

Musculoskeletal ultrasonographic evaluation of lower limb enthesopathy in ankylosing spondylitis and Behçet's disease: Relation to clinical status and disease activity

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Received 26 October 2015

Accepted 12 November 2015

Egyptian Rheumatology & Rehabilitation
2016, 43:108–116

Aim of the work

Using clinical and musculoskeletal ultrasonographic (MSUS) examination, we aimed to compare the frequency, pattern, and main sites of peripheral enthesopathies in the lower limbs of ankylosing spondylitis (AS) and Behçet's disease (BD) patients, and to evaluate their relation with different clinical, laboratory, and functional parameters of both diseases.

Patients and methods

Fifteen AS patients (group I) and 22 BD patients (group II) were examined clinically and by carrying out MSUS for enthesopathy at five enthesal sites of the lower limbs. A control group of 20 apparently healthy male volunteers was also included. An enthesopathy score was calculated for each patient according to the Glasgow ultrasound enthesitis scoring system (GUESS). Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index and the Behçet's disease current activity form in both groups, respectively.

Results

The GUESS score was significantly higher ($P < 0.05$) in group I than in group II (7.27 ± 3.88 vs. 4.68 ± 3.67). In the two patients' groups, tendon thickening was the most frequent finding detected. Bone erosions and enthesophytes were significantly ($P < 0.05$) more frequent in group I than in group II. The most commonly affected enthesal sites were the distal Achilles tendon, followed by the proximal plantar fascia. In group I, the GUESS scores significantly correlated with the fatigue scores ($P < 0.05$), peripheral joint pain scores ($P < 0.05$), and Bath Ankylosing Spondylitis Functional Index scores ($P < 0.05$), whereas it showed insignificant correlations with patients' ages ($P > 0.05$), disease duration ($P > 0.05$), spinal pain scores ($P > 0.05$), local tenderness scores ($P > 0.05$), morning stiffness score ($P > 0.05$), total Bath Ankylosing Spondylitis Disease Activity Index ($P > 0.05$), Bath AS metrology indices ($P > 0.05$), AS quality of life scores ($P > 0.05$), radiographic scores ($P > 0.05$), erythrocyte sedimentation rate ($P > 0.05$), and C-reactive protein levels ($P > 0.05$). In group II, the mean GUESS score was significantly higher ($P < 0.05$) for BD patients with arthritis than for BD patients without arthritis, but it showed insignificant correlation ($P > 0.05$) with disease activity.

Conclusion

Ultrasonographic changes at the enthesal sites of the lower limbs are prevalent in both AS and BD. These changes are more frequently related to functional and articular involvement. MSUS is more sensitive than clinical examination in detecting enthesopathies of the lower limbs in both AS and BD patients.

Keywords:

ankylosing spondylitis, Behçet's disease, enthesopathy, Glasgow ultrasound enthesitis scoring system

Egypt Rheumatol Rehabil 43:108–116

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1110-161X

Introduction

Spondyloarthropathies (SpA) are a family of related disorders characterized by an increased frequency of the HLA-B27 marker, familial aggregation, axial skeleton involvement, and enthesal involvement. They mainly include ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated SpA [1,2].

Behçet's disease (BD) is described as a systemic, vasculitic disorder with protean manifestations.

Its clinical picture is not homogeneous, and there are various clusters of disease expression [3]. Musculoskeletal involvement in BD is one of the most frequent finding; particularly arthritis and arthralgia are most common, followed by enthesopathy, avascular necrosis, myalgia, and myositis [4].

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The inflammation, which may occur at any peripheral enthesal site, is considered as a primary lesion that may underlie all skeletal manifestations of SpA [5,6] and it sometimes manifests for a long period as an isolated clinical manifestation of an HLA-B27-associated disease [7]. Mechanical factors, physiological and anatomical characteristics of the enthesis, have been proposed as contributing factors that may influence the localization of enthesitis. This might explain the finding that most of the clinically relevant enthesitis sites are present in the lower limbs, particularly at the heel (Achilles enthesitis and Planter fasciitis) [8,9].

Musculoskeletal ultrasonography (MSUS) has an increasingly important role in the diagnosis, assessment, and follow-up of AS as it can detect synovial and tendon involvement as well as accurate imaging of enthesitis, the clinical hallmark feature of SpA [10,11].

The Outcome Measures in Rheumatology (OMERACT) ultrasound group suggested a definition of enthesopathy as 'An abnormal hypoechoic region with loss of normal fibrillar architecture and/or thickened tendon or ligament in its bony attachment, seen in 2 perpendicular planes that may exhibit a Doppler signal and/or bony changes including enthesophytes, erosions or irregularity.' [12]. This study aimed to compare the frequency, pattern, and main sites of peripheral enthesopathies in the lower limb by carrying out clinical and MSUS examinations in both AS and BD patients, and to evaluate their relation with different clinical, laboratory, and functional parameters of both diseases.

Patients and methods

This study included 15 male patients with AS who fulfilled the modified New York criteria for the diagnosis of AS (group I) [13], 22 male patients with BD who met the criteria of the International Study Group for Behçet's Disease (group II) [14], and 20 apparently healthy male volunteers as a control group. Patients were recruited from the outpatient clinic and inpatients' department of Rheumatology, Rehabilitation and Physical Medicine, Benha University Hospitals. Patients less than 18 years of age, those with other inflammatory rheumatic diseases, musculoskeletal problems in the spine or thoracic cage, cardiopulmonary disease or a concurrent severe medical condition that could be reasonably expected to affect the patient's functional level or quality of life were excluded from the study.

Clinical examination

After approval of the study scheme by the ethical committee of Benha Faculty of Medicine and obtaining an informed consent from all participants, they were subjected to a full history-taking (age, disease duration, and family history) and a thorough clinical examination. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [15] and the Bath Ankylosing Spondylitis Functional Index (BASFAI) [16] were used to assess the AS patients' disease activity and functional impairment, respectively. The BASDAI consists of six questions on fatigue, pain of the spine and hips, pain or swelling of peripheral joints, localized tenderness as a proxy for enthesitis, and severity and duration of morning stiffness. The questions were answered on a 10 cm visual analogue scale, anchored with the labels 'none' and 'very severe' at the either end of the first five questions, and with '0 h' and '2 h' at the either end of the question on duration of morning stiffness. The mean of the two scores for morning stiffness count was taken as one variable. The final score was defined by calculating the mean of the five items. Scores ranged from 0 (best) to 10 cm (worst). The BASFAI comprised 10 questions assessing functional limitations and the level of physical activity at home and work. Visual analogue scale was used to score each question from 0 (easy) to 10 (impossible), and the average value over the 10 questions was the BASFAI score. Fatigue was assessed by the first question in BASDAI. A disease-specific measure entitled AS quality of life (ASQoL) was carried out [17]. ASQoL comprised 18 items and each item was scored as '1' or '0'. Total scores ranged from 0 to 18, with a higher score indicating poor quality of life. AS patients' spinal mobility was assessed by measuring chest expansion and Bath Ankylosing Spondylitis Metrology Index [18] through five physical tests: (a) lateral lumbar flexion, (b) tragus to wall, (c) modified Schober's test, (d) maximum bimalleolar distance, and (e) cervical rotation. Disease activity was assessed in BD patients' group by using the Behçet's disease current activity form [19].

Clinical assessment of enthesopathies

Five sites for enthesopathy were clinically examined in both lower limbs of each participant. They were the quadriceps tendon insertion at the superior pole of the patella (SP), the patellar ligament origin at the inferior pole of the patella (IP), the patellar ligament insertion at the tibial tuberosity (TT), the Achilles tendon insertion in the superior calcaneus (SC), and the plantar aponeurosis attachment at the inferior calcaneus (IP). Clinical enthesopathy was considered by the presence of at least one of the following findings: (a) spontaneous pain, (b) tenderness elicited by pressure, mobilization, or contraction against resistance of the

corresponding tendons, and (c) local swelling of the enthesis by palpation [20].

Radiographic examination

Plain radiographs of the sacroiliac joints (anteroposterior view), cervical, and lumbar spine (lateral views) were obtained for the evaluation of radiological damage in the AS patients' group. The anterior angles of the cervical vertebra (lower C2 to upper T1) and lumbar vertebra (lower T12 to upper S1) were scored according to the Modified Stoke Ankylosing Spondylitis Spinal Score [21]. Each anterior vertebral angle was scored at 0 (normal), 1 (erosion, squaring, or sclerosis), 2 (syndesmophyte), or 3 (bridging), with total scores ranging from 0 to 72.

B-mode and power Doppler musculoskeletal ultrasonographic examination of enthesopathies

A commercially available real-time scanner (LOGIQUE e, GE Healthcare, Wauwatosa, USA) was used for the ultrasound (US) examination using with a multilinear high-frequency (8–13 MHz) transducer. Examination of the quadriceps tendon insertion at the SP of the patella, patellar ligament origin at the IP of the patella, and the patellar ligament insertion at the TT was carried out with the participant in the supine position with the knee flexed at 30°. The Achilles tendon insertion in the SC and the plantar aponeurosis attachment at the IC were examined with the patient lying prone with the feet hanging over the edge of the examination table at 90° of flexion. Each enthesis was scanned in both the longitudinal and transverse planes. Each site was carefully examined and the presence of structure thickness, bony erosions, enthesophytes, or bursitis was recorded. Bursitis was defined as a well circumscribed, localized anechoic or hypoechoic area at the site of an anatomical bursa, which was compressible by the transducer, with a normal bursa being less than 2 mm in the short axis [22]. Bony erosions were defined as a cortical breakage with a step-down contour defect, and an enthesophyte was defined as a step-up bony prominence at the end of the normal bone contour according to the OMERACT ultrasound group-suggested definition of enthesopathy [12].

Ligament, aponeurosis, and tendon thickness were measured at the point of maximal thickness proximal to the bony insertion. In this study, only thickened enthesis, fluid collection, erosions, and bony spurs were accepted as US signs of enthesitis. Abnormalities were quantified using the Glasgow ultrasound enthesitis scoring system (GUESS) and an enthesopathy score was calculated for each patient [10], giving a possible maximum total score of 36. Points were assigned for each enthesal abnormality (thickened tendon,

bursitis, erosions, and enthesophyte). Power Doppler musculoskeletal ultrasonographic (PDUS) examination was carried out after the B-mode ultrasonography at each enthesal site. The settings were standardized with a pulse repetition frequency of 750 MHz, and the gain was set to a point at which no signal was detected under the bone. One point was given for each enthesal site with a signal, and a cumulative score (maximum possible 10) was obtained.

Laboratory investigations

Routine laboratory investigations were carried out for all patients. The erythrocyte sedimentation rate (ESR) first hour was measured by using the Westergren method and C-reactive protein (CRP) by using the latex agglutination slide test.

Statistical analysis

Analysis of data was performed by using a personal computer using SPSS (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Quantitative variables were expressed as mean, SD, and range. Qualitative variables were expressed as number (*n*) and percentage (%). Comparisons were performed by the *t* test for qualitative variable. Student's *t*-test was used to compare two independent groups with respect to a quantitative variable. Spearman's correlations coefficient (*r*) was calculated for the detection of nonparametric correlations between variables in one group.

Results

This study included 15 AS patients (group I); all of them were men with ages ranging between 19 and 45 years (mean \pm SD = 30.67 \pm 8.26 years). The demographic, clinical, laboratory, and radiological characteristics of group I (AS) patients are shown in Table 1.

In addition, 22 men patients with BD (group II), with ages ranging between 18 and 50 years (mean \pm SD = 30.27 \pm 7.48 years), were also included in the study. The demographic and clinical features of group II (BD) patients are shown in Table 2.

Twenty apparently healthy male volunteers, with ages ranging between 20 and 47 years (mean \pm SD = 33.8 \pm 7.45 years), served as the control group. The studied groups were matched for age and sex (*P* > 0.05).

A total of 570 enthesal sites (10 sites \times 57 subjects) were examined clinically by palpation for tenderness and swelling and by using MSUS. In group I, enthesopathy was determined clinically at 42/150 (28%) enthesal

Table 1 Demographic, clinical, laboratory, and functional characteristics of group I (ankylosing spondylitis patients)

Characteristics	Range	Mean±SD
Age (years)	19-45	30.67±8.26
Disease duration (years)	1-17	6±4.52
Fatigue (BASDAI I)	1-9	5.13±2.5
Spinal pain (BASDAI II)	1-9	5.4±1.99
Peripheral joint pain (BASDAI III)	0-8	3.6±2.59
Local tenderness (BASDAI IV)	1-8	3.67±2.47
Severity and duration of morning stiffness	1-7	4.2±1.9
BASDAI total	1.4-7	4.5±1.74
BASFAI	0.6-7.2	3.62±1.85
BASMI	0-8	3.93±1.94
ASQoL	2-12	6.8±3.12
mSASS	1-60	24.6±22.26
ESR (mm/first hour)	12-35	21.8±7.24
CRP (mg/l)	6-48	12.88±10.84

AS, ankylosing spondylitis; ASQoL, AS quality of life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFAI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; mSASS, Modified Stoke Ankylosing Spondylitis Spinal Score.

Table 2 Demographic, clinical, and laboratory characteristics group II (Behçet's disease patients)

Characteristics	Range	Mean±SD
Age (years)	18-50	30.27±7.48
Disease duration (years)	1-12	4.45±3.17
Oral ulcers (n (%))	22 (100)	
Genital ulcers (n (%))	13 (59.1)	
Papulopustular lesions (n (%))	6 (27)	
Erythema nodosum (n (%))	5 (22.7)	
Arthritis (n (%))	9 (40.9)	
Deep vein thrombosis (n (%))	6 (27.3)	
Eye involvement (n (%))	8 (36.4)	
Neurologic involvement (n (%))	3 (13.6)	
ESR (mm/first hour)	13-76	39.14±18.95
CRP (mg/l)	6-48	14.73±12.24
BD-CAF	1-11	4.45±3.67

BDCAF, Behçet's disease current activity form; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

sites, 41/150 (27.33%) were tender on palpation, whereas 12/150 (8%) examined enthesal sites were swollen. In group II, enthesopathy was determined clinically in 36/220 (16.36%) enthesal sites, 36/220 (16.36%) were tender on palpation, and 10/220 (4.5%) of the examined enthesal sites were swollen. Clinically detected enthesitis were significantly ($P < 0.05$) more frequent in group I than in group II (Table 3).

In the control group, enthesopathies were determined clinically in 4/200 (2%) enthesal sites; all of them were tender on palpation. Clinically detected enthesitis were significantly ($P < 0.05$) more frequent in group I than in group II and highly significantly ($P < 0.001$) more frequent in both groups than in the control group (Table 3).

By using MSUS, in group I, enthesopathy was detected in 72/150 (48%) sites. The highest number of elemental lesions seen at the enthesal sites was tendon thickening (42/150, 28%), followed by enthesophytes (37/150, 24.6%), erosions (16/150, 10.6%), bursitis (11/150, 7.3%), whereas power Doppler (PD) signals were detected in 7/150 (4.6%) sites. In group II, the highest number of elemental lesions seen at the enthesal sites was also tendon thickening (50/220, 22.7%), followed by bursitis (26/220, 11.8%), enthesophytes (21/220, 9.54%), erosions (5/220, 2.27%), and PD signals were detected in 14/220, (6.3%) sites (Fig. 1). In the control group, enthesopathies were detected in 6/200 (3%) sites. The highest number of elemental lesions seen at the enthesal sites was tendon thickening (5/200, 2.5%), followed by enthesophytes (2/200, 1%) and bursitis seen at one enthesal site (1/200, 0.5%) (Table 3).

Bone erosions and enthesophytes were significantly more frequent in AS patients compared with BD patients ($P < 0.05$ each) (Table 3). In addition, group I patients showed statistically significantly higher GUESS score ($P < 0.05$) than did patients of group II (7.27 ± 3.88 and 4.68 ± 3.67 , respectively).

There was no statistically significant difference between group I and group II regarding the frequency of the affected enthesal sites except for the patellar ligament insertion at TT, which was significantly more affected in group I than in group II (Table 3).

In both studied groups, the most commonly affected enthesal site was the Achilles tendon insertion in the SC, which was found to be affected in 22/72 (30.5%) sites in group I and 27/65 (41.5%) in group II, followed by the plantar aponeurosis attachment at the IC, which was found to be affected in 20/72 (27.78%) sites of group I and 23/65 (35.38%) in group II (Table 3).

MSUS diagnosis of pathology at the examined enthesal sites was significantly more accurate ($P < 0.05$) than was the clinical diagnosis of enthesopathy in both group I and group II [(48 vs. 28%) and (29.55 vs. 16.3%), respectively] (Table 3).

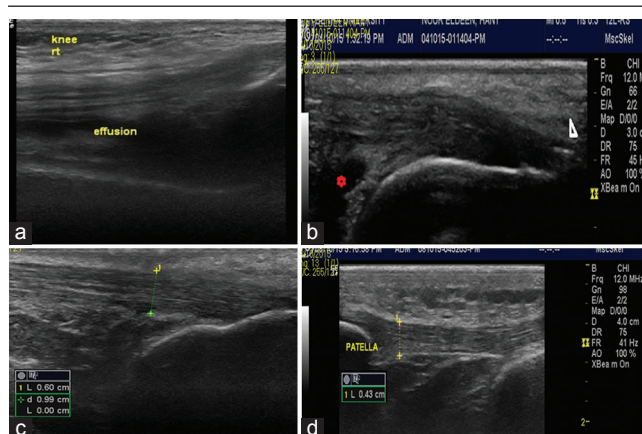
In group I and II, 5/42 (11.9%) and 6/36 (16.67%) of the clinically detected enthesopathies were normal on MSUS (both grey scale and PDUS) examination, whereas 35/72 (48.6%) and 35/65 (53.8%) of the MSUS detected enthesopathies in group I and II, respectively, were clinically silent.

In group I, there were statistically significant positive correlations between the GUESS scores and fatigue

scores (BASDAI) ($r = 0.41, P \leq 0.05$), peripheral joint pain scores (BASDAI III) ($r = 0.51, P \leq 0.05$), BASFAI scores ($r = 0.48, P \leq 0.05$), whereas there were statistically insignificant correlations between the GUESS scores

and patients' ages ($r = 0.18, P > 0.05$), disease durations ($r = 0.12, P > 0.05$), BASDAI II ($r = 0.14, P \geq 0.05$), BASDAI IV ($r = 0.21, P \geq 0.05$), morning stiffness score ($r = 0.16, P \geq 0.05$), total BASDAI ($r = 0.28, P \geq 0.05$), BASMAI ($r = 0.21, P \geq 0.05$), ASQoL ($r = 0.18, P \geq 0.05$), Modified Stoke Ankylosing Spondylitis Spinal Score ($r = 0.24, P \geq 0.05$), ESR values ($r = 0.16, P \geq 0.05$), and CRP levels ($r = 0.22, P \geq 0.05$) (Table 4).

Figure 1



Ultrasonographic appearance of lower limb enthesopathies. (a) Longitudinal sonogram of the suprapatellar recess in a 20-year-old male with Behçet's disease (BD) showing suprapatellar bursitis with effusion, (b) longitudinal sonogram of Achilles tendon insertion in a 35-year-old male ankylosing spondylitis (AS) patient showing Achilles tendonopathy (arrow head=enthesophyte star=bursa), (c) longitudinal sonogram of Achilles tendon insertion in a 43-year-old male patient with BD showing thickened Achilles tendon, (d) longitudinal sonogram in a 35-year-old patient with AS showing thickened proximal patellar tendon.

In group II, there were statistically insignificant differences in the mean GUESS scores between the subgroups of BD patients except being significantly higher ($P < 0.05$) for BD patients with arthritis than for BD patients without arthritis (7 ± 3.61 and 3.07 ± 2.84 , respectively) (Fig. 2). There was an insignificant correlation between the GUESS scores and the BD current activity form scores in BD patients (group II) ($r = 0.09, P > 0.05$) (Fig. 3 and Table 5).

Discussion

It is well known that enthesitis is considered to be the initial site of inflammation in SpA group of diseases, which later extends to the adjacent synovial tissues [6].

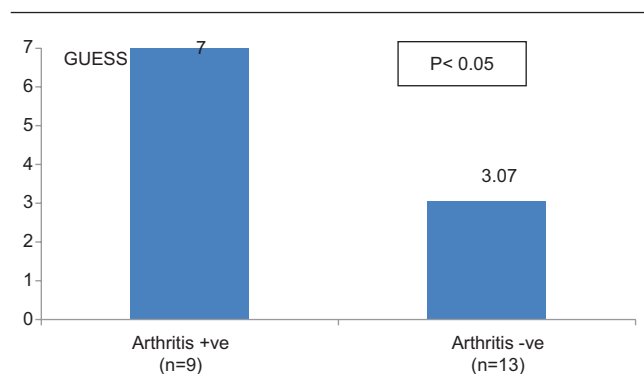
In our study, we aimed to compare the frequency, pattern, and main sites of peripheral enthesopathies

Table 3 Clinical and ultrasonographic enthesal findings in group I, group II, and controls

Clinical examination (n (%))	Group I (150 (100%))	Group II (220 (100%))	Control group (200 (100%))	P^a	P^b	P^c
Tender/painful entheses (n (%))	41 (27.33)	36 (16.36)	4 (2)	<0.05*	<0.001**	<0.001**
Swollen entheses (n (%))	12 (8)	10 (4.55)	0	>0.05	-	-
Total (n (%))	42 (28)	36 (16.36)	4 (2)	<0.05*	<0.001**	<0.001**
Components of GUESS enthesopathy score (n (%))						
Tendon thickening	42 (28)	50 (22.7)	5 (2.5)	>0.05	0.001**	0.001**
Bursitis	11 (7.3)	26 (11.81)	1 (0.5)	>0.05	0.001**	0.001**
Bone erosion	16 (10.67)	5 (2.27)	0	<0.05*	-	-
Enthesophyte	37 (24.67)	21 (9.54)	2 (1)	<0.05*	0.001**	0.001**
Total GUESS score (range, mean±SD)	0-13 (7.27±3.88)	0-12 (4.68±3.67)	0-2 (0.4±0.68)	<0.05*	0.001**	0.001**
Doppler positive (n (%))	7 (4.6)	14 (6.3)	0	>0.05	-	-
Total number of MSUS diagnosed enthesopathy (n (%))	72 (48)	65 (29.55)	6 (3.33)	<0.001**	<0.001**	<0.001**
Superior pole of the patella (quadriceps tendon) (n (%))	10 (13.89)	6 (9.23)	0	>0.05	-	-
Inferior pole of the patella (proximal patellar ligament) (n (%))	9 (12.5)	6 (9.23)	0	>0.05	-	-
Tibial tuberosity (distal patellar ligament) (n (%))	11 (15.28)	3 (4.62)	0	<0.05*	-	-
Superior pole of the calcaneus (Achilles tendon) (n (%))	22 (30.56)	27 (41.54)	2 (33.33)	>0.05	>0.05	>0.05
Inferior pole of the calcaneus (plantar aponeuroses) (n (%))	20 (27.78)	23 (35.38)	4 (66.67)	>0.05	>0.05	>0.05

Suprapatellar (quadriceps tendon) >6.1 mm, infrapatellar (proximal patellar ligament) >4 mm, tibial tuberosity (distal patellar ligament) >4 mm, Achilles tendon >5.29 mm, plantar aponeurosis >4.4 mm. GUESS, Glasgow ultrasound enthesitis scoring system; MSUS, musculoskeletal ultrasonography. P^a =comparison between group I and II. P^b =comparison between group II and controls. P^c =comparison between group II and control. * $P < 0.05$ =significant. ** $P < 0.001$ =highly significant.

Figure 2



Comparison between the mean Glasgow ultrasound enthesitis scoring system (GUESS) score for patients with Behcet's disease (BD) with and without arthritis.

Table 4 Number and frequency of clinical and musculoskeletal ultrasonography diagnosed enthesopathies

	Group I (150 (100%))	Group II (220 (100%))	Control group (200 (100%))
Clinically positive enthesopathy (n (%))	42 (28)	36 (16.36)	4 (2)
Normal by MSUS (n (%))	5 (11.9)	6 (16.67)	0 (0)
Abnormal by MSUS (n (%))	37 (88.1)	30 (83.33)	4 (100)
MSUS positive enthesopathy (n (%))	72 (100)	65 (100)	6 (100)
Clinically normal (silent) (n (%))	35 (48.6)	35 (53.8)	2 (33.33)

MSUS, musculoskeletal ultrasonography.

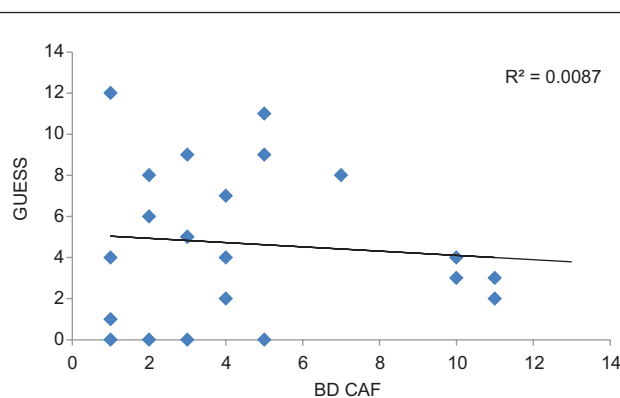
Table 5 Correlations between the Glasgow ultrasound enthesitis scoring system score and the clinical, laboratory, and functional characteristics of group I (ankylosing spondylitis patients)

GUESS scores	r	P
Age (years)	0.18	>0.05
Disease duration (years)	0.12	>0.05
Fatigue (BASDAI I)	0.41	<0.05*
Spinal pain (BASDAI II)	0.14	>0.05
Peripheral joint pain (BASDAI III)	0.51	<0.05*
Local tenderness (BASDAI IV)	0.21	<0.05
Morning stiffness score	0.16	>0.05
BASDAI total	0.28	>0.05
BASFAI	0.48	<0.05*
BASMI	0.21	>0.05
ASQoL	0.18	>0.05
mSASS radiograph	0.24	>0.05
ESR (mm/first hour)	0.16	>0.05
CRP (mg/l)	0.22	>0.05

AS, ankylosing spondylitis; ASQoL, AS quality of life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFAI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GUESS, Glasgow ultrasound enthesitis scoring system; mSASS, Modified Stoke Ankylosing Spondylitis Spinal Score. *Significant at $P < 0.05$.

in the lower limb through clinical and MSUS examinations of both AS and BD patients, and to

Figure 3



Correlation between Behcet's disease current activity form (BDCAF) values and Glasgow ultrasound enthesitis scoring system (GUESS) scores for patients with Behcet's disease.

evaluate their relation with different clinical laboratory and functional parameters in both diseases.

Enthesitis may occur at any entheses in the axial and peripheral sites of the skeleton in AS but the most prominent and common enthesitis mostly occur in the lower limbs [23]. It is thought that microtrauma of fibrocartilage structure is the principle of enthesitis development SpA [24]. In this regard the evaluation of target areas at anatomical locations prone to trauma injuries such as the foot and the knee could be enough to reflect total enthesitis [25].

We demonstrated that clinically detected enthesitis, especially being tender on palpation, were significantly more frequent in AS patients (28%) than in BD patients (36%). In their study, Francois *et al.* [26] stated that inflammatory enthesitis was clinically detectable only in 10% of the patients with early-stage AS and 50% of those with established AS. Our results confirm the high prevalence of enthesal alteration found in AS in the literature [10,27,28] and are in agreement with that found in a study by Alcalde *et al.* [25], who reported that up to 25% of the total entheses examined in AS cohort showed abnormalities.

Great variations in the prevalence of enthesal involvement in patients with BD, ranging between 3.4 and 38%, have been reported in the literature, but the exact percentage is unclear [29,30].

Imaging techniques such as radiography and computed tomography only detect and evaluate structural bone changes and do not inform about the presence of inflammatory activity in the enthesis at the time of examination. MRI only detects subcutaneous tissue or soft tissue edema (perienthesitic edema) and bone edema; less frequently it detects entheses edema

through their connection between fibroblasts and collagen fibers in the fibrous part of the enthesis, and thus MRI is insensitive and nonspecific for assessing enthesitis; histological examination of the enthesis is the potential gold standard for evaluating enthesitis, but is rarely obtained because of ethical and practical constraints [31].

MSUS is a noninvasive tool to assess the presence of enthesopathy; moreover, the use of PDUS allows the detection of abnormal vascularization of soft tissues in inflammatory articular diseases [5].

Our study revealed that MSUS examination was significantly more sensitive than was the clinical diagnosis of enthesopathy in both AS and BD patients, being 48 vs. 28% and (29.6 vs. 16.3%), respectively. In fact, this is not surprising, because enthesopathies could be asymptomatic, as demonstrated in the studies by Lehtinen *et al.* [28] and Alcalde *et al.* [25], and it has been documented that US detects more enthesal abnormalities than does clinical examination [10,27]. Although MSUS can be considered subjective in performance and in evaluation, it certainly eliminates the bias from manual pain-triggering methods; there is an increasing interest in its use for the assessment of enthesal pathology [32].

This low sensitivity of the clinical examination in detecting enthesopathies is in agreement with the results of a study by Balint *et al.* [10] despite the fact that they used grey B-mode only.

In our study, although it did not yield statistical significance, higher number of patients with BD (6.3%) had at least one abnormality by PDUS than in the AS patients (4.6%). This may be attributed to the possibility that BD patients may have an active disease compared with AS patients.

In our study, the prevalence of PD signals in AS patients' group was lower than that reported in previous studies [10,22,25,27]. In their study, Spadaro *et al.* [33] reported a prevalence of 6% in the examined enthesal sites, attributing this lower prevalence of PD signals to the high percentage of patients treated with antitumor necrosis factor- α drugs. This discrepancy in the prevalence of PD signals reported in our results and the literature can be explained by the different enthesal sites examined; in our study, we examined the lower limb entheses only, whereas the others have examined both the upper and lower enthesal sites. In addition, the technique is highly operator and machine-dependant, which may account for this discrepancy.

Enthesopathies were more tender to palpation than swollen in the clinical examination; however, it has been

suggested that structures in the proximity, such as bone marrow, rather than the enthesis itself, could account for the pain [24]. This would explain our finding that 11.9% of the clinically positive enthesopathies were normal on MSUS examination, which was similar to the findings in studies by Spadaro *et al.* [33] and Alcalde *et al.* [25].

In both studied groups, distal Achilles tendon insertion (30.5, 41.5%) was the most commonly affected enthesal site, followed by the proximal plantar fascia insertion (27.78 and 35.38%, respectively). This result is consistent to a large extent with that obtained in previous studies [10,25,27,34,35]. The existence of thick skin and subcutaneous tissue overlying the plantar fascia may decrease the sensitivity of the MSUS [34]. Enthesopathy at the inferior patellar tendon insertion was the least frequent to be detected in our study; several anatomical factors such as bone widening and sharp changing in the fiber orientation can lead to an anisotropic misleading artifact [25]. In their study, Kiris *et al.* [36] showed that MSUS-detected enthesopathies were more prevalent in the lower extremity entheses in a group of 30 AS patient, whereas a study by Lehtinen *et al.* [28] reported more frequent enthesopathic abnormalities at the distal part of the lower limb such as the Achilles tendon, plantar fascia, and patella insertions with respect to the proximal part of the lower limbs as the ischial tuberosity, greater trochanter, and adductor muscles insertions. This predilection for the distal part of lower limbs enthesitic process can be explained by anatomic; in addition, physiological factors might play a role. In fact, the great length of the Achilles tendon or its movement on the adjacent bursa may be responsible of a more relevant mechanical injury at this enthesal site [10,28,37].

In BD patients' group, the highest number of elemental lesions of enthesal sites seen was tendon thickening (22.7%), followed by enthesophytes (11.8%), bursitis (9.54%), erosions (2.27%), and PD signals (6.3%).

This result differs from that obtained in a study by Ozkan *et al.* [34], who reported that the most frequent abnormality found in a total of 432 enthesal sites in 36 patients with BD examined by US was calcification (18.1%); however, in their study, the mean tendon thickness was greater for patients with BD than for the controls ($P < 0.05$), and this was attributed to the underlying inflammatory process in BD.

Similar to the results found in a study by Hatemi *et al.* [3], the number of AS patients in our study with bony components (bone erosions and enthesophytes) of the GUESS enthesopathy score was statistically significantly higher ($P < 0.05$) than that of BD patients.

In addition, the mean GUESS score was significantly increased ($P < 0.05$) in AS patients than in BD patients, and in BD patients with arthritis than in those without arthritis.

In our study, the GUESS scores were significantly positively correlated with fatigue ($P < 0.05$), peripheral joint pain and swelling ($P < 0.05$), and BASFAI scores ($P < 0.05$). GUESS scores did not significantly correlate with spinal pain scores ($P > 0.05$), may be because our study included peripheral enthesopathies in the lower limb only. A study by McGonagle *et al.* [6] has shown that synovitis that occur in patients with SpA is 2ry to the release of proinflammatory cytokines from the enthesis, which is unlike rheumatoid arthritis (RA) where a primary autoimmune synovitis is induced. It has been demonstrated that inflammation of the enthesis is responsible for the symptoms and explains the multitude of painful sites in these patients at both axial level – like inflammatory back pain, sacroiliac pain, chest pain and peripheral levels, causing stiffness and functional limitation [38]. There were insignificant correlations of GUESS scores with total BASDAI scores and laboratory markers of activity (ESR and CRP levels). Despite that, the BASDAI and BASFAI are instruments that were developed to overcome the poor sensitivity of the acute phase reactant as ESR and CRP; they failed to specifically address enthesitis as only one of the six items in the BASDAI and none of the BASFAI refers to this feature.

Our results confirmed the studies of Ezzat *et al.* [39] and Rudwaleit *et al.* [40], who showed no significant correlation between the GUESS score and the BASDAI, and coincided with a study by Balint *et al.* [10], who found no correlation between the US scores and acute phase reactants. The poor sensitivity of the systemic parameters such as the ESR and CRP to assess disease activity in AS patients had been recognized [41,42].

Regarding radiological damage, the GUESS scores did not correlate with the measures of radiographic deterioration as they are objective parameters, which may change over time, but the US examination is a subjective parameter that reflects enthesopathy at the time of physical examination.

From these results, we can conclude that ultrasonographic changes at the enthesal sites of the lower limbs are prevalent in both AS and BD. These changes are more frequently related to functional and articular involvement. MSUS is more sensitive than is clinical examination in detecting enthesopathies of the lower limbs in both AS and BD patients.

Acknowledgements

Many thanks for Dr. Adham Aboul Fotouh Khalil, EULAR MSUS tutor, Rheumatology Division, Department of Internal Medicine, Cairo University Hospitals, Cairo, Egypt for his generous support and encouragement in learning MSUS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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