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ORIGINAL ARTICLE

# The relationship between clinical parameters and ultrasonographic enthesitis assessment in patients with spondyloarthritis

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***ABSTRACT***

**Objectives:** The study aimed to evaluate the role of ultrasonographic assessment of enthesitis in patients with spondyloarthritis (SpA) in terms of disease activity, functionality, and quality of life.

**Patients and methods:** Ninety SpA patients (57 males, 33 females; mean age: 37.5±9.7 years; range, 18 to 60 years) were included in cross-sectional study between November 2016 and January 2017. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), Short Form-12 (SF-12), and Ankylosing Spondylitis Quality of Life (ASQoL) were utilized for clinical evaluation. The clinical evaluation of enthesitis was performed with the Spondyloarthritis Research Consortium of Canada (SPARCC) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) via an algometer calibrated to 4 kg/cm² of pressure. Ultrasound evaluation was performed according to Madrid Sonographic Enthesitis Index (MASEI). A total of 2,610 entheseal sites were examined clinically, and 1,080 were assessed ultrasonographically.

**Results:** A significant proportion of enthesitis (463/1,080) was detected on ultrasonographic evaluation but not with clinical enthesitis score (MASES and SPARCC). Although ultrasonographic entheseal evaluation detected enthesitis in at least one enthesis of all patients, 35 of the patients had no enthesitis with clinical examination. The sites most frequently involved in the entheses were the proximal patellar tendon and Achilles tendon. The MASEI score did not correlate with the MASES, SPARCC, BASDAI, SF-12, and ASQoL but moderately correlated with the C-reactive protein (CRP) level (r=0.348), ASDAS-CRP (r=0.294), and BASFI score (r=0.244).

**Conclusion:** The association of ultrasonography scores with CRP levels and ASDAS-CRP indicates that ultrasonography is effective in detecting inflammation. The MASEI score weakly correlates with functionality but not with quality of life. Ultrasonographic evaluation is invaluable and merits to be incorporated into SpA disease scoring system.

***Keywords:*** Disease activity, enthesitis, spondyloarthritis, ultrasonography.

An enthesis is a region where the tendon, ligament, fascia, or joint capsules adhere to the bone. The inflammatory involvement of "the enthesis organ" that consists of fibrocartilage, synovium, and bone is defined as enthesitis.[1] Enthesitis is one of the major manifestations of spondyloarthritis (SpA), and neutrophils in the enthesis organ were suggested to be responsible for the early phase of enthesitis.[2] Enthesitis also plays a significant role in the pathogenesis of SpA.

Pain and swelling in the enthesis allow clinical diagnosis of enthesitis. Inflammation and mechanical loading generate pain and swelling by providing invasion of nerves and blood vessels into the enthesis organ that should be avascular and does not have plenty of nerve endings in a healthy entheseal region.[3] Conventionally, clinical evaluation has been an important part of enthesis assessment, and clinical enthesitis scoring systems have been developed to evaluate enthesitis and to standardize studies in SpA. Firstly, Mander et al.[4] published an instrument, the Mander enthesis index (MEI), that investigates 66 entheses and grades pain intensity on a scale of 0 to 3. MEI was time-consuming to apply and thus could not be used widely, and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) has been

developed by modifying MEI.[5] MASES is achieved by palpating 13 entheses: right and left first and seventh costochondral joint, spina iliaca posterior superior, spina iliaca anterior superior, iliac crest, Achilles tendon proximal insertion, and the fifth lumbar spinous process. MASES is a valuable option with a much better feasibility.[5] Afterward, the Spondyloarthritis Research Consortium of Canada (SPARCC) developed an enthesis index that evaluates eight peripheral entheses bilaterally: the supraspinatus tendon insertion site, medial epicondyle, lateral epicondyle, greater trochanter, quadriceps tendon, patellar tendon, Achilles tendon, and plantar fascia.[6] MASES and SPARCC enthesis indexes are frequently used in studies. SPARCC includes peripheral enthesis sites that are easy to image by ultrasound. However, one of its important shortcomings is that the SPARCC index does not contain axial entheseal regions.

Poor interobserver reliability and lack of accuracy in clinical evaluation have made imaging methods an essential part of the enthesis examination.[7] Conventional radiographs provide limited information about entheseal sites for the reason that they cannot visualize soft tissue, and other imaging modalities, such as magnetic resonance imaging (MRI) and ultrasound (US), have been used to reveal soft-tissue changes and inflammation. Compared to US, MRI has also the ability to evaluate bone marrow edema, which is a part of the enthesis organ. US has considerable benefits including ease of access and inexpensive, real-time, and dynamic evaluation. US has allowed rheumatologists to diagnose, assess disease severity, and monitor changes in disease status.

In the last decade, the use of US has become widespread in the evaluation of peripheral entheses. Large-scale studies of US in SpA were first performed by Lehtinen et al.[8] in 1994 and then by Balint et al.[9] in 2002. In 2003, D'Agostino et al.[10] first described the use of power Doppler to image hyperemia and neovascularization. The Outcome Measures for Rheumatoid Arthritis Clinical Trials (OMERACT) Ultrasound Working Group defined ultrasonographic lesions to help standardization. Enthesitis was defined as "hypoechoic and/or thickened insertion of the enthesis close to the bone (within 2 mm from the bony cortex) which exhibits Doppler signal if active and that may show erosions, enthesophytes/calcifications as a sign of structural damage."[11]

Ultrasonography allows the exploration of a specific enthesis for getting information about the local area or multiple selected entheses. Various combinations of enthesis locations and elemental lesions form US enthesis indexes that may demonstrate the global disease state. Several sonographic scoring systems have been developed to evaluate peripheral enthesitis. The first used US enthesis index was the Glasgow Ultrasound Enthesitis Scoring System (GUESS), which evaluates only the enthesis of lower limbs in greyscale.[9] GUESS evaluates four types of lesions including thickness, bursa, erosion, and enthesophytes. Afterward, D'Agostino et al.[10] first added the power Doppler signal and developed five possible stages instead of scores. In 2007, the Sonographic Entheseal Index described lesions as acute and chronic based on GUESS.[12] In 2009, the Madrid Sonographic Enthesitis Index (MASEI) was developed and has been the second most utilized index after GUESS.[13] The use of MASEI is favored since it assesses the upper extremity and uses power Doppler. Lastly, the Belgrade Ultrasound Enthesitis Score (BUSES) was found useful for enthesitis evaluation in patients with SpA in 2015.[14] Common extensor tendon enthesis is assessed in BUSES instead of brachial triceps tendon and grades Doppler signal and erosion on 0 or 4 instead of 0 or 3 compared to MASEI.

Ultrasonographic scoring systems have been used for early diagnosis, monitoring of progression, and response to treatment. There are limited studies that aim to compare disease activity, quality of life, and functional status with ultrasonographic enthesitis assessment. These studies were performed with only one tendon or only the lower extremity or without using any scoring system. Falcao et al.[15] aimed to find out whether ultrasonographic enthesitis scores are associated with disease activity and evaluated only Achilles enthesis based on MASEI. In 2011, Hamdi et al.[16] sought a correlation among clinical parameters such as disease activity, functionality, and quality of life and clinical (MASES and SPARCC) and ultrasonographic enthesitis scores that include five lower limb entheses based on no sonographic enthesitis score. In studies comparing BUSES with clinical parameters, either clinical enthesitis scores or functionality and quality of

life were not evaluated.[17,18] In a study utilizing MASEI, authors investigate the correlation among sonographic and clinical evaluation of entheseal sites in MASEI, disease activity, and quality of life but clinical enthesitis indices were not used, functional status was neglected, and the correlation between C-reactive protein (CRP), an important marker of inflammation and disease activity in SpA, was not investigated.[19] This study aimed to comprehensively evaluate many parameters, including disease activity, quality of life, functional status, clinical enthesitis scores, and ultrasonographical enthesitis assessment, with the MASEI index and to determine how valuable ultrasonographic enthesitis is to assess disease activity, functionality, and quality of life.

## PATIENTS AND METHODS

Ninety SpA patients (57 males, 33 females; mean age: 37.5±9.7 years; range, 18 to 60 years) who applied to the Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Physical Medicine and Rehabilitation Department, Rheumatology Clinic between November 2016 and January 2017 were enrolled in the cross-sectional study. Inclusion criteria were defined as being between 18 and 60 years old and fulfilling the 2009 Assessment of Spondyloarthritis International Society SpA criteria.[20] Exclusion criteria were defined as having concomitant rheumatologic disease, having a history of elbow, ankle, or knee surgery, local injection at the examination sites within six weeks, peripheral neuropathy, infection, and wound in the entheses which would be evaluated clinically and ultrasonographically. Patients who met the modified New York criteria were described as having ankylosing spondylitis, and patients who did not meet the modified New York criteria were described as having nonradiographic axial SpA.[21] The patients were classified in accordance with cut-off values of CRP values and disease activity scales.

Clinical history was taken and physical examination was performed by the first clinician. Human leukocyte antigen-B27 positivity, CRP, and erythrocyte sedimentation rate (ESR) levels were recorded. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and ASDAS-ESR was evaluated for disease activity, and Bath Ankylosing Spondylitis Functional Index (BASFI) was assessed for functionality. Short Form-12 (SF-12) and Ankylosing Spondylitis Quality of Life (ASQoL) was measured for quality of life. Mental Component Score (MCS) and Physical Component Score (PCS) were subscales of SF-12. The clinical evaluation of enthesitis was performed with SPARCC and MASES via an algometer (Jamar Hand Evaluation Kit, Sammons Preston Inc., Bolingbrook, IL, USA) calibrated to 4 kg/cm$^2$ of pressure. In addition to enthesis indices, the bilateral distal triceps tendon insertions were evaluated with the same algometer and pressure.

### Ultrasound evaluation

The US evaluations were performed by a 10-year experienced specialist using a MyLab70 US system (Esaote Biomedica, Genoa, Italy) with a 7-12 MHz linear probe. Power Doppler settings were standardized with a wall filter of 3, pulse repetition frequency of 750 Hz, and a Doppler frequency of 4-13 MHz. Gain was adjusted until the background signal disappeared. US examiner was blind to the patients' information, and patients were asked not to inform the sonographer about their clinics.

All patients underwent US examinations of the following bilateral six entheseal sites: the distal brachial triceps tendon, plantar aponeurosis, Achilles tendon, proximal and distal patellar tendon, and quadriceps tendon. All of the US findings were documented in accordance with MASEI.[22] Each enthesis site was scanned in two planes: longitudinal and transverse. The triceps tendon insertion was evaluated with the arm flexed at 90° and internal rotation in a sitting position. Knee enthesis sites (quadriceps tendon, proximal, and distal patellar tendon insertions) were examined when the knee was flexed at 70°, and the ankles were fixed on the table. The Achilles tendon and plantar aponeurosis examination was performed with the patients lying prone. Doppler examination was performed with the patients' joints in neutral position to reduce tendon tension.

MASEI index evaluated five elemental lesions (scores) of enthesis: structure (0 or 1), thickness (0 or 1), erosions (0 or 3), calcifications (0, 1, 2, or 3), bursae (only at distal patellar tendon

and Achilles tendon) (0 or 1), power Doppler signal (0 or 3).[22] Calcifications were scored as 0 if it was absent, 1 if <5 mm, 2 if 5-10 mm, or 3 if they were >10 mm.[23] Bursitis was defined as a compressible by the transducer, localized anechoic or hypoechoic, well-circumscribed area at Achilles enthesis and distal patellar enthesis. Erosion was defined as a cortical breakage with a step-down contour defect in two planes. A thickness assessment was made by measuring the maximal thickness at the bone insertion site. Based on enthesis-specific values (plantar aponeurosis >4.4 mm, Achilles tendon >5.29 mm, proximal and distal patellar tendon >4 mm, quadriceps tendon >6.1 mm, and triceps enthesis >4.3), it was determined whether there was an increase in thickness. Structural evaluation was defined as pathological in the presence of any of the loss of fibrillar pattern, hypoechoic appearance, and fusiform thickening in the enthesis area. The total score ranged from 0 to 136. The MASEI-Inflammatory score was recorded as entheseal thickness, structural changes, bursitis, and power Doppler findings, and MASEI-Damage score was recorded as calcifications and erosions (Figures 1, 2).[23]

### Statistical analysis

The sample size was calculated with Statstodo (https://www.statstodo.com/) and calculated as 84, with a correlation coefficient of 0.3, a margin of error of 0.05, and power (1-B) of 0.8. Considering data loss, the required sample size was accepted as 90.

Statistical analysis was performed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Normality distribution was assessed by the Kolmogorov-Smirnov test. Mean, standard deviation, median, and range were used to present descriptive analyses. All of the continuous variables except for MCS, PCS, and ASDAS-CRP were distributed asymmetrically. Because of asymmetrical distribution, nonparametric tests were applied. The Mann-Whitney U test was used to compare continuous variables between two groups. Spearman's correlation coefficient was used to analyze the relation between two continuous variables. A p-value <0.05 was considered statistically significant. The Bonferroni correction was used to calculate the adjusted p-value.

## RESULTS

Eighty patients were ankylosing spondylitis, and 10 were nonradiographic axial spondyloarthritis. Fifty-four percent of patients were using biologic drugs. The mean body mass index was 26.04±4.2. Median disease duration and diagnostic delay were 12 and 4 years, respectively. Median CRP, ESR, BASDAI, ASDAS-ESR, BASFI, and ASQoL values and mean ASDAS-CRP, PCS and MCS scores are shown in Table 1.

### Enthesitis evaluation

A total of 2,610 entheseal sites were examined clinically and 1,080 were assessed via US. The proportion of total entheseal sites (peripheral and axial) exhibiting clinically detectable enthesitis was 413/2,610 (15%). Although at least one enthesitis was detected in all patients in the ultrasonographic entheseal evaluation, no enthesitis was detected in 35 (38%) of the patients in the clinical examination. The median score of both MASES and SPARCC was 2.

The proportions of peripheral entheseal sites exhibiting clinically and ultrasonographically detectable enthesitis were 262/1,620 (16%) and 635/1,080 (58%), respectively. Hence, 463/1,080 (42%) enthesitis detected by US were not clinically detected. The most frequent US findings were calcification (32%) and an increase in thickness (25%). The two most frequently ultrasonographically involved enthesis sites are the proximal patellar enthesis (149/180; 82%) and Achilles enthesis (146/180; 81%). The least sonographic involvement was observed in plantar aponeurosis (52/180; 28%). Ultrasonographic involvement in triceps enthesis was 86/180 (47%). Median (range) MASEI, MASEI-Inflammatory, MASEI-Damage, and MASEI-Doppler were 16 (1-68), 9 (0-31), 7 (0-38), and 3 (0-21), respectively. The correlation of clinical parameters and clinical enthesitis scores is given in Table 2. Both MASES and SPARCC were correlated with BASDAI, ASDAS, BASFI, ASQoL, MCS, and PCS. There was no correlation between clinical enthesitis score and CRP and ESR.

The comparisons of clinical parameters, clinical enthesitis scores, and US scores are presented in Table 3. There was no correlation between

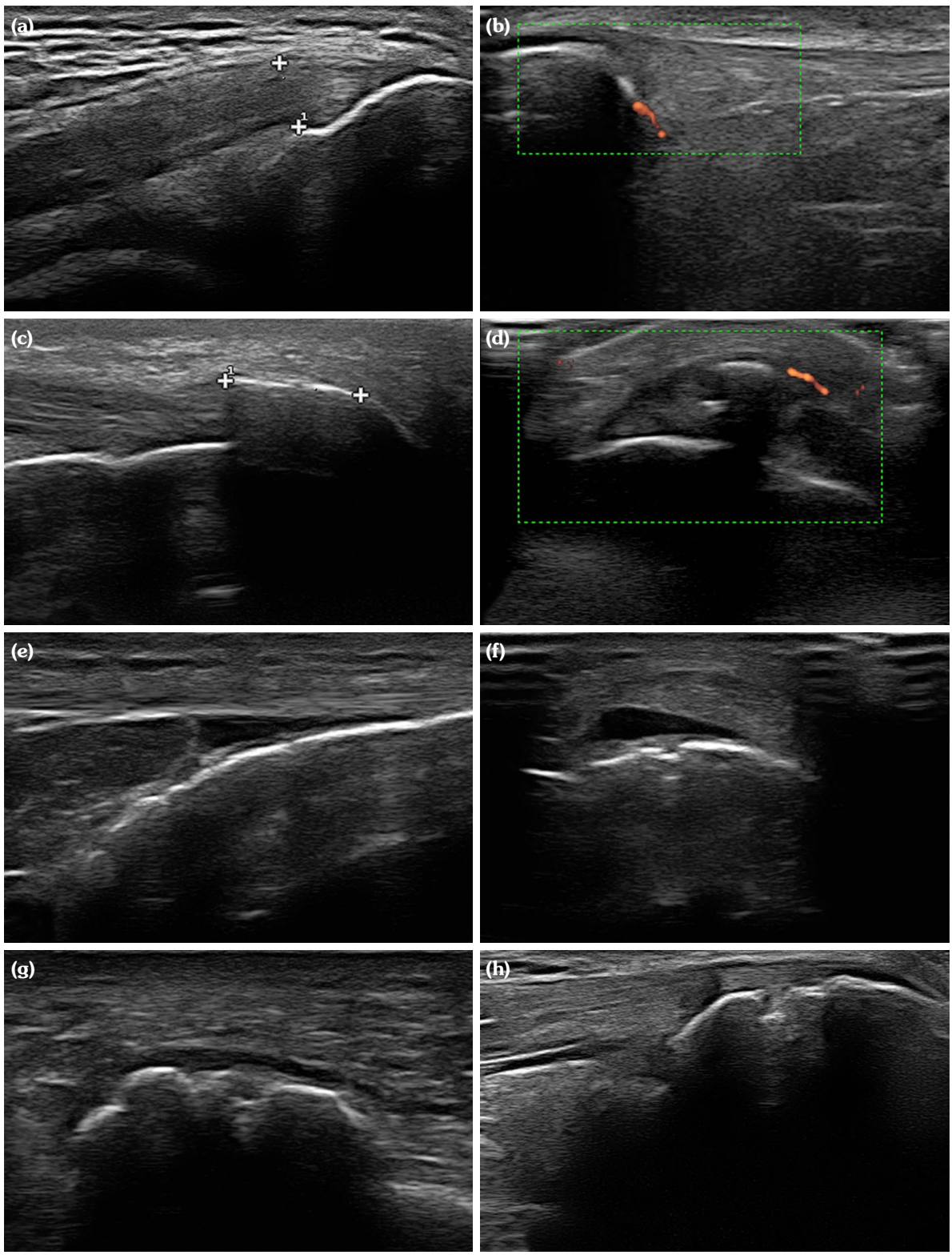


**Figure 1.** Gray-scale findings in ultrasound. In the distal patellar tendon **(a)**, hypoechogenicity, increase in thickness, and loss of fibrillar pattern are shown. In the proximal patellar tendon **(b)**, Doppler signal accompanying structural findings is noteworthy. Calcification are visible in longitudinal **(c)** and transverse **(d)** planes. Infrapatellar bursitis is present in longitudinal **(e)** and transverse **(f)** planes. Erosion are observed in the longitudinal **(g)** and transverse **(h)** planes.

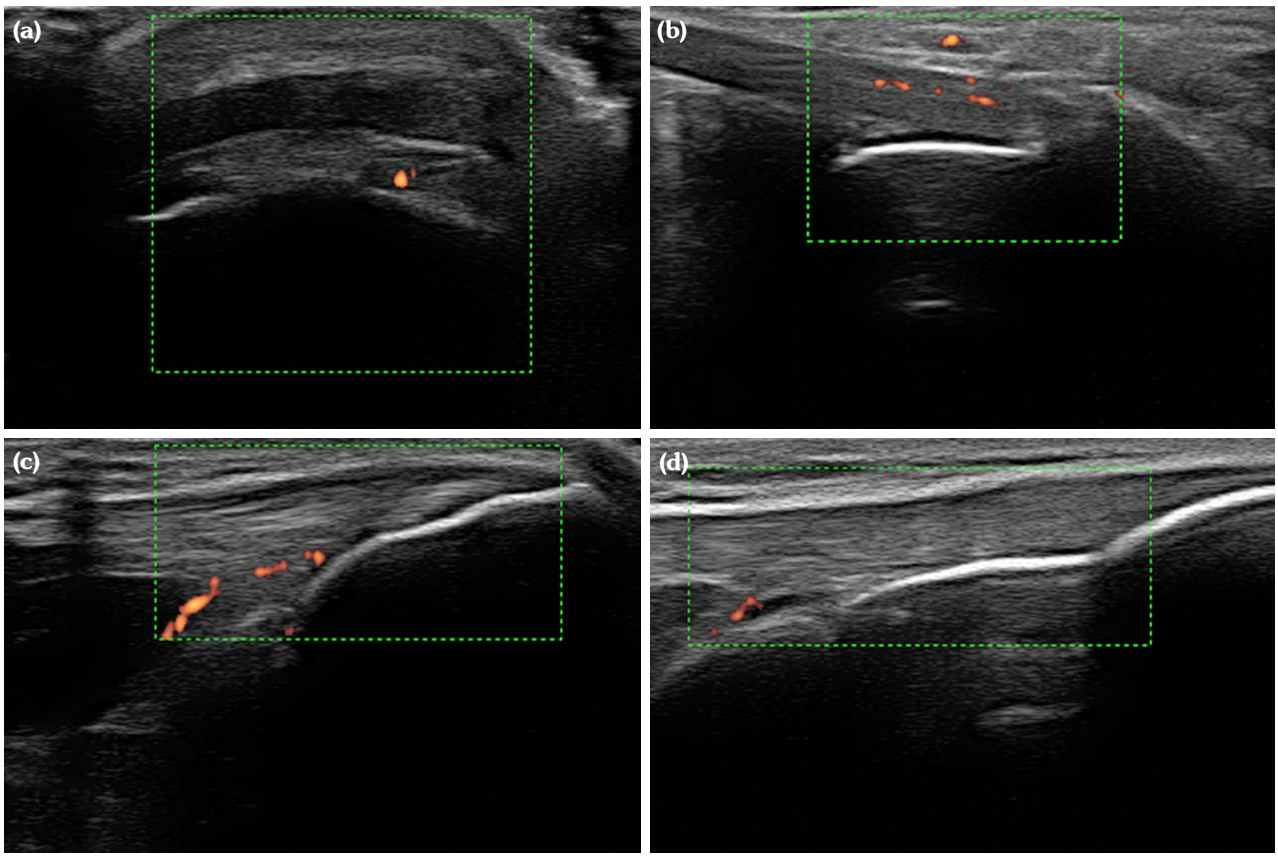


**Figure 2.** Ultrasonographic power Doppler findings. **(a, b)** Power Doppler signals are visible at transverse and longitudinal planes. **(c, d)** Signals are also present adjacent to tendon and bursa.

**Table 1.** The distribution of the clinical features

| | Mean±SD | Median | Min-Max |
|---|---|---|---|
| CRP (mg/L) | | 2.64 | 0.02-44 |
| ESR | | 8 | 1-52 |
| BASDAI | | 3.5 | 1-7.9 |
| ASDAS-CRP | 3.5±1.17 | | |
| ASDAS-ESR | | 2.2 | 0.9-5.3 |
| BASFI | | 2.5 | 1-7.6 |
| ASQoL | | 7 | 0-18 |
| Mental Component Score | 44.1±11.2 | | |
| Physical Component Score | 41.7±9.07 | | |

SD: Standard deviation; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire.

**Table 2.** Correlations of clinical parameters and clinical enthesitis scores

| | MASES | | SPARCC | |
|---|---|---|---|---|
| | Spearman correlation results | Correlation coefficient | Spearman correlation results | Correlation coefficient |
| CRP | 0.871 | –0.017 | 0.791 | –0.030 |
| ESR | 0.099 | 0.176 | 0.240 | 0.135 |
| BASDAI | **0.000** | **0.477** | **0.000** | **0.511** |
| ASDAS-CRP | **0.036** | **0.222** | **0.023** | **0.256** |
| ASDAS-ESR | **0.000** | **0.363** | **0.000** | **0.400** |
| BASFI | **0.000** | **0.384** | **0.000** | **0.396** |
| ASQoL | **0.000** | **0.511** | **0.000** | **0.498** |
| Physical Component Score | **0.000** | **–0.571** | **0.000** | **–0.495** |
| Mental Component Score | **0.012** | **–0.264** | **0.013** | **–0.280** |

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Score Patients.

**Table 3.** Correlations of clinical parameters, clinical enthesitis scores, and ultrasonographic enthesis score

| | MASEI | | MASEI-Damage | | MASEI-Inflammatory | | MASEI-Doppler | |
|---|---|---|---|---|---|---|---|---|
| CRP | **0.001*** | **0.348‡** | **0.028*** | **0.232‡** | **0.000*** | **0.362‡** | **0.019*** | **0.246‡** |
| ESR | **0.196*** | **0.138‡** | **0.057*** | **0.202‡** | **0.923*** | **0.010‡** | **0.533*** | **0.067‡** |
| BASDAI | 0.373* | 0.095‡ | 0.743* | 0.035‡ | 0.353* | 0.099‡ | 0.413* | 0.087‡ |
| ASDAS-CRP | **0.005*** | **0.294‡** | 0.084* | 0.294‡ | **0.003*** | **0.308‡** | 0.052* | 0.206‡ |
| ASDAS-ESR | 0.150* | 0.137‡ | 0.206* | 0.116‡ | 0.380* | 0.082‡ | 0.651* | 0.033‡ |
| BASFI | **0.021*** | **0.244‡** | **0.039*** | **0.217‡** | 0.054* | 0.204‡ | 0.188* | 0.140‡ |
| ASQoL | 0.278* | 0.116‡ | 0.395* | 0.091‡ | 0.318* | 0.106‡ | 0.063* | 0.197‡ |
| MCS | 0.802* | 0.027‡ | 0.671* | 0.045‡ | 0.829* | –0.023‡ | 0.352* | –0.099‡ |
| PCS | 0.202* | –0.136‡ | 0.598* | –0.056‡ | 0.137* | –0.158‡ | 0.066* | –0.194‡ |
| MASES | 0.903* | –0.013‡ | 0.658* | –0.047‡ | 0.854* | 0.020‡ | 0.088* | 0.181‡ |
| SPARCC | 0.241* | 0.133‡ | 0.246* | 0.132‡ | 0.357* | 0.105‡ | 0.085* | 0.195‡ |

* Spearman correlation p value is seen; ‡ Correlation coefficients seen parenthetically; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; MCS: Mental Component Score; PCS: Physical Component Score; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Score Patients; MASEI: Madrid Sonographic Enthesitis Index.

BASDAI, ASDAS-ESR, MASES, SPARCC, ASQoL, MCS, PCS, and sonographic scores ($p>0.05$). ASDAS-CRP was moderately correlated with MASEI ($r=0.294$) and MASEI-Inflammatory ($r=0.308$) scores ($p<0.01$). There was a moderate correlation between the BASFI score and MASEI ($r=0.244$) and MASEI-Damage ($r=0.217$; $p<0.05$). CRP was moderately correlated with all sonographic scores.

The patients were classified in accordance with cut-off values of CRP values and disease activity scales. The values of subgroups were compared to greyscale findings and sonographic scores (Table 4). The number of cases that had an ASDAS-CRP <1.3 and an ASDAS-ESR >3.5 was inadequate to investigate (two and six, respectively); therefore, the mentioned groups could not be compared. No significant

**Table 4.** Comparison of clinical and laboratory parameters and ultrasonography lesion and scores

| | ASDAS-ESR | | ASDAS-CRP | | BASDAI | CRP |
|---|---|---|---|---|---|---|
| | <1.3 *vs.* >1.3 | <2.1 *vs.* >2.1 | <2.1 *vs.* >2.1 | <3.5 *vs.* >3.5 | <4 *vs.* >4 | <5 *vs.* >5 |
| Number of patients | 14 *vs.* 76 | 43 *vs.* 47 | 12 *vs.* 78 | 45 *vs.* 45 | 59 *vs.* 31 | 60 *vs.* 30 |
| Structure* | 0.736 | 0.241 | 0.054 | **0.017** | 0.119 | 0.150 |
| Thickness* | 0.507 | 0.586 | **0.026** | 0.063 | 0.365 | 0.051 |
| Bursitis* | 0.077 | 0.103 | 0.302 | 0.368 | 0.172 | 0.661 |
| Erosion* | 0.707 | 0.660 | 0.281 | 0.153 | 0.183 | 0.524 |
| Calcification* | 0.963 | 0.895 | 0.077 | 0.810 | 0.387 | 0.388 |
| MASEI* | 0.475 | 0.711 | **0.009** | 0.052 | 0.350 | **0.020** |
| MASEI-I* | 0.478 | 0.947 | **0.009** | **0.039** | 0.247 | **0.011** |
| MASEI-D* | 0.967 | 0.621 | **0.036** | 0.275 | 0.855 | 0.167 |
| MASEI-PD* | 0.549 | 0.330 | 0.143 | 0.418 | 0.588 | 0.122 |

ASDAS: Ankylosing Spondylitis Disease Activity Score; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MASEI: Madrid Sonographic Enthesitis Index; MASEI-I: MASEI-Inflammatory; MASEI-D: MASEI-Damage; MASEI-PD: MASEI-power Doppler; * P values are given.

difference was found in comparisons made in both ASDAS and BASDAI subgroups. There were significant differences between the patients with ASDAS-CRP above and below 2.1 in thickness scores and in all US scores except for Doppler scores. There were significant differences in structure and MASEI-Inflammatory scores between the patients with ASDAS-CRP above and below 3.5. Those with CRP values >5 had significantly higher MASEI and MASEI-Inflammatory scores.

## DISCUSSION

Enthesitis is one of the most characteristic lesions of SpA and plays an important role in its pathogenesis. US is highly valuable in evaluating enthesis as an "organ complex."[24] It has been shown that the evaluation of entheses with US is helpful and reliable in diagnosing SpA.[25] In patients with SpA, it is complicated to evaluate clinical parameters such as disease activity and quality of life, and US may assist physicians to obtain accurate answers. In our study, we found that US detected 463 (42%) sites of enthesitis that were missed by clinical examination, and the US scores moderately correlated with the CRP level, ASDAS-CRP, and BASFI score compared to the disease-related parameters in patients with SpA.

Several studies have demonstrated that a US examination is better and more sensitive for detecting enthesitis than a clinical examination.[9,26,27] Ruta et al.[28] detected 60.8% (331/544 entheseal sites) asymptomatic enthesis on US examination. Our study findings are in agreement as we also detected a significant proportion of enthesitis (42%) missed during a clinical examination. Thus, there are evidently a considerable number of sites with subclinical enthesitis involvement that can be detected by US. These results indicate that US should be a part of the diagnostic evaluation in rheumatology departments, particularly for patients with SpA.

In our study, the most frequently affected entheses were the proximal patellar tendon and the Achilles tendon, while the least involved was the plantar aponeurosis. The reason for the lesser detection of plantar aponeurosis enthesitis may be the difficulty in US evaluation of this site. While other entheses are located superficially, excessive skin thickness and the heel fat pad make the location of the plantar aponeurosis deeper. Since the involvement of the lower extremities is more common in patients with SpA, the upper extremity entheses may be neglected clinically. Studies evaluating entheses by US examination initially only included the lower extremity sites; however, recent studies have started including the upper extremity sites for a more thorough

enthesis evaluation.[9,10] Our study also highlighted a significant involvement in the distal triceps tendon (47%). It is recommended that upper extremity sites should not be ignored in clinical and radiological evaluation of entheses.

In the present study, clinical enthesitis evaluation was performed with both MASES, which mostly evaluates axial entheses, and SPARCC, which evaluates only peripheral entheses. Clinical enthesitis scores have been found to be correlated with clinical parameters in previous studies.[29-31] In the present study, it was found that MASES and SPARCC were correlated with other clinical parameters, but not with acute phase reactants. In previous studies, no correlation was found between acute phase reactants and clinical enthesitis scores.[6,26] The probable reason for the correlation between clinical enthesitis scores and clinical parameters is that these evaluations are subjective and based on the patient's response.[16] Peripheral entheses can be easily evaluated on US, and SPARCC has been used to compare clinical and sonographic evaluation of enthesitis. In previous studies, both BUSES and lower extremity enthesis scores were found to be correlated with SPARCC.[16,17] Since the sonographic evaluation of axial entheses is relatively troublesome, it was wondered whether the ultrasonographic evaluation of peripheral entheses would be associated with a clinical axial enthesitis score. If the association was detected, only US peripheral evaluation might have been adequate to show also axial enthesitis. However, no correlation was found between clinical and ultrasonographic enthesitis scores in the present study. Although it was found to be correlated with lower extremity enthesitis score and MASEI,[16,32] we believe that sonographic peripheral enthesis evaluation may not reflect axial enthesitis. Only bilateral Achilles entheses, which are included in MASES, are a part of MASEI. As far as we know, no sonography score for the evaluation of axial entheses has been developed yet. It is believed that adding axial enthesis, such as costochondral enthesis, may provide a better correlation with axial entheses.

Although the values of both CRP level and ESR are elevated in patients with SpA, the CRP levels are more indicative. Elevated CRP levels have been found to be associated with increased disease activity, good response to treatment, and radiological progression.[33-35] In our study, we did find that CRP levels moderately correlated with all the US scores. Studies evaluating the correlation of the US scores with CRP levels and ESR have shown variable results. Some studies have failed to show any correlation;[9,12,17,18,36,37] however, in agreement with our study, few studies have found a relationship between the US scores and CRP levels.[38-40] CRP is an objective marker of active disease in SpA, and a moderate correlation between the US scores and CRP levels may indicate the role of US score as a potential marker of active disease.

Measuring "real disease state" is generally difficult, particularly in SpA. Although enthesitis plays an important role in its pathogenesis, it is frequently ignored in the evaluation of real disease states. In our study, we evaluated enthesitis in SpA patients and did not find any significant relationship between the US enthesitis scores and disease activity scales other than ASDAS-CRP. ASDAS-CRP was moderately correlated with the MASEI and MASEI-Inflammatory scores (correlation coefficients of 0.294 and 0.308, respectively). Most of the previous studies have failed to show any correlation between US and BASDAI,[12,17,36,38,39,41,42] besides a few studies.[18,19,40] Although these studies may suggest that US may be insufficient for disease activity evaluation, some authors have also argued that the current disease activity scales may be inadequate in expressing the real disease state.[43,44] BASDAI is a subjective measure of symptoms and is based on patients' responses on a self-administered questionnaire; hence, the score may be affected by other concurrent pain-causing illnesses, such as chronic pain and fibromyalgia. We speculated that the reason for the correlation between the US scores and ASDAS-CRP in our study is that it includes the objective inflammatory scale and CRP level. The other disease activity scales included in the study are subjective in nature and might not represent the true disease activity. We recommend that new SpA disease activity scales, perhaps incorporating US scores, should be developed.

In our study, we also investigated which ultrasonographic lesion or score was associated with subgroups of disease activity scores and CRP. Falcao et al.[15] aimed to find out which elemental lesion and the score of Achilles enthesis was associated with cut-off values of

ASDAS, BASDAI, and CRP. They did find that the Doppler signal and structure of the Achilles tendon were significantly associated with higher CRP. In our study, there was no association between higher CRP values and elemental lesions. Patients with higher CRP (>5) had higher MASEI and MASEI-Inflammatory scores but not higher MASEI-Doppler scores in the present study. Our results may suggest that evaluating only Doppler signals is insufficient to reveal real inflammation. Elementary lesions, such as structural change, thickness, and accompanying bursitis, that give MASEI-Inflammatory scores should be evaluated as a whole since none of them were found to be correlated with CRP elevation alone. When the disease activity scores were compared according to cut-off values, no difference was found between the sonographic lesions and scores in the BASDAI and ASDAS-ESR subgroups. Falcao et al.[15] did find that patients with very high disease activity (ASDAS-CRP >3.5), and high disease activity (BASDAI >4) had a significantly higher Achilles US score. None of the elementary lesions in Achilles enthesis were associated with BASDAI or ASDAS.[15] In the ASDAS-CRP subgroups, the thickness scores were found to be significantly higher in patients who had ASDAS-CRP >2.1, and the structure scores were found to be significantly higher in those with very high disease activity (ASDAS-CRP >3.5). Sonography scores except for MASEI Doppler were detected to be significantly higher in patients with ASDAS-CRP >2.1. However, only the MASEI-Inflammatory score was significantly different between patients with and without very high disease activity. Based on these results, it could be suggested that the MASEI-Inflammatory score may be sufficient and a time saver to evaluate real-time disease activity.

Spondyloarthritis is a disease that can cause significant functional loss with joint movement limitation and stiffness. BASFI is often used to evaluate the loss of function in SpA. We found a moderate correlation between the BASFI and MASEI and MASEI-Damage scores. No study other than Milutinovic et al.'s[18] study, evaluating BASFI and various peripheral enthesis US indices, has reported any correlation between these parameters.[12,17,36,41] The reason for functional loss in SpA is mainly the involvement of the spine and axial joints. Since we can only evaluate peripheral enthesis sites via US, it was expected that US scores would moderately correlate with functionality. The US evaluation of the sacroiliac joint, root joints (shoulder and hip joints), and perhaps even the paravertebral regions may help us obtain a reliable score that correlates with functionality.

Studies that evaluate the relation between the quality of life scales (ASQoL or SF-12) and US scores are limited. In our study, we did not find any correlation between the quality of life scales and US scores. Similar to our results, Falcao et al.[41] found no correlation between US findings and ASQoL. Hamdi et al.[16] found that Doppler scores were correlated with ASQoL. Suleyman et al.[19] found a moderately significant correlation between ASQoL and MASEI. Nonetheless, further studies are needed to provide adequate information on this subject.

OMERACT defines enthesitis as a "hypoechoic and/or thickened insertion of the enthesis close to the bone (within 2 mm from the bony cortex) which exhibits Doppler signal if active and that may show erosions, enthesophytes/calcifications as a sign of structural damage." In the present study, enthesitis was identified as the presence of one of the elemental lesions that met the definition regardless of the US score. The reliability of the OMERACT US Task Force's definition of enthesitis was investigated on a web-based using images and videos.[45] The results underlined that bone erosions, power Doppler signal, and enthesophytes/calcifications showed good reliability, but the reliability of thickness and hypoechogenicity was low. The normal thickness changes with age, sex, and body mass index, and the evaluation of thickness may be affected by position, location, and the type of enthesis; consequently, the threshold to name a tendon as thickened is not clear.[46] More focal and less distinct regions of hypoechogenicity may be confusing. The definitions of the lesions or enthesitis need to be clarified. The absence of a threshold for enthesitis in any sonographic score, including MASEI, may lead us to overdiagnose. Due to the absence of a gold standard imaging technique to detect enthesitis, it is uncertain which sonographic score defines enthesitis.

In our study, the evaluation of enthesitis was performed only by US, which is insufficient to assess bone marrow edema, a part of enthesitis pathophysiology. MRI may be the best modality to evaluate bone marrow edema but makes simultaneous and multiple joint evaluations challenging. It has been reported that the US and MRI findings provide dissimilar information, making it challenging to determine which of these constitutes the standard method in the enthesitis evaluation.[47] In the present study, the MASEI scoring system, widely used in US examinations, was utilized. However, MASEI includes evaluation of the plantar aponeurosis, which is difficult to evaluate, and a single upper limb site (the distal triceps tendon) for enthesis evaluation. Belgrade Ultrasound Enthesis Score, developed later than MASEI, also includes plantar aponeurosis and a single upper extremity site (common extensor tendon) for enthesis evaluation. Additionally, its sensitivity and specificity are lower than those of the MASEI scoring system.[14] We believed that new sonographic scoring systems need to evaluate more than one upper extremity entheses.

There are some limitations to this study. One of the limitations of our study is the evaluation of peripheral enthesis sites alone. We recommend including joint evaluation, particularly the sacroiliac joint, and axial enthesis sites, such as paravertebral and costochondral regions, in the US examination in future studies. Nonetheless, a scoring system examining all the aspects of SpA has not been developed yet and is limited to scores based on enthesitis evaluation. In the present study, only MASEI was compared with the clinical parameters. Other sonographic scores could also be utilized, and it could be determined which sonographic score is better at revealing the real disease state. Another limitation of our study is that the presence of concomitant fibromyalgia was not questioned. Fibromyalgia significantly affects the results of the scales based on the subjective complaints of the person. In studies in which the presence of fibromyalgia is an exclusion criterion, ultrasonographic enthesitis scores may be correlated with other clinical parameters, such as quality of life and BASDAI. Finally, the lack of sample size is also a limitation of our study.

In conclusion, it is well known that US is a better and more sensitive method of evaluation of enthesitis than clinical examination. US assessment should be a part of disease evaluation in SpA patients. The association of US scores with CRP levels and ASDAS-CRP may indicate that US is sensitive to inflammation. The MASEI score moderately correlates with functionality but not with quality of life. New disease activity scores with more objective markers are needed in SpA, incorporating invaluable ultrasonographic evaluation parameters.

**Ethics Committee Approval:** The study protocol was approved by the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (date: 22.09.2016, no: 83045809-604.01.02). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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