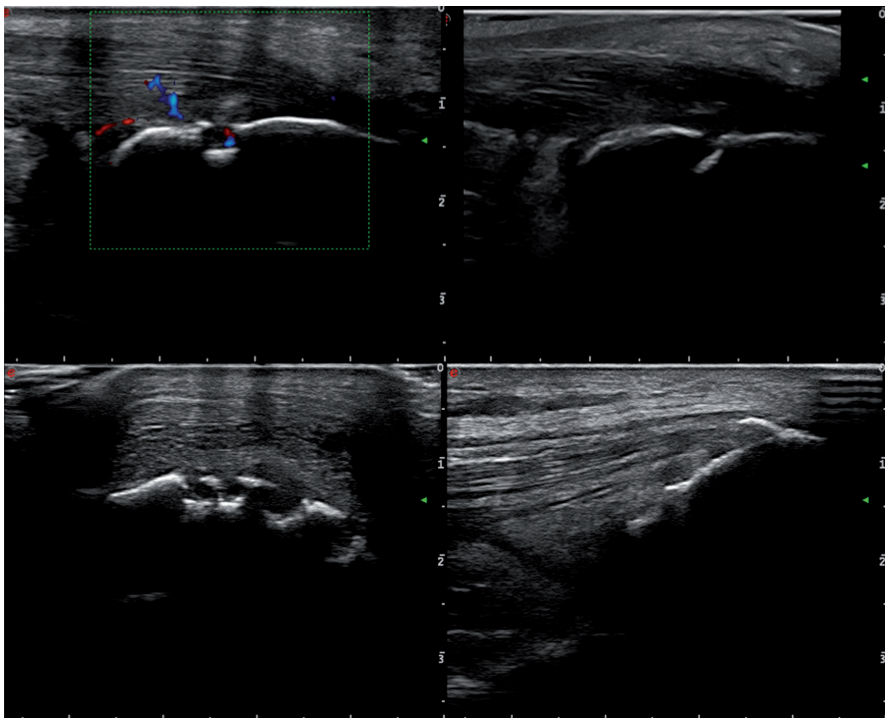

Fig. 1. US detected elementary enthesitis lesions. *Upper left*: Lack of the homogeneous fibrillar patern, positive power Doppler signals and erosion at the enthesis of the Achilles tendon (longitudinal view); *upper right*: Increased thickness, lack of the homogeneous fibrillar patern and erosion at the enthesis of the Achilles tendon (longitudinal view); *lower left*: Erosions at the enthesis of the Achilles tendon (transversal view); *lower right:* Lack of the homogeneous fibrillar patern and enthesophyte at the enthesis of the quadriceps tendon (longitudinal view).

Statistical analysis

Data were summarised by descriptive statistics (frequencies, mean and standard deviation). Logistic regression and receiver operating characteristic (ROC) curve analysis were used to determine predictive diagnostic value of each elementary lesion of US detected enthesitis. BUSES was created as a cumulative score of elementary lesion scores at examined entheses. Comparisons of BUSES total scores between groups of patients with SpA and without SpA (RA or MRE) were performed using independent-samples Welch *t*-test. Validity of BUSES for diagnosis of SpA was determined by its sensitivity and specificity. Cut-off point was chosen as the smallest value of BUSES with specificity of at least 90%. Cut-off value of BUSES was chosen to distinguish patients with SpA pts from patients without SpA. Reliability of BUSES was assessed by intra-class correlation coefficient (ICC) between two blinded operators. Feasibility was evaluated by recording the time spent by the operators. *P*-values <0.05 were considered statistically significant. Data analysis was performed in statistical software R, version 3.1.0 (using methods implemented in R packages *rms, pROC, ROCR, MKmisc, irr* (30-34).

Results

Demographic, clinical and laboratory characteristics in study population are summarised in Table I.

Value of the Belgrade Ultrasound Enthesitis Score (BUSES)

As mentioned above, BUSES represents the cumulative score of elementary lesion scores at all examined entheses. The appropriate value of each enthesitis lesion was determined fitting the logistic regression model and calcu-

Table I. Demographic, clinical and laboratory characteristics of all patients.

Data	SpA	AS	RA	MRE
Number of patients	76	39	26	25
(male/female)	(49/ 27)	(30/ 9)	(6/20)	(8/17)
Ages mean (SD) years	45.7 (11.9)	41.2 (10.2)	54.92 (10.12)	54.21 (9.94)
Disease duration mean (SD) years	10.0 (7.9)	12.0 (8.3)	9.77 (7.40)	3.36 (2.48)
ESR mean (SD) mm/Hg	25.01 (24.06)	23.87 (23.46)	42.19 (18.9)	11.82 (5.94)
CRP mean (SD) mg/L	7.36 (0.92)	7.46 (7.12)	10.72 (6.85)	1.06 (1.29)
HLAB27 (positive/negative)	58/18	36/3	26/0	25/0
RF (positive/negative)	0/76	0/39	24/2	0/25
BASDAI mean (SD)		3.97 (2.85)		
BASFI mean (SD)		3.76 (2.67)		
ASDAS-esr mean (SD)		2.48 (1.37)		

Table II. Belgrade Ultrasound Enthesitis Score (BUSES).

US data	PD assessment Score
Achilles tendon enthesis	
Increased thickeness of enthesis	0 or 1
Hipoechogenicity combined with lack of the normal fibrillar pattern	0 or 1
Enthesophyte with/without calcification at the area of the insertion	0 or 1
Doppler signal at the enthesis (up to 2 mm near the bony cortex)	0 or 4
Erosions	0 or 4
Plantar fascia enthesis	
Increased thickeness of enthesis	0 or 1
Hipoechogenicity combined with lack of the normal fibrillar pattern	0 or 1
Enthesophyte with/without calcification at the area of the insertion	0 or 1
Doppler signal at the enthesis (up to 2 mm near the bony cortex)	0 or 4
Erosions	0 or 4
Patellar tendon distal enthesis	
Increased thickeness of enthesis	0 or 1
Hipoechogenicity combined with lack of the normal fibrillar pattern	0 or 1
Enthesophyte with/without calcification at the area of the insertion	0 or 1
Doppler signal at the enthesis (up to 2 mm near the bony cortex)	0 or 4
Erosions	0 or 4
Patellar tendon proximal enthesis	
Increased thickeness of enthesis	0 or 1
Hipoechogenicity combined with lack of the normal fibrillar pattern	0 or 1
Enthesophyte with/without calcification	0 or 1
Doppler signal at the enthesis (up to 2 mm near the bony cortex)	0 or 4
Erosions	0 or 4
Quadriceps tendon enthesis	
Increased thickeness of enthesis	0 or 1
Hipoechogenicity combined with lack of the normal fibrillar pattern	0 or 1
Enthesophyte with/without calcification at the area of the insertion	0 or 1
Doppler signal at the enthesis (up to 2 mm near the bony cortex)	0 or 4
Erosions	0 or 4
Common extensor tendon enthesis on lateral epycondyle	
Increased thickeness of enthesis	0 or 1
Hipoechogenicity combined with lack of the normal fibrillar pattern	0 or 1
Enthesophyte with/without calcification at the area of the insertion	0 or 1
Doppler signal at the enthesis (up to 2 mm near the bony cortex)	0 or 4
Erosions	0 or 4

The total score of BUSES is 132.

lating area under the ROC curve. This was done in stepwise procedure, changing a value of one of the elementary lesions in every step, calculating the area under ROC curve and validating the model through bootstrap sampling. The BUSES range is 0–132. (Table II).

Considered logistic regression model fits well (le Cessie-van Houwelingen goodness of fit test, Z= -0.1511, p=0.8799).

BUSES total score was as follows (mean±SD): 9.9±12.4 in patients with SpA, 11.8±13.5 in patients with AS, 3.1±4.2 in a group of patients without SpA (RA and MRE). Statistically significant differences were found between means of BUSES in patients with SpA and patients without SpA (t=-4.418 with df=98.498, p<0.001), as well as in patients with AS and patients without SpA (t=-3.882 with df=43.597, p<0.001).

Determination of BUSES cut-off points in patients with SpA are illustrated in Table III. In Table IV. are presented sensitivity, specificity and percentage of correctly classified cases for chosen cut-off points of BUSES and area under ROC curve for SpA and AS.

Agreement between blinded US operators was excellent. Intra-class correlation coefficient (ICC) was 0.990 with 95% CI (0.985, 0.993). The BUSES requires up to 15 min to perform.

Discussion

Diagnosis of SpA is often delayed due to poor specificity of SpA symptoms. Enthesitis as a characteristic feature of SpA is commonly misdiagnosed or under-diagnosed by clinical assessment. Several US enthesitis scoring systems have been developed to improve accuracy of enthesitis examination (11, 12, 35, 36). However, neither of these scoring systems properly and sufficiently discriminated patients with inflammatory from patients with noninflammatory enthesitis. We have created a new US enthesitis score which combines grey-scale abnormalities and Doppler findings to better discriminate patients with SpA from patients without SpA. There are some important different characteristics of BUSES with respect to previous US enthesitis scores (1): BUSES use the definition of increased thickness of enthesis only when there was a difference between the thickness of enthesis and thickness of the tendon body and does not measure thickness in mm measurement. There has not been enough evidence to establish the normal diameter of the examined entheses in mm measurement in the healthy population (2). We considered hypoechogenicity of enthesis as US signs of enthesitis only when hypoechogenicity was combined with the lack of normal fibrillar pattern. The loss of the normal fibrillar

Table III. Determination of the cut-off points of BUSES for patients with SpA.

Cut-off point	Sensitivity (%)	Specificity (%)	Correctly classified (%)	LR+	LR-
≥0	100.0	0.0	59.8	1.00	
≥1	84.2	27.5	61.4	1.16	0.58
≥2	76.3	39.2	61.4	1.26	0.60
≥3	63.2	56.9	60.6	1.46	0.65
≥4	57.9	70.6	63.0	1.97	0.60
≥5	52.6	78.4	63.0	2.44	0.60
≥6	52.6	80.4	63.8	2.68	0.59
≥7	47.4	90.2	64.6	4.83	0.58
≥8	44.7	90.2	63.0	4.56	0.61
≥9	39.5	94.1	61.4	6.71	0.64
≥10	38.2	94.1	60.6	6.49	0.66
≥12	31.6	96.1	57.5	8.05	0.71
≥15	25.0	98.0	54.3	12.75	0.76
≥16	23.7	98.0	53.5	12.08	0.78
≥17	22.4	98.0	52.8	11.41	0.79
≥18	21.1	98.0	52.0	10.74	0.81
≥20	15.8	98.0	48.8	8.05	0.86
≥21	14.5	98.0	48.0	7.38	0.87
≥22	13.2	98.0	47.2	6.71	0.89
≥24	11.8	98.0	46.5	6.04	0.90
≥25	9.2	98.0	44.9	4.70	0.93
≥26	9.2	100.0	45.7		0.91
≥31	7.9	100.0	44.9		0.92
≥32	6.6	100.0	44.1		0.93
≥33	5.3	100.0	43.3		0.95
≥36	3.9	100.0	42.5		0.96
≥51	2.6	100.0	41.7		0.97
≥69	1.3	100.0	40.9		0.99
>69	0.0	100.0	40.2		1.00

Table IV. Sensitivity, specificity and accuracy at BUSES cut-off points and area under ROC curve for patients with SpA and patients with AS.

BUSES	Cut-off point	Sensitivity (%)	Specificity (%)	Correctly classified (%)	AUC (95% CI)
SpA	7	47.4	90.2	64.6	0.687 (0.596, 0.777)
AS	7	59.0	90.2	76.7	0.757 (0.653, 0.861)

AUC: area under curve.

pattern can be found in not hypoechoic insertion of the tendon and should be considered as the initial feature of the mucoid degeneration or focal tear (37, 38, 39). Due to the subjectivity of operators the presence of only hypoechogenicity of enthesis without presence of the lack of normal fibrillar pattern is not be accepted as US signs of enthesitis (11, 12, 20) (3). BUSES scored only the presence of the entesophytes, regardless of its size. We consider that it is difficult to precisely semi quantitatively determine size of the entesophytes as it was applied in MASEI (36). Those findings would be difficult to compare between different US operators (4). BUSES di not include corresponding bursitis as perientheseal features and (5). By our knowledge, for the first time definition of the US characteristics of enthesitis that was used in our study was practically in the line of the first consensus on US definition of enthesitis elementary lesions and for the first time chosen examined entheses were in accordance with the latest recommendations about the optimal choice of entheses in SpA (19, 20). BUSES has face and content validity because it measures what is theoretically supposed to measure and it covers different aspects of the enthesis such as thickness, echogenicity, calcifications, power Doppler signal and erosions. Another aspect of face validity is the determination of which entheses should be scanned. For this purpose, the most representative and most commonly affected entheses were chosen, following the last recommendations adopted by the consensus (19, 20). Discriminatory capacity of BUSES was determined by its sensitivity and specificity. Sensitivity is the proportion of true positives that are correctly identified by a test. Specificity is the proportion of true negatives that are correctly identified. For screening test is critical high sensitivity, while for confirmatory test is critical high specificity. Cut-off point of BUSES was chosen to our objective to identify patients with enthesitis having SpA with high specificity of at least 90%. The best cut-off point of BUSES for SpA with excellent specificity (90.2%) is 7. Explanation for fair sensitivity (47.4%) partly lies in the relatively moderate activity of the disease in our AS patients. Their Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (40) was 3.97 (2.85). The sensitivity of the score would probable increase with a higher activity of disease. The difference in sensitivity between BUSES and MASEI (83.3%) (36) could be explained with: (1) a significantly larger number of SpA patients and shorter duration of SpA in our study; (2) high discriminating value of MASEI (36) was found between group of patients and the control group consisted of healthy individuals, since our control group were only patients with enthesitis and RA or mechanically-related enthesitis.

High specificity of BUSES for diagnosis of SpA, as well as for AS, is very clinical significant. That allows clinicians to be almost certain that patients with enthesitis and suspected SpA, in whom the value of BUSES ≥7 was determined, actually have SpA, particularly AS. Accordingly, because of the high specificity, BUSES could be used to reduce the time between the onset of SpA and its diagnosis. Reliability of BUSES was confirmed by the excellence of interobserver agreement which was close to 1. BUSES has good feasibility as well.

Key message

- BUSES could be used to distinguish patients with enthesitis having SpA from patients with enthesitis without SpA.
- BUSES is a valid, reliable and feasible test whose value ≥7 is highly specific for diagnosis of SpA.

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