# The Association of Achilles Sonoelastography Findings with Disease Activity, Functional Status and Enthesitis Index in Patients with Axial Spondyloarthritis

## Die Assoziation von Achilles-Sonoelastographie-Befunden mit Krankheitsaktivität, Funktionsstatus und Enthesitis-Index bei Patienten mit axialer Spondyloarthritis

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Key words

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## ABSTRACT

**Background** Sonoelastography (SE) is a new ultrasound (US)-based technique able to assess tissue elasticity. Using conventional US, it is sometimes difficult or even impossible to distinguish pathologic tissue because it often presents with the same echogenicity as the surrounding healthy tissue. This study aimed to evaluate SE findings in Achilles tendons of patients with axial spondyloarthritis (axSpA) and to assess how these findings are associated with disease-related parameters.

**Material and Methods** Sixty-four consecutive patients (37 men, 27 women; mean age 39.7 years; range 20–65 years) with axSpA and 30 sex and age-matched healthy controls were enrolled in the study. Disease activity was evaluated using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), whereas functional capacity was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index were recorded. All participants underwent an SE examination of the Achilles tendon and measurement of the strain index (SI).

**Results** The mean right and left SI were significantly higher in axSpA patients than in controls (2.96 ± 0.94 vs. 1.90 ± 0.45; $p < 0.001$; 2.95 ± 0.95 vs. 1.92 ± 0.48, $p < 0.001$, respectively). In axSpA patients, both right and left SI were significantly correlated with the BASDAI, BASFI and SPARCC enthesitis indices, but not with ESR or CRP.

**Conclusion** AxSpA patients had an increased SI compared with healthy subjects and these values were associated with disease activity, functional capacity and the enthesitis index. SE may be a useful tool for the evaluation of Achilles tendons in patients with axSpA.

## ZUSAMMENFASSUNG

**Hintergrund** Die Sonoelastographie (SE) ist ein neuer Ultraschall (US)-basiertes Verfahren zur Beurteilung der Gewebeelastizität. Mit konventionellem US ist es manchmal schwierig oder sogar unmöglich, pathologisches Gewebe zu unterscheiden, da es oft die gleiche Echogenität aufweist wie das umgebende gesunde Gewebe. Das Ziel dieser Studie war es, diese Befunde der Achillessehne bei axialer Spondyloarthri-

tis (ax-SpA) zu bewerten und ihren Zusammenhang mit krankheitsbezogenen Parametern zu beurteilen.

**Material und Methoden** 64 aufeinanderfolgende Patienten (37 Männer, 27 Frauen; Durchschnittsalter 39,7 Jahre; Bereich 20–65 Jahre) mit ax-SpA und 30 geschlechts- und altersgleichen gesunden Kontrollpersonen wurden in die Studie aufgenommen. Die Krankheitsaktivität wurde unter Verwendung des Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) bewertet, während die funktionelle Kapazität unter Verwendung des Bath Ankylosing Spondylitis Functional Index (BASFI) bewertet wurde. Erythrozytensedimentationsrate (ESR), C-reaktives Protein (CRP), Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis-Index wurden aufgezeichnet. Bei allen Teilnehmern wurde eine SE-Untersuchung der Achillessehne durchgeführt und der Strain index (SI) gemessen.

**Ergebnisse** Der mittlere rechte und linke SI war bei ax-SpA Patienten signifikant höher als bei den Kontrollen (2,96 ± 0,94 vs 1,90 ± 0,45, P <0,001; 2,95 ± 0,95 vs 1,92 ± 0,48, P < 0,001, jeweils). Bei ax-SpA Patienten waren sowohl die rechte als auch die linke SI signifikant mit dem BASDAI, dem BASFI und dem SPARCC-Enthesitis-Index korreliert, nicht aber mit ESR oder CRP.

**Schlussfolgerung** Ax-SpA-Patienten hatten im Vergleich zu gesunden Probanden einen erhöhten SI und diese Werte waren mit Krankheitsaktivität, funktioneller Kapazität und Enthesitis-Index assoziiert. SE kann ein nützliches Hilfsmittel für die Bewertung der Achillessehne bei ax-SpA sein.

## Introduction

The term spondyloarthritis (SpA) represents a condition characterised by a broad spectrum of clinical manifestations, laboratory abnormalities and imaging features; in particular, SpA is an inflammatory condition in which both peripheral and axial joints might be affected [1].

Enthesitis, that is the inflammation of insertions of tendons, ligaments and capsules into the bone, is the characteristic sign of ankylosing spondylitis (AS) and related pathologies, which are commanly regrouped as axial(ax)-SpA [2]. Clinical assessment of enthesitis is performed by eliciting tenderness at the affected entheseal site. Clinical diagnosis of enthesitis, however, is neither sensitive nor specific and it often relies on typical abnormalities seen in imaging studies [3]. Considering entheses involvement as critical in ax-SpA, it would be useful to develop reliable tools to assess enthesitis in order to improve the management of patients. Ultrasound (US) has a greater sensitivity than clinical examination and other imaging techniques for the detection of peripheral involvement of ax-SpA [4].

Sonoelastography (SE) is a method that can assess the mechanical properties of soft tissue qualitatively and quantitatively through US imaging techniques [5]. SE has demonstrated feasibility in the diagnosis of cancers of the breast and liver, and in some preliminary work, in several musculoskeletal disorders. It is based on the principles that the compression of soft tissue produces strain that is greater in tissues that are softer and more elastic than in harder, more rigid tissues. Pathological and healthy tissues can present with similar echogenicity and morphology on conventional US. However, alterations in tissue elasticity often occur with degeneration or other pathological changes that involve the sof tissues [6].

The clinical utility of SE for the diagnosis of common tendinopathies and plantar fasciitis has been reported previously in the literature [7–9]. The SE findings of Achilles tendon in patients with AS compare to healthy subjects have been reported only Turan et al. [10]. However, to the best of our knowledge, there is no report evaluating the association of strain index (SI) with disease related parameters in patients with ax-SpA. The aims of this study were to assess semiquantative SI provided during the SE examination compared to healthy controls and to evaluate the association of SI with spinal pain, disease activity, functional status, or enthesitis index in patients with ax-SpA.

## Material and Methods

This prospective observational cross-sectional study was approved by the local ethics committee of our institution and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to the study.

Sixty-four ax-SpA patients without clinical symptom of enthesitis, who was admitted to outpatient clinic of physical therapy and rehabilitation between September 2015 and June 2016, were included in the study. All patients fulfilled the Assessment of Spondyloarthritis International Society (ASAS) classification criteria [11] for nonradigraphic ax-SpA and/or Modified New York diagnosis criteria for AS [12]. None of the patients had achilles tendon enthesitis within the 3 months prior to the study and psoriasis vulgaris. Patients with a known history of metabolic or endocrine diseases and sports-related or traumatic injuries were excluded from the study. A total of 30 volunteers who did not have any tendon complaint or systemic inflammatory disorders that might influenced the results were matched with the study subjects according to age and gender, and were included as controls.

### Clinical evaluation

The demographic and clinical characteristics of all participants were recorded. Disease activity was measured via the self-administered 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (0: no disease activity, 10: the highest disease activity) [13]. Patients with a BASDAI ≥ 4 were defined as having active disease. Functional capacity was measured via the self-administered 10-question Bath Ankylosing Spondylitis Functional Index (BASFI) (0: lowest activity, 10: the highest activity) [14]. Weight and height were measured and body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Spinal pain intensity was evaluated visual analog scale (VAS).

The Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index was used to assess the severity of enthesitis [15].

This index was calculated by the evaluation of following 16 enthesitis sites: the greater trochanter right/left (R/L), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L) and the supraspinatus insertion (R/L). Tenderness at each site was quantified on a dichotomous basis: 0 = non-tender and 1 = tender.

### Sonoelastography

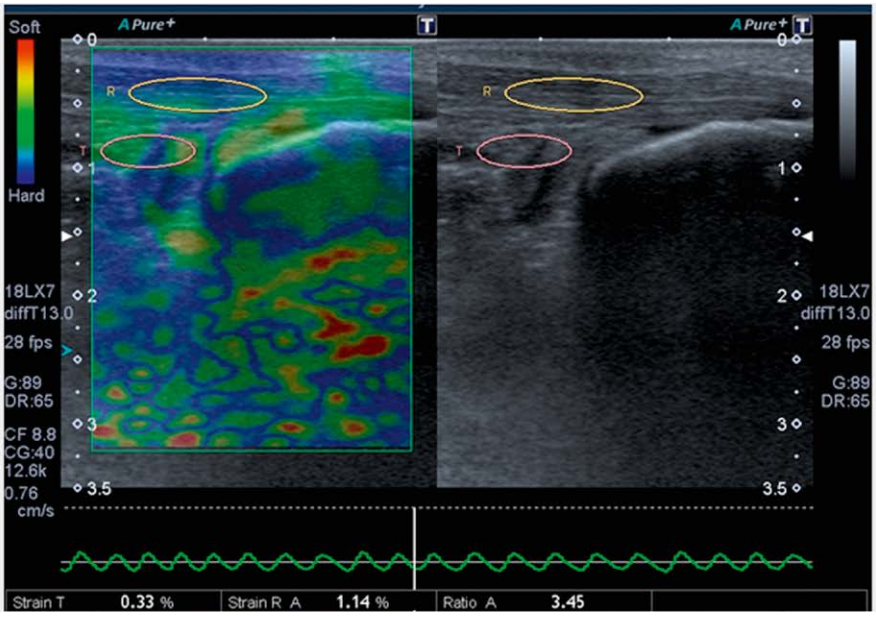
Toshiba (Toshiba Medical Systems Corporation, Otawara, Japan) Aplio 500 US device and 12-MHz linear probe was used for SE examinations. The Achilles tendons were examined axially and longitudinally by a radiologist who was experienced in musculoskeletal US and blinded to the clinical data while the patient was lying in the prone position with the foot hanging over the edge of the examination table in a relaxed position. During US examination, the anterior-posterior thickness and width of the tendon was determined by measuring the diameter in a transverse view at the level of the medial malleolus. SE images of the tendon were obtained in the longitudinal plane in the same position. The transducer was perpendicular to the tendon in order to avoid anisotropy. The compression and decompression were applied to the area of examination by the probe. Light repetitive compressions were performed to obtain elastography images using a free-hand technique. Repetitive compressions cause sinusoidal waves. If the pressure of compression and decompression is periodic and regular, symmetric sinusoidal wave can be obtained. If the symmetric sinusoidal wave could not be obtained, compression and decompression should be performed again. The compression phase was observed above the baseline and the decompression phase was observed below the baseline. The measurements were performed during the decompression phase. Region of interest (ROI) was placed on the Achilles tendon and adjacent Kager's fat pad. The software calculates the SI (tendon strain/Kager's fat pad strain) based on the displacement using the ratio of the lesion and adjacent Kager's fat pad. All patients scanned by the same sonographer. The SE imaging of ax-SpA patient is demonstrated in ▶ **Fig. 1**.

### Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22 > , for Windows (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentage. Compliance of the variables with normal distribution was assessed by the Kolmogorov-Smirnov test. Inter-group analyses were performed with Student's t-test for normally distributed variables and the Mann-Whitney U test for non-parametric variables. The Chi-square test was used for the analysis of categorical variables. To determine the correlation between the variables, Spearman's rank or Pearson's correlation analyses were performed according to the distribution of the data. A P value of $< 0.05$ was considered as statistically significant.

## Results

The demographic and clinical characteristics of the patients are presented in ▶ **Table 1**. No significant difference was observed between the groups in terms of age, gender, and BMI (age: 39.7 ± 10.8 vs. 37.2 ± 5.8 years, P = 0.289; female/male: 27/37 vs. 15/15, P = 0.522; BMI: 28.1 ± 4.6 vs. 27.8 ± 3.8, P = 0.184, respectively). The mean disease duration in patients with ax-SpA was 5.11 ± 5.0 years. The mean BASDAI and BASFI scores were 3.7 ± 2.2, 3.2 ± 2.5 respectively. HLA-B27 positivity was observed in 65.6 % of the patients with ax-SpA. In addition, 21 patients were receiving non-steroidal




▶ **Fig. 1** Sonoelastography image of the Achilles tendon of a 35 years old male patient with axial spondyloarthritis. The monitor is divided into two windows. The right windowis longitudinal gray-scale ultrasound image, left window is colour-coded sonoelastography image.Below these windows is the sinusoidal wave of compression and decompression.The strain index (tendon strain/Kager's fat strain) was calculated as 3.45.

anti-inflammatory drugs (NSAIDs) and 43 patients were receiving biological agents. The biological agents used consisted of adalimumab in 19 patients, etanercept in 12 patients, infliximab in 9 patients, and golimumab in 3 patients.

▶ **Table 1** Demographic and clinical characteristics of patients with axial spondyloarthritis.

| ax-SpA patients | (n = 64) |
|---|---|
| Age (years), mean ± SD | 39.7 ± 10.8 |
| Sex (Female/male) n (%) | 27/37 (42.2/57.8) |
| BMI (kg/m²), mean ± SD | 28.1 ± 4.6 |
| Disease duration (years), mean ± SD | 5.11 ± 5.0 |
| History of peripheral arthritis n (%) | 13 (20.3) |
| History of uveitis n (%) | 14 (21.9) |
| HLA-B27 positivity n (%) | 42 (65.6) |
| ESR mm/h, mean ± SD | 18.8 ± 13.6 |
| CRP mg/dL, mean ± SD | 0.82 ± 0.9 |
| BASDAI, mean ± SD | 3.7 ± 2.2 |
| BASFI, mean ± SD | 3.2 ± 2.5 |
| SPARCC, mean ± SD | 2.5 ± 4.1 |
| **Medication** n (%) | |
| NSAID | 21 (32.81) |
| ETN | 12 (18.8) |
| INF | 9 (14) |
| ADA | 19 (29.69) |
| GOL | 3 (4.69) |

*ax-SpA* axial spondyloarthritis, *SD* Standard deviation, *BMI* body mass index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, SPARCC Spondyloarthritis Research Consortium of Canada, *NSAID* non-steroidal anti-inflammatory drugs, *ETN* etanercept, *INF* infliximab, *ADA* adalimumab, *GOL* golimumab.

The US examination findings of the patients and controls are presented in ▶ **Table 2**. Although the mean anterior-posterior thickness and width of left Achilles tendon did not significantly differ between the patients and the controls (4.8 ± 2.1 vs. 4.4 ± 0.5 mm, P = 0.184; 15.9 ± 2.5 vs. 15.1 ± 1.2 mm, P = 0.088, respectively), the mean anterior-posterior thickness and width of right Achilles tendon were significantly higher in ax-SpA patients than in the controls (5.02 ± 2.6 vs. 4.44 ± 0.46 mm, P = 0.033; 16.3 ± 2.7 vs 15.3 ± 1.1 mm, P = 0.042). Ax-SpA patients had significantly higher right and left SI than the controls (2.96 ± 0.94 vs. 1.90 ± 0.45, P < 0.001; 2.95 ± 0.95 vs. 1.92 ± 0.48, P < 0.001, respectively). When the patients were classified into two subgroups according to the types of medication they received (NSAIDs: 21 patients, biological agents: 43 patients), there were no significant differences between these groups in terms of BASFI, ESR, CRP, and SI (P > 0.05 for all). However, the mean BASDAI score was significantly higher in the NSAIDs group than in the biological agent group (4.7 ± 2.1 vs. 3.3 ± 2.2, P = 0.02). There was no significant difference in righ and left Achilles SI between male (n = 37) and female (n = 27) ax-SpA patients (2.93 ± 1.01 vs 2.99 ± 0.84, p = 0.759; 2.92 ± 1.02 vs 2.98 ± 0.86, P = 0.807, respectively).

The correlations of SI with disease related parameters are presented in ▶ **Table 3**. In ax-SpA patients, SI of right and left Achilles tendons showed significantly positive correlations with spinal VAS, BASDAI, BASFI, and SPARCC enthesitis index (for right side; P = 0.016, r = 0.300; P = 0.001, r = 0.408; P = 0.001, r = 0.401; P = 0.002, r = 0.378, respectively; for left side; P = 0.004, r = 0.357; P < 0.001, r = 0.452; P < 0.001, r = 0.451; P = 0.007, r = 0.336, respectively). However, there were no significant correlation between SI and age, sex, ESR, CRP, BMI, or mean disease duration (for all P > 0.05).

## Discussion

Our study results demonstrated that ax-SpA patients had higher SI of Achilles tendon compared to healthy subjects and SI was significantly associated with spinal pain score, disease activity, functional status, and enthesitis index.

One difficulty faced by clinicians is the inability to establish early diagnosis due to poor specifity symptoms of ax-SpA [3]. With the

▶ **Table 2** The ultrasonography and sonoelastography examination findings of the patients and controls.

| | ax-SpA patients (n = 64) | Controls (n = 30) | P value |
|---|---|---|---|
| Age (years), mean ± SD | 39.7 ± 10.8 | 37.2 ± 5.8 | P = 0.289 |
| Sex (Female/male) n (%) | 27/37 (42.2/57.8) | 15/15 (50/50) | P = 0.522 |
| BMI (kg/m²), mean ± SD | 28.1 ± 4.6 | 27.8 ± 3.8 | P = 0.184 |
| Left AP thickness (mm), mean ± SD | 4.8 ± 2.1 | 4.4 ± 0.5 | P = 0.184 |
| Right AP thickness (mm), mean ± SD | 5.02 ± 2.6 | 4.44 ± 0.46 | P = 0.033 |
| Left width (mm), mean ± SD | 15.9 ± 2.5 | 15.1 ± 1.2 | P = 0.088 |
| Right width (mm), mean ± SD | 16.3 ± 2.7 | 15.3 ± 1.1 | P = 0.042 |
| Left strain index, mean ± SD | 2.95 ± 0.95 | 1.92 ± 0.48 | P < 0.001 |
| Right strain index, mean ± SD | 2.96 ± 0.94 | 1.90 ± 0.45 | P < 0.001 |

*ax-SpA* axialspondyloarthritis, *SD* Standard deviation, *BMI* body mass index, *AP* anterior-posterior.

▶ **Table 3** The correlation of strain index with disease related parameters.

| | Right Strain index | | Left Strain index | |
|---|---|---|---|---|
| | r | P value | r | P value |
| Age (years) | 0.078 | 0.538 | 0.093 | 0.466 |
| BMI (kg/m²) | 0.197 | 0.119 | 0.174 | 0.169 |
| Disease duration (years) | 0.134 | 0.291 | 0.133 | 0.296 |
| BASDAI | 0.408 | 0.001 | 0.452 | <0.001 |
| BASFI | 0.401 | 0.001 | 0.451 | <0.001 |
| sVAS | 0.300 | 0.016 | 0.357 | 0.004 |
| SPARCC | 0.378 | 0.002 | 0.336 | 0.007 |
| CRP (mg/dL) | 0.027 | 0.831 | 0.148 | 0.243 |
| ESR | 0.049 | 0.700 | 0.029 | 0.823 |

*BMI* body mass index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *sVAS* spinal visual analog scale, *SPARCC* Spondyloarthritis Research Consortium of Canada, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate.

introduction of novel effective therapies for ax-SpA that can reduce disease activity and improve quality of life, early correct diagnosis, and classification of patients presenting with symptoms suggestive of ax-SpA becomes crucial. Peripheral enthesitis, an important feature that can be observed in all forms of ax-SpA, usually manifests as isolated pain or tenderness at physical examination [16]. The reliability and accuracy of the clinical examination to assess entheses are not satisfactory, so imaging technigues have potential use in their objective assessment [17]. X-rays and computed tomograpy only detect and evaluate structural bone changes that correspond to past episodes of activity or injury and do not inform us of the presence of inflammatory activity in enthesis at the time of examination. Thus, more sensitive methods, such as US and magnetic resonance imaging (MRI) are often used. However, MRI is limited by its costs, accessibility, inconvenience to the patient, and the inability to image multiple entheseal sites simultaneously [3].

Sonoelastography is a relatively new US-based imaging technique that provides information on the elastic properties and stiffness of various tissues and lesions [18]. SE is based on the principle that tissue displacement in response to external compression produces strain within the tissue and the strain is lower in harder tissue than in softer tissue. This strain information can be presented either as a visual map (gray scale or color coded, depending on the user's preference) or semiquantitative measurement of strain ratio [19]. To date, several clinical studies applying SE in differential diagnosis of breast, thyroid, and prostat cancers and characterization of lymph node have been reported in literature previously [20–24]. It has been demonstrated that healthy Achilles tendons showed mainly hard structered pattern on SE; however, mild softening was found in 12.1 % of the tendons in the study by Zordo et al. [25].

Using conventional US, it is sometimes difficult or even imposible to distinguish pathological changes from surrounding healthy tissue, as they often present with the same echogenicity [26]. In such cases, SE could detect or differentiate abnormalities, which are thought to correspond to sub-clinical changes not yet evident on B-mode evaluation, providing suplementary information useful for diagnostic, therapeutic (US guided procedures) and follow-up purposes [9]. In the study by Klauser et al., it has been demonstrated that SE showed a better histologic agreement when compared with conventional B-mode US in Achilles tendon of cadavers [27]. Galletti et al. found that a case series of patients with negative or inconclusive US exam where SE allowed to show tendon pathologies in an observational study evaluating the value of SE in the diagnosis of tendinopathies [9]. In an another study, it has been also demonstrated that the diagnostic accuracy of B-mode US, SE and color Doppler US in confirming clinically symtomatic Achilles tendinopathy was 94.7 %, 97.8 %, and 82.5 % respectively [19].

In the present study, the stiffness of Achilles tendon in patients with ax-SpA was evaluated by the measurement of SI. SI calculates the strain differences between the two user-defined areas in an elastogram, hence providing more objective estimation of the tissue strain properties compared to color-coded images of the SE method [7]. The SI can be used as a comparative index among different subjects rather than as an absolute strain measurement [28]. Although the patient with symptomatic Achilles tendons were excluded from the present study, there were statistically significant differences in SI between patients and healthy controls. Also, significant correlations of SI with disease activity, functional status, enthesitis index, and spinal VAS score were demonstrated in this ax-SpA population. To the best of our knowledge, no study in the literature has investigated the association of SI with such disease related parameters in ax-SpA patients. But, there was no correlation between SI and age, sex, disease duration, ESR, or CRP in patients with ax-SpA. However, it is known that elevated CRP levels and ESR are frequently absent in AS [29]. In the study by Turan et al., B mode and SE findings had moderate to good correlation in the assessment of Achilles tendon abnormalities and SE abnormalities were more common in the distal third of the Achilles tendons in the AS group when compared to the controls. However, the association of SE findings with disease activity, enthesitis index, or functional status were not evaluated in that study. Recently, Zardi et al. have demonstrated no diffences in the Achilles tendon stiffness ratio between AS patients and controls in their study [30]. But, only 11 AS patients and 13 controls with an older mean age were included in that study. Also, they did not report any information about the relationship of stiffness ratio with disease related clinical parameters in that study. We also assessed the effect of biological treatment on SE findings, but we found no significant differences between the patients on NSAID and on biological treatment.

However, because of the cross-sectional study design, we could not evaluate the SE findings before and after biological treatment. The study by Ooi et al. has also demonstrated that patients with symptomatic Achilles tendinopathy had significantly higher SI than the healthy volunteers [19].

The present study has some limitations. Firstly, we did not asses the presence of calcaneal spur and the level of physical activity of participants which may have affected the SE findings. Also, the pa-

tients with symptomatic Achilles tendon were excluded from the study. So, we could not compare SI between patients with symptomatic and asymptomatic Achilles tendons. In addition, power doppler USG was not performed to confirm SE findings. Finally, the patients were on various drug treatments and the results could have been affected by these treatment regimes.

In conclusion, SE may be a useful tool for the evaluation of subclinical enthesitis in patients with ax-SpA in clinical practice. However, prospective longitudinal studies with sufficiently large samples are required to characterize the specifity and the prognostic value of SE in patients with ax-SpA.

## Conflict of Interest

The authors declare that they have no conflict of interest and financial support.

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