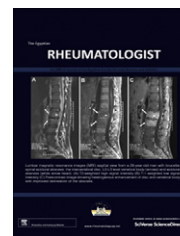




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ORIGINAL ARTICLE

## Ultrasonographic evaluation of lower limb entheses in patients with early spondyloarthropathies

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### KEYWORDS

Spondyloarthropathy;  
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**Abstract** *Introduction:* The enthesopathy of seronegative spondyloarthropathies (SpA) is the hallmark of these diseases, the ultrasound examination of these entheses confirms the frequency of their involvement.

*Aim of the work:* To detect enthesal abnormalities with ultrasound (US) in the lower limb of patients with early spondyloarthropathy (SpA) and to evaluate US as a valuable tool in detecting early enthesitis.

*Patients and methods:* A total of 45 patients with early disease duration of  $11.7 \pm 8.5$  months, including 10 patients with psoriatic arthritis (PsA), 10 patients with ankylosing spondylitis (AS), 10 patients with reactive arthritis (ReA), eight patients with ulcerative colitis (UC) and seven patients with Crohn's disease and 20 healthy controls of matched age and sex underwent ultrasonographic evaluation of Achilles, quadriceps, patellar entheses and plantar aponeurosis. Ultrasonographic findings were scored according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS).

*Results:* On US examination a total of 290/450 (64.4%) of the enthesal sites were abnormal. Mean GUESS score was significantly higher in patients with SpA as compared with controls

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( $p < 0.001$ ), with a higher mean value in patients with PsA, ReA and AS. The mean thickness of all tendons examined was significantly higher in SpA patients than in controls ( $p < 0.0001$ ) as well as the mean number of enthesophytes and bursitis in all sites examined ( $p = 0.002$ ,  $p = 0.003$ ), with a higher prevalence amongst patients with PsA and ReA. The GUESS score was correlated to duration of the disease and the anti-tumour necrosis factor alpha medications.

*Conclusion:* Enthesis involvement occurs early in spondyloarthritis, the entheses US score appears to be reliable and useful for improving the diagnostic accuracy of early SpA, further studies are needed as US is an evolving technique.

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## 1. Introduction

The seronegative spondyloarthropathies comprise a group of related inflammatory arthritides, the principal clinical entities of this group include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), enteropathic spondylitis (inflammatory bowel disease). All of them demonstrate the absence of serum rheumatoid factor (seronegativity), association with the human leucocyte antigen B27 (HLA-B27), familial clustering, predominant axial and peripheral asymmetric joint involvement, and extra-articular manifestations [1].

Enthesis is defined as a site of insertion of tendons, ligaments, fascia, or articular capsule into bone. The involvement of the entheses in any pathologic process, whether metabolic, inflammatory, traumatic, or degenerative, is referred to as enthesopathy, while the term “enthesitis” is restricted to inflammation of the entheses [2].

The enthesopathy of seronegative spondyloarthropathy (SpA) is an example of enthesal involvement in a systemic process. Peripheral enthesitis has been repeatedly described in all forms of SpA and all phases of disease evolution [2,3]. It has been suggested that the presence of fibrocartilage and microtrauma are two major factors associated with disease localisation in SpA [4]. A hypothesis that mechanically induced enthesopathy may trigger autoimmunity towards fibrocartilage/bone in HLA B27 positive patients has been proposed on the basis of a strong correlation between the extent of bone pathology on MRI and the presence of HLA B27, in patients with plantar fascia enthesopathy [5].

Accordingly, the Achilles tendon and plantar fascia, which are the most commonly implicated sites in SpA-associated enthesitis, along with the spinal ligaments usually affected by the disease, have a prominent fibrocartilage component [4].

Enthesitis may occur at any attachment site in SpA, but detected enthesitis is more frequently depicted in the entheses of the lower limbs, probably for mechanical reasons.

The ultrasound examination of these entheses confirms the frequency of their involvement [6–8].

Multiple imaging modalities are available to evaluate the seronegative spondyloarthropathies. These include conventional radiography, conventional tomography, computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy, and ultrasonography (US). Ultrasound is very cost efficient and does not convey radiation exposure that is inherent to CT or conventional radiography. Compared with clinical examination, ultrasound is superior in the detection of enthesal abnormalities of the lower limbs in spondyloarthropathy [6]. Previous studies reported the usefulness of US in the

evaluation of the tendon and its insertional pathology [9,10] with a sensitivity comparable to MRI [11,12].

The first extensive description of enthesal involvement in SpA patients by ultrasound was initially provided by Lehtinen et al. [8] in 1994 followed by Balint et al. [6] in 2002 and D’Agostino et al. [7] in 2003. Grey-scale enthesitis was mostly characterised by the loss of normal fibrillar echogenicity of the tendon insertion (83%) with or without an increase in tendon thickness or by intralesional focal changes at the tendon insertion, such as calcium deposits, fibrotic scars and periosteal changes (erosions or new bone formation). The anatomical borders of the entheses are of capital importance. Some ultrasound studies studied enthesitis in the concept of ‘entheses organ’ leading sonographers to include the involvement of surrounding structures far from the bony attachment (i.e. tendon and bursa) in the evaluation of enthesitis [13,14].

Our aim was to detect ultrasonographic enthesal abnormalities in the lower limb of patients with early spondyloarthropathy and to evaluate US as an objective and reliable tool for diagnosis of early enthesal involvement.

## 2. Patients and methods

Our study was performed on a total of 45 patients with a mean age of  $34.3 \pm 6.22$  years, early disease duration of  $11.7 \pm 8.5$  months and 20 healthy controls matched for age and sex with a mean of  $36.9 \pm 5.7$  years, the control group was without any known mechanical, inflammatory or musculoskeletal disease. The patients included 10 with psoriatic arthritis (PsA), 10 patients with ankylosing spondylitis (AS), 10 patients with reactive arthritis (ReA), eight patients with ulcerative colitis (UC) and seven patients with Crohn’s disease. All patients were diagnosed according to assessment in spondyloarthritis international society (ASAS) diagnostic criteria [15].

All patients with PsA fulfilled the classification criteria for psoriatic arthritis (CASPAR) [16]. Endoscopic and histopathologic diagnoses were performed in all patients with inflammatory bowel disease (UC and Crohn’s disease). BASDAI score was done to all patients with AS.

Ophthalmological examination including fundus and slit lamp was done in all patients, in addition full laboratory and X ray studies were performed to all patients that included a complete blood cell count, biochemistry, C-reactive protein, antinuclear antibodies, rheumatoid factor, HLA-B27 as well as radiographs of the pelvis, sacroiliacs, tendo achillis, cervical, dorsal and lumbar spine. Full musculoskeletal examination was done to the all study group and the controls. All subjects

**Table 1** Clinical laboratory and demographic characteristics of the studied groups of patients.

Characteristics	PsA N = 10	AS N = 10	ReA N = 10	UC N = 8	Crohn's disease N = 7
<i>Demographic data</i>					
Male, No. (%)	4 (40)	10 (100)	5 (50)	4 (33)	0
Female, No. (%)	7 (70)	0	0	8 (66)	7 (100)
Age*	50.9 ± 13.3	30.2 ± 2.9	27.8 ± 6.4	31.8 ± 7.1	37.6 ± 4.8
Disease duration/month*	12.5 ± 5.1	8.5 ± 5.2	3.3 ± 1.2	3.2 ± 2	3.3 ± 1.9
<i>Clinical manifestations</i>					
Peripheral synovitis, No. (%)	5 (50)	4 (40)	7 (70)	2 (25)	2 (28.5)
Clinical enthesitis, No. (%)	4 (40)	2 (20)	5 (50)	1 (12.5)	1 (14.2)
Sacroilitis, No. (%)	4 (40)	8 (80)	4 (40)	1 (12.5)	2 (28)
Nail dystrophy, No. (%)	8 (80)	0 (0)	0 (0)	0 (0)	0 (0)
Spinal disease, No. (%)	3 (30)	10 (100)	3 (30)	1 (12.5)	2 (28)
Slit lamp changes, No. (%)	2 (20)	5 (50)	2 (40)	0 (0)	0 (0)
<i>Laboratory manifestations</i>					
ESR, mm/Hg*	43.8 ± 6.9	33.5 ± 13	27 ± 6.2	48.2 ± 17.7	52.9 ± 19.1
CRP, mg/L*	33.7 ± 33.2	13.57 ± 11.5	12.2 ± 6.7	4.8 ± 1.1	8.4 ± 3.3
Haemoglobin (g %)*	12.7 ± 0.6	12.2 ± 1.1	9.9 ± 2.8	10.7 ± 2.6	9.3 ± 1.3
WBCs (×10 <sup>3</sup> /mm <sup>3</sup> )*	7.8 ± 1.4	7.8 ± 0.8	6.71 ± 1.5	11 ± 3.7	7.4 ± 1.1
Platelets (×10 <sup>3</sup> /mm <sup>3</sup> )*	272.7 ± 36.9	244 ± 28	260 ± 13.7	335 ± 75	208 ± 54.6
AST (U/L)*	19 ± 6.2	11 ± 3.2	12 ± 3.3	18 ± 14	13 ± 2.7
ALT (U/L)*	17.5 ± 1.2	17.2 ± 4.3	16.3 ± 4.3	18.2 ± 7.7	15.5 ± 5.1
Creatinine (mg/dl)*	0.8 ± 0.2	0.6 ± 0.001	0.7 ± 0.1	0.8 ± 0.2	0.6 ± 0.2
HLA-B27 + VE, No. (%)	4 (40)	9 (90)	5 (50)	2 (25)	2 (25)
<i>Treatment, No. (%)</i>					
Methotrexate (mg/dl)	5 (50)	0 (0)	2 (20)	1 (12.5)	1 (14.2)
Steroids (mg/dl)	0 (0)	0 (0)	0 (0)	7 (90)	7 (100)
Sulfasalazine	2 (20)	0 (0)	2 (40)	0 (0)	1 (14.2)
Mesalamine	0 (0)	0 (0)	0 (0)	8 (100)	7 (100)
Azathioprine	0 (0)	0 (0)	0 (0)	7 (90)	7 (100)
Anti-TNF	4 (40)	5 (50)	1 (10)	0 (0)	3 (42)

PsA: psoriatic arthritis; AS: ankylosing spondylitis; ReA: reactive arthritis; UC: ulcerative colitis, spinal disease: inflammatory back pain; ESR: erythrocyte sedimentation rate; AST: aspartate transaminase; ALT: alanine transaminase; Rf: rheumatoid factor; HLA-B27: human leucocyte antigen-B-27; TNF: tumour necrosis factor.

\* Mean ± SD.

were informed about the aim of the study and gave their consent. Patients were collected from the Rheumatology and Rehabilitation Department, Cairo and Fayoum University Hospitals.

### 2.1. Ultrasonography

Real-time ultrasonography was performed by both an experienced radiologist and a rheumatologist, using an ATL HDI 3000 machine with a linear 7–12 MHz probe. The radiologist was blinded, that is, he was not aware if patients were affected by a rheumatological disease, and the ultrasonographic examination was performed in a darkened room. Examination of a total of bilateral five enthesal lower limb sites was done with a total of 450 enthesal sites including superior pole of the patella (quadriceps tendon insertion), inferior pole of the patella (patellar ligament origin) and the patellar ligament insertion at the tibial tuberosity was performed with the patient in the supine position with the knee flexed at 30°. The Achilles tendon and the plantar aponeurosis were examined with the patient lying prone with the feet hanging over the edge of the examination table at 90° of flexion. Ultrasonographic assessment of structure, thickness and the presence or absence of

bony erosions, enthesophytes and bursitis was recorded at each site. The following criteria were used for abnormal structure thickness: quadriceps tendon thickness >6.1 mm (ref), proximal and distal patellar ligament >4 mm (ref), Achilles tendon >5.29 mm (ref), plantar aponeurosis >4.4 mm (ref). Ultrasonographic findings were scored according to Glasgow Ultrasound Enthesitis Scoring System (GUESS), which was validated by Balint et al. [6]. GUESS is an easily reproducible standardised measure of lower limb enthesal ultrasonographic abnormalities, ranging from 0 to 36. It incorporates the assessment of tendon thickness, and the presence of bone erosions, enthesophytes and bursitis recorded at the Achilles, quadriceps and patellar tendons and plantar aponeurosis.

Statistical analysis: Quantitative variables were described using mean ± standard deviation (SD) and categorical data by frequency and percentage. Pearson Chi-square test was used to test differences amongst categorical variables amongst the groups of patients and nonparametric Kruskal–Wallis test was used to compare quantitative variables amongst the groups. Fisher's exact test was used to calculate an exact probability value for the relationship between two dichotomous variables between positive and negative patients with respect to enthesitis, and Student's *t* test was used to compare quanti-

**Table 2** Ultrasonographic enthesis involvement in patients and controls.

	Controls <i>n</i> = 20	SpA group <i>n</i> = 45	Significance
GUESS score**	1.1 ± 0.2	6.8 ± 2.1	0.001*
Tendon thickened**	0.79 ± 1.28	0.91 ± 0.82	0.0001*
Bursitis**	0.67 ± 1.2	1.35 ± 1.29	0.003*
Enthesophyte**	3.2 ± 2.1	6.7 ± 3.69	0.002*
Bone erosion**	0	0	0

GUESS: Glasgow Ultrasound Enthesitis Scoring System.

\* Significantly different at  $p < 0.001$ .

\*\* Mean ± SD.

tative variables between groups of patients with respect to enthesitis. In all tests,  $p$  value  $< 0.05$  was considered to be statistically significant.

### 3. Results

#### 3.1. Demographic data

Our study included 45 patients with SpA, 23 males (51%) and 22 females (48.8%) with a mean age  $34.3 \pm 6.22$  years and 20 healthy controls 11 males (55%) and nine females (45%) with a mean age  $36.9 \pm 5.7$  years. The average evolution time of the spondyloarthritis group was  $11.7 \pm 8.5$  months.

The mean ESR in SpA group was  $11.19 \pm 9.22$  and C-reactive protein (CRP) was  $7.76 \pm 11.6$ , antinuclear antibodies and rheumatoid factor were negative in all patients, HLA-

B27 positivity was found in 22 patients (48%), the mean BASDAI was  $5.4 \pm 2.8$  in patients with AS.

On clinical examination of the enthesal sites of lower limbs, we found inflammation in the form of tenderness and swelling in a total of 13/45 (28.8%) patients. Peripheral synovitis involving the knees and ankles was found in 20 (44%) patients, spinal disease in the form of inflammatory low back, insidious onset, more than 3 month duration was found in 19 (42%) patients, radiographic sacroilitis was present in 19 (42%) patients. Slit lamp examination showed anterior uveitis in nine (20%) patients. Detailed demographic, laboratory and clinical characteristics of the study groups are illustrated in Table 1.

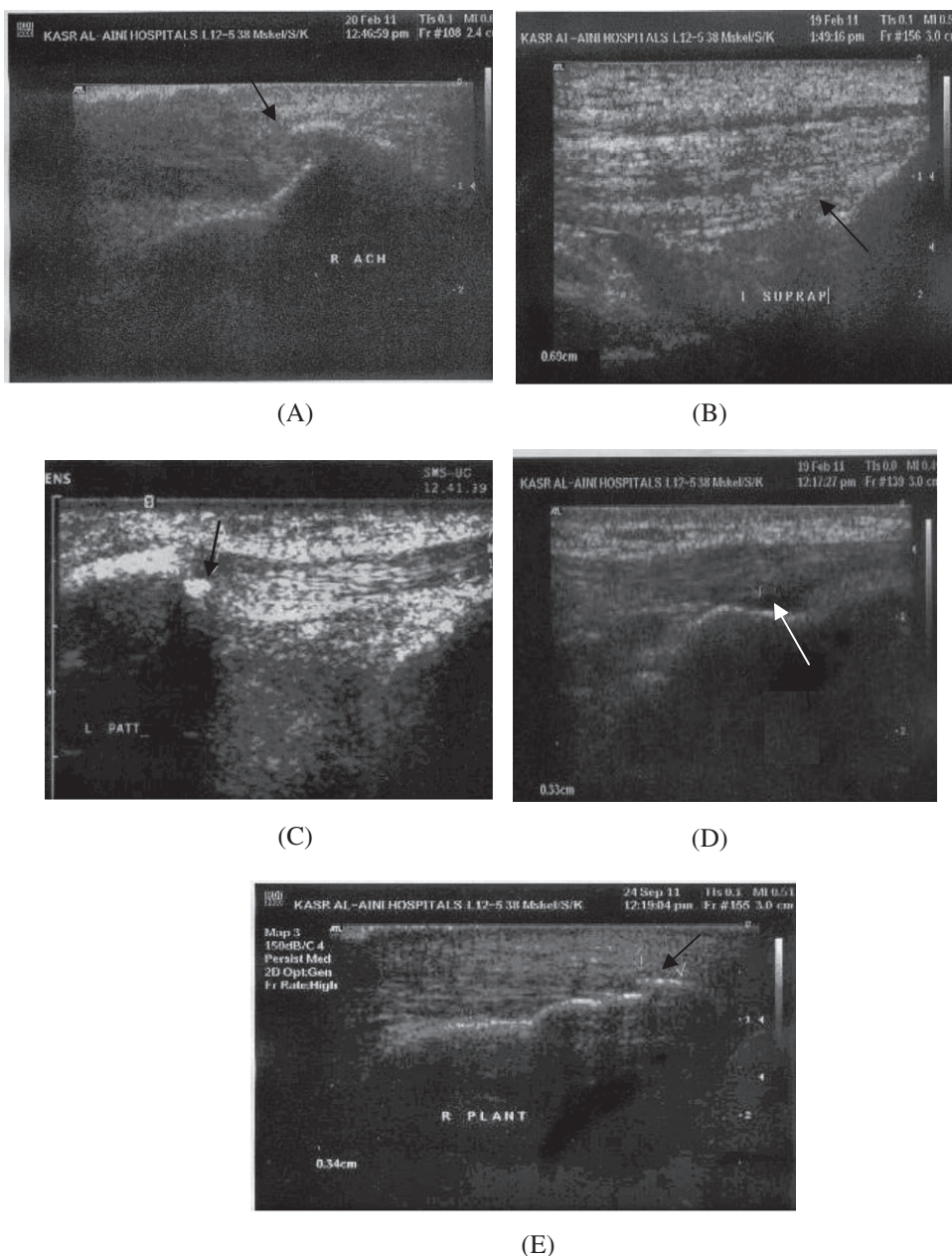
#### 3.2. Ultrasonographic results

All enthesal sites examined in the 20 control patient were normal, 450 enthesal sites in the 45 patients were examined by US and showed a total of 290/450 (64.4%) of the enthesal sites were abnormal (Table 3), Fig. 1 shows the ultrasonographic findings of the entheses. Mean GUESS score was significantly higher in patients with SpA as compared with controls ( $p < 0.001$ ). The mean thickness of all tendons examined was significantly higher in SpA patients than in controls ( $p < 0.0001$ ) as well as the mean number of enthesophytes and bursitis in all sites examined ( $p = 0.002$ ,  $p = 0.003$ , respectively) (Table 2), we did not observe bone erosions either in cases or in controls. GUESS score was correlated to the duration of the disease in patients with SpA ( $p = 0.005$ ), while there was no significant difference between GUESS score and either the age, gender of the patients, ESR, CRP and HLA-B27 or the clinical manifestations in the form of sacroilitis, spinal and eye affection or nail changes and the BASDAI score.

**Table 3** Ultrasonographic examination of the Enthesal insertions amongst SpA patients.

	PsA <i>N</i> = 10	AS <i>N</i> = 10	ReA <i>N</i> = 10	UC <i>N</i> = 8	Crohn's disease <i>N</i> = 7
GUESS score	4.5 ± 3	3.8 ± 1.6	5.8 ± 2.3	0.4 ± 0.7	0.6 ± 0.9
Manifestations, No. (%)					
Bursitis					
Suprapatellar	4 (40)	0	4 (40)	1 (12.5)	0
Infrapatellar	6 (60)	1 (10)	6 (60)	0	1 (14.2)
Tibial tuberosity	3 (30)	5 (50)	4 (40)	0	1 (14.2)
Achilles tendon	1 (10)	3 (30)	6 (60)	0	0
Plantar aponeuroses	4 (40)	4 (40)	6 (60)	1 (12.5)	2 (28)
Enthesophytes					
Suprapatellar	6 (60)	5 (50)	6 (60)	1 (12.5)	1 (14.2)
Infrapatellar	5 (50)	6 (60)	8 (80)	2 (25)	3 (42.8)
Tibial tuberosity	4 (40)	7 (70)	6 (60)	2 (25)	1 (14.2)
Achilles tendon	6 (60)	4 (40)	4 (40)	4 (50)	1 (14.2)
Plantar aponeuroses	6 (60)	3 (30)	6 (60)	2 (25)	2 (28)
Tendon thickened,* No. (%)					
Suprapatellar	7 (70)	8 (80)	6 (60)	1 (12.5)	2 (28)
Infrapatellar	6 (60)	7 (70)	8 (80)	4 (50)	3 (42.8)
Tibial tuberosity	8 (80)	5 (50)	8 (80)	3 (37.5)	1 (14.2)
Achilles tendon	7 (70)	6 (60)	6 (60)	2 (25)	1 (14.2)
Plantar aponeuroses	6 (60)	7 (70)	4 (40)	4 (50)	3 (37.5)

\* 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 aponeuroses  $> 4.4$  mm.



**Figure 1** Ultrasonographic appearances of enthesitis, (A) inferior patellar enthesophyte, (B) thickened suprapatellar tendon, (C) superior patellar enthesophyte, (D) infrapatellar bursitis, (E) planter enthesophyte.

In addition we found a significant negative correlation between GUESS score and the anti-TNF medications used amongst the selected groups ( $p < 0.001$ ).

*3.3. Differences between spondyloarthritis groups*

The mean GUESS score was higher amongst patients with PsA, ReA and AS ( $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.002$ , respectively). Ultrasonographic enthesiophytes, thickened tendons and bursitis were found to be more common in PsA, and ReA groups ( $p = 0.002$ ,  $p = 0.01$ , respectively) while no erosions were found amongst the examined groups. Detailed ultrasonographic findings amongst the SpA groups are shown in Table 3.

**4. Discussion**

There is a growing interest in early diagnosis for patients with spondyloarthropathy, all experts agree that enthesitis is a hallmark of spondyloarthropathy and that the detection of inflammatory changes in the joints is crucial to the diagnosis of the seronegative spondyloarthropathies, especially early in the disease course, when patients present with back pain of an unknown cause [6,7].

The diagnostic validation of a technique implies several steps, and in the case of enthesitis in SpA, at least two steps are predominant and frequently evaluated at the same time: the ability to distinguish between normal and abnormal findings at enthesitis level and the capability of the tool for helping

in the diagnostic process. In the field of rheumatology, SpA is one of the situations in which there is no reference standard based on histological or biochemical changes, and the disease condition is defined by a combination of symptoms and signs [17].

Therefore, the utility and accuracy of a new potentially useful diagnosis test, such as ultrasound evaluation of entheses, can be difficult to assess because of this important limitation. In that case, the correct steps of validation of the test as well as the design of an accuracy study are crucial [18], and for this reason the OMERACT (Outcome Measures in Rheumatology) Task Force produced the first preliminary ultrasound consensus definitions of the most frequently detected pathologies [19]. The group at that time (2005) decided to define enthesopathy instead of enthesitis, but is now working on a clear definition of enthesitis in SpA [20].

The aim of our study focused to show if entheses is a hallmark of early spondyloarthropathies, and if ultrasound can be used to improve the accuracy of spondyloarthritis classification diagnosis.

In our current work ultrasound showed to be a sensitive tool in detecting enthesitis, showing early enthesal inflammation in 290/450 (64.4%) of the enthesal sites in patients with disease duration of  $11.7 \pm 8.5$  months, in agreement, was de Miguel et al. [21] who determined early enthesal affection in SpA patients with US.

The mean GUESS score was found to be higher in SpA patients more than controls in addition to the mean of the thickened tendons, enthesophytes and bursitis in all sites examined, which shows that the entheses US score appears to be valid and maybe useful for improving the diagnostic accuracy of early SPA, in accordance with the results of the studies of Secundini et al. [22] who studied the clinico-radiological correlation of entheses in seronegative SpA and Gerster [23] who examined 150 patients with SpA and Balint et al. [6] who showed that US GUESS score is superior in detecting enthesal abnormalities in the lower limbs of SpA.

In our study, we observed that ultrasonographic enthesiophytes, thickened tendons and bursitis to be more common in patients with PsA, and ReA, which suggest that a form of subclinical synovitis may exist in these patients which can be missed during routine clinical examination, these data were confirmed by Galluzzo et al. [24] who found a high prevalence of involvement of the tendons and entheses of the ankle in clinically asymptomatic PsA patients, suggesting that clinical evaluation underestimates these manifestations. GUESS score was directly correlated to the duration of the disease in patients with SpA but not the age or the gender of the patients, the role of ageing on tendon thickness is uncertain, although more recently it has been reported that Achilles tendon thickness was similar in young and middle aged people [25]. Our study did not show significant difference between GUESS score and HLA-B27 or BASDAI which coincides with the studies of Rudwaleit et al. [26].

In our current work we had found a negative significant correlation between GUESS score and anti-TNF used amongst SpA patients, in agreement were several data which showed anti-TNF treatments to reduce spinal enthesal inflammation [27,28].

In summary, entheses involvement occurs early in spondyloarthritis, the entheses US score appears to be valid and useful for improving the diagnostic accuracy of early SpA. However,

further validation is still needed as US is an evolving technique. It should be kept in mind that differences in the US equipment and settings, as well as correct knowledge of anatomy of entheses may have an influence on the ability of US as a diagnostic tool.

### Conflict of interest

The authors have no conflict of interest.

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