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Enthesitis and Foot Disability in Patients with Ankylosing Spondylitis

Ankilozan Spondilitli Hastalarda Entezit ve Ayak Dizabilitesi

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ABSTRACT Objective: Enthesitis is a primary clinical feature of ankylosing spondylitis (AS). Lower extremity enthesopathy may cause foot pain and functional disability. The aims of this study were to evaluate enthesitis by using musculoskeletal ultrasonography (US) and foot disability in patients with AS. **Material and Methods:** One hundred and one patients with AS and 42 healthy controls were examined for enthesal site abnormalities by using gray-scale US. The findings were assessed by using the Glasgow Ultrasound Enthesitis Scoring System (GUESS). The Foot Function Index (FFI), which comprised of pain, disability, and activity limitation subscales, was measured in all the patients with AS and healthy controls for assessment of foot function. Disease activity and functional status were assessed using the Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI) and Bath AS Metrology Index (BASMI) respectively, in patients with AS. **Results:** The mean age of patients with AS was 41.5 years and 28.7% of the patients were women. The median GUESS score was 8.00 (1.00-23.00), and, the median total FFI and scores in all the pain, disability, and activity limitation subscales were 14.70 (0.00-75.20), 16.60 (0.00-82.80), 16.10 (0.00-84.40), and 4.00 (0.00-60.00), respectively in patients with AS. The GUESS score, total FFI, and all the subscales scores were significantly higher in the patients with AS than in the controls (p=0.001). GUESS score showed a correlation with BASDAI and BASMI (p=0.031, p=0.001). **Conclusion:** The severities of enthesitis and foot disability were higher in patients with AS. Foot involvement and disability should be evaluated either clinicily or ultrasonographicily and managed properly in patients with AS. Presence of enthesitis and high level of foot disability negatively affect the disease activity and flexibility in patients with AS.

Keywords: Ankylosing spondylitis; enthesitis; foot disability

ÖZET Amaç: Entezit ankilozan spondilitin (AS) primer klinik bulgularındandır. Alt ekstremite entezopatileri ayak ağrısına ve fonksiyonel yetersizliğe neden olabilir. Bu çalışmanın amacı, AS'li hastalarda kas-iskelet ultrasonografisi kullanılarak enteziti ve ayak yetersizliğini değerlendirmektir. **Gereç ve Yöntemler:** AS'li 101 ve 42 sağlıklı kontrol hastası enthesal anormallikler açısından gri skala ultrasonografi ile incelendi. Bulgular, Glasgow Ultrason Entesit Skorlama Sistemi (GUESS) kullanılarak değerlendirildi. Ağrı, yetersizlik ve aktivitede kısıtlanma alt ölçeklerinden oluşan Ayak Fonksiyon İndeksi [Foot Function Index (FFI)], ayak fonksiyonunun değerlendirilmesi için AS ve sağlıklı kontrol grubundaki tüm hastalara uygulandı. Hastalık aktivitesi ve fonksiyonel durum AS'li hastalarda sırasıyla Bath AS Hastalık Aktivite İndeksi [Bath AS Disease Activity Index (BASDAI)], Bath AS Fonksiyonel İndeksi [Bath AS Functional Index (BASFI)] ve Bath AS Metroloji İndeksi [Bath AS Metrology Index (BASMI)] kullanılarak değerlendirildi. **Bulgular:** AS'li hastaların yaş ortalaması 41,5 idi ve hastaların %28,7'si kadındı. AS'li hastaların ortalama GUESS skoru 8,00 (1,00-23,00) idi ve ortalama total FFI ve ağrı, yetersizlik ve aktivitede kısıtlanma alt ölçeklerindeki skorları sırasıyla 14,70 (0,00-75,20), 16,60 (0,00-82,80), 16,10 (0,00-84,40) ve 4,00 (0,00-60,00) idi. AS'li hastalarda GUESS skoru, total FFI ve tüm alt ölçek skorları kontrol grubuna göre anlamlı olarak yüksek bulundu (p=0,001). GUESS skoru BASDAI ve BASMI ile korelasyon gösterdi (p=0,031, p=0,001). **Sonuç:** AS'li hastalarda entezit ve ayakta yetersizlik daha yüksek orandaydı. Ayak tutulumu ve buna bağlı gelişen yetersizlik klinik veya ultrasonografik olarak değerlendirilmeli ve AS'li hastalarda uygun şekilde yönetilmelidir. Entezit varlığı ve ayakta yetersizliğin yüksek olması, AS'li hastalarda hastalık aktivitesini olumsuz etkilemektedir.

Anahtar Kelimeler: Ankilozan spondilit; entezit; ayak dizabilitesi

Ankylosing spondylitis (AS) is a chronic inflammatory condition primarily characterized by involvement of the axial skeletal, peripheral articular and extra-articular structures which reduces mobility and leads to functional deterioration.[1-3]

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Enthesitis is inflammation of tendons, ligaments, joint capsules and fasciae at the site of bone attachment, and is a characteristic feature of AS.[2-5] While the frequency of peripheral enthesitis in AS has been reported to be between 25 and 58%, its actual frequency varies depending on the evaluation method (clinical, imaging, histological).[6] Clinically there may be pain, swelling and tenderness at the entheseal site, however the patients are usually asymptomatic and clinical examination often remains inadequate in the detection of enthesitis.[3,7,8] Histological assessment, the gold standard in the evaluation of enthesitis, is used rarely because of the ethical considerations and the practical difficulties.[2,6] Imaging methods, namely conventional radiography, bone scintigraphy, magnetic resonance imaging (MRI) and ultrasonography (US) may also be used to diagnose enthesitis.[6] Conventional radiography gives normal results during early stages while showing erosions, bone proliferation changes, fragmentation and crystal deposits during advanced stages, however it provides very limited information about soft tissues.[1,9] Technetium 99m methylene diphosphonate scintigraphy is a method with high sensitivity in the detection of calcaneal enthesitis, but its specificity has not been reported. On the other hand, MRI is important as it is capable of detecting soft tissue swelling, bone marrow edema and bursal swelling as well as enthesitis, however its high cost limits its use.[6] Moreover, MRI has low sensitivity and specificity in the evaluation of peripheral enthesitis.[4]

As in other rheumatic diseases, the use of US is becoming increasingly widespread in daily practice and clinical studies.[4] US is more sensitive than MRI in the detection of enthesitis in patients with early inflammatory AS, and ensures a more objective and reliable evaluation of entheseal sites than clinical examination.[1,2,5] US allows evaluation of tendon thickness, local calcification, enthesophyte and bone erosions, and with its power Doppler feature, allows evaluation of abnormal vascularization of soft tissues. With US, it is also possible to comparatively and non-invasively evaluate multiple sites and the other extremity.[4,6]

In AS, enthesitis may develop in the axial skeleton and peripheral joints, but is seen more frequently in the feet at the insertion sites of the Achilles tendon (AT) and plantar fascia (PF).[3] Involvement of the feet can lead to pain, structural damage and functional impairment in patients with AS.[1]

Our study aimed to evaluate the entheseal sites with US, to compare with healthy controls, and to compare Foot Function Index (FFI) with enthesitis score in patients with AS.

MATERIAL AND METHODS

PATIENTS

One hundred and one patients who had been diagnosed with AS according to the modified New York criteria and were being followed-up at our outpatient clinics, and 42 age-and gender-matched healthy individuals without primary feet problems were included in the study. The study was approved by the Ethics Committee of Dışkapı Training and Research Hospital Clinical Researches (January 16 2017, 34/06) and the study was conducted in compliance with the Helsinki Declaration. All patients and the control group signed the informed consent form. Patients who had undergone knee and ankle surgery, had received steroid injection to the examined structures within the last 6 weeks, had peripheral neuropathy and deformities such pes planus or pes cavus that may affect feet functions were not included in the study.

The participants' demographic data including the parameters of age, gender, diagnosis time, and smoking and exercise habits were queried. During examination of the patients, their lumbar lateral flexion, tragus wall distance, modified Schober, cervical rotation and intermalleolar distance were measured to calculate Bath AS Metrology Index (BASMI) scores.[10] The Turkish versions of the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI) were completed to assess the disease activity and functional capacity, respectively.[11,12] The drugs they were using, i.e. nonsteroidal anti-inflammatory drugs (NSAIDs), sulphasalazine, anti-tumor necrosis factor (TNF) were queried and recorded. The pain status was assessed using the 0-10 cm visual analog scale (VAS). The results of the laboratory tests of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also recorded.

The Turkish version of the FFI was used to assess the foot function in the patient and control groups.[13] The FFI is a scale consisting of 23 questions in total, 9 of which assess pain, 5 which assess activity limitation and 9 which assess disability. The participants were asked to answer the questions using the VAS between 0 and 10 according to their status within the last 1 week. Both the total scores and the individual scores for the sub-parameters of pain, disability and activity limitation were calculated.

ULTRASONOGRAPHIC EVALUATION

A Logiq P5, GE Medical Systems, USA model US equipped with 7-12 MHz linear probe was used to examine the entheseal sites of the foot. All US examinations were performed by a radiologist who was expert in soft tissue sonography and unaware of the patient's clinical findings. The patients were placed into the appropriate position, and the tendon, bursa and entheseal sites were bilaterally evaluated, both longitudinally and transversely. Tendon thickness measurements were made at the bone insertion site, and a hyperechoic dot or linear area was considered tendon calcification, discontinuation of the bone surface was considered bone erosion, a hyperechoic protrusion in the entheseal site was considered enthesophyte, and a movable and a compressible abnormal hypoechoic anechoic intra-bursal material was considered bursitis (Figure 1, Figure 2). Tendons of the superior pole of the patella (quadriceps tendon insertion), the inferior pole of the patella (patellar ligament origin), the patellar ligament insertion at the tibial tuberosity, the AT, and the PF were examined in both lower limbs. Examinations of the superior pole of the patella, the inferior pole of the patella, and the patellar ligament insertion at the tibial tuberosity were performed with the patient in the supine position with the knee flexed at 30. The AT and the plantar aponeurosis were examined with the patient lying prone with the feet hanging over the edge of the examination table at 90 degrees. The Glasgow Ultrasound Enthesitis Scoring System (GUESS) was used for ultrasonographic enthesitis scoring. According to this, each abnormality detected in the lower extremity was scored as 1 point. The total scores were between 0 and 36.[14]

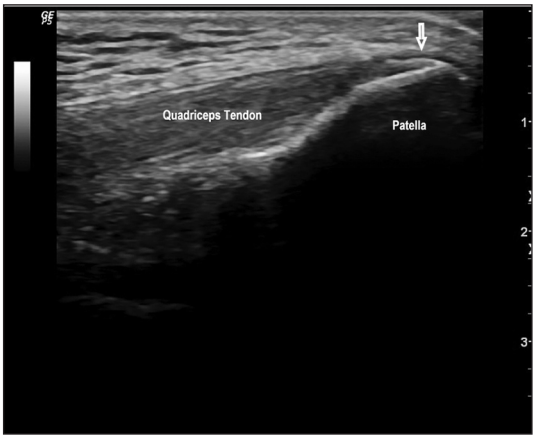

FIGURE 1: Enthesitis and enthesophyte of quadriceps tendon.

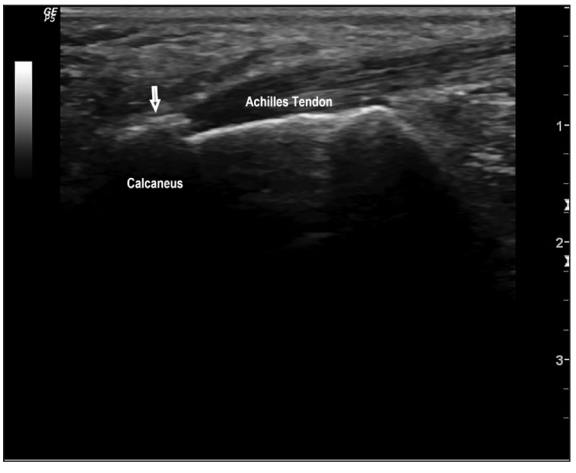

FIGURE 2: Enthesitis of Achilles tendon.

STATISTICAL ANALYSIS

The SPSS Inc., USA for Windows 22.0 software was used to evaluate the results obtained from the study. The Mann-Whitney U and chi-square tests were used to determine differences between groups. The relationships between the FFI and GUESS, and the other parameters were evaluated using the Spearman correlation analysis. Pearson correlation coefficients were calculated to evaluate the relationship between the disease activity measures and the ultrasonographic features. Values of p less than 0.05 were accepted as significant.

RESULTS

One hundred and one AS patients and a control group consisting of 42 healthy individuals were included in

the study. The clinical and laboratory variables of the patients are shown in Table 1. There was no difference between the 2 groups in terms of age, gender, regular exercise habit and smoking frequency (p=0.005). The mean disease duration of the patients was 10 years (between 0 and 46 years).

Seventy seven (76.2%) of the patients were receiving NSAIDs, 38 (37.6%) were receiving sulfasalazine and 35 (34.7%) were receiving anti-TNF therapy while 4 were being followed-up without medication.

The scores of GUESS and FFI total, and of the sub-parameters of pain, disability and activity limitation calculated following the ultrasonographic evaluation of the patients were statistically significantly higher in the patient group than in the control group (p=0.001). All patients (n=101, 100%) had at least one pathological finding in the entheseal sites assessed using the GUESS scores. The foot-related superior and inferior pole of the calcaneus total score, a sub-parameter of GUESS, were significantly higher in the patient group than in the control group (p=0.001).

Additionally, the bilateral AT and PF thickness measures, which were foot region assessments, were significantly increased in the patient group than in the control group (p=0.001) (Table 2).

No significant relationship was found between the GUESS total score and the FFI total, pain, disability and activity limitation sub-parameter scores (p=0.479, p=0.530, p=0.726, p=0.059).

A positive correlation was found between the GUESS score and the VAS pain, BASDAI, BASMI, disease duration and age parameters (p=0.031 r=0.215, p=0.001 r=0.384, p=0.001 r=0.496, p=0.001 r=0.384, p=0.001 r=0.437) (Table 3). There was no significant relationship between the GUESS score and the ESR and CRP values (p=0.073 r=0.179, p=0.144 r=0.146).

A positive correlation was found between the FFI total and sub-parameter scores and the VAS pain, BASDAI and BASFI (p=0.001 r=0.628, p=0.001 r=0.669, p=0.001 r=0.501).

DISCUSSION

Enthesitis is a primary lesion in all spondyloartropathy (SpA) subtypes which is characterized by inflammatory involvement of the enthesis and the adjacent bone.[2,15] It is clinically manifested by pain and tenderness at rest or upon palpation, and restricted movements of related joint and/or tendons, but is frequently asymptomatic.[16] One of the most important problems encountered in daily practice is the diagnosis and follow-up of enthesitis.[15] It has been suggested that imaging techniques are superior to clinical examination in the diagnosis and follow-up of enthesitis. However, it has also been suggested that US may be superior to MRI in the detection of early signs of enthesopathy.[4,15,17]

Entheseal inflammatory changes can cause proliferation, erosion and peripheral ossification of the bone. Such changes may not always be detected by clinical examination, and direct radiographic techniques remain inadequate in the detection of soft tissue changes.[1] Clinical examination has low sensitivity and specificity in the diagnosis of enthesitis, and US seems more effective for use for this purpose and has been used effectively during the recent years both during the diagnosis stage and for the follow-up of the disease.[2,15] With US, it is possible to evaluate erosion and enthesopathy even during early stages of the disease.[1,14] The GUESS index is a useful tool which has been increasingly used during the recent years and allows an objective evaluation of enthesitis areas using US.[14]

The most common anomalies in ultrasonographic evaluation of entheseal sites of AS patients are enthesophyte, tendon calcification, increased thickness and hypoechogenicity.[6] In their study on patients with rheumatoid arthritis and AS, Genc et al. with respect to the areas assessed using the GUESS system found more involvement in the suprapatellar area, infrapatellar area and AT than in the control group while the involvement of the plantar was not found to be different from the control group.[9] Balint et al. found US abnormalities in 56% of five entheseal sites of the lower limbs (superior pole and inferior pole of patella, tibial tuberosity, AT and plantar aponeurosis) in 35 SpA patients.[14] Lehtinen et al. re-

TABLE 1: Clinical characteristics of the patient groups and healty controls.

	AS (n=101)	Control (n=42)	p value
Age, years	41.5±10.8[a]	38.5±10.7[a]	0.135
Gender (woman)	29 (28.7%)[b]	14 (33.3%)[b]	0.583
Regular exercise habit	27 (26.7%)[b]	11 (26.2)[b]	0.947
Smokers	53 (52.5%)[b]	21 (50%)[b]	0.079
Disease duration, years	10 (0-46)[c]		
ESR, mm/h	12 (2-72)[c]		
CRP, mg/L	5.5 (0.19-66)[a]		
Pain VAS (0-10 cm)	3 (0-9)[c]		
BASM	1 (0-10)[c]		
BASDAI	2.4 (0-8.6)[c]		
BASFI	1.3 (0-9.2)[c]		
Medication (%)			
NSAID	77 (76.2%)[b]		
Sulfasalazine	38 (37.6%)[b]		
Anti-TNF	35 (34.7%)[b]		
Drug free	4 (4%)[b]		
GUESS	8 (1-23)[c]	1 (0-7)[a]	0.000
Superior pole of the patella	2 (0-6)	0 (0-4)	0.000
Inferior pole of the patella	1 (0-5)	0 (0-1)	0.000
Tibial tuberosity	2 (0-6)	0 (0-3)	0.000
Superior pole of the calcaneus	2 (0-7)	0 (0-3)	0.000
Inferior pole of the calcaneus	1 (0-4)	0 (0-2)	0.000
FFI			
Total	14.7 (0-75.2)[c]	0 (0-13.3)[c]	0.000
Pain	16.6 (0-82.8)[c]	0 (0-14.2)[c]	0.000
Disability	16.1 (0-84.4)[c]	0 (0-21.1)[c]	0.000
Activity limitation	4 (0-60)[c]	0 (0-0)[c]	0.000

[a]: Mean±standard deviation; [b]: n (%); c: Median (minimum-maximum); ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: Visual analog scale; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NSAID: Non-steroidal anti-inflammatory drug; Anti-TNF: Anti tumor necrosis factor; GUESS: Glasgow Ultrasound Enthesitis Scoring System; FFI: Foot Function Index.

TABLE 2: Tendon thickness of the AT and PF.

	AS (n=101)	Control (n=43)	p value
AT thickness (R), mm	3,8 (2.7-6.2)[a]	2.4 (2.2-4.2)[a]	0.001
AT thickness (L), mm	3.7 (2.3-6.1)[a]	2.4 (2.1-4.6)[a]	0.001
PF thickness (R), mm	2.4 (1.2-4.3)[a]	1.9 (1.8-3.1)[a]	0.001
PF thickness (L), mm	2.4 (1.4-4)[a]	1.9 (1.7-3.2)[a]	0.001

[a]: Median (minimum-maximum); AT: Achille tendon; PT: Plantar fascia.

TABLE 3: Correlation analysis of GUESS and FFI with BASDAI, BASFI and BASMI.

		VAS pain	BASDAI	BASFI	BASMI
GUESS	r value	**0.215**	**0.384**	0.078	**0.496**
	p value	**0.031**	**0.001**	0.439	**0.001**
FFI	r value	**0.628**	**0.669**	**0.501**	0.030
	p value	**<0.001**	**0.001**	**0.001**	0.768

GUESS: Glasgow Ultrasound Enthesitis Scoring System; FFI: Foot Function Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; VAS: Visual analog scale.

ported that enthesopathic abnormalities were more frequently (66%) found at the distal part of lower limbs (i.e. as patella insertion, AT and PF insertions) with respect to the proximal part of lower limbs (i.e. ischial tuberosity, great trochanter and insertion of adductor muscles) in 31 patients with SpA.[18] Similarly to the previous studies, we found that the GUESS scores calculated based on the US assessment of the entheseal sites were significantly higher in the AS group than in the healthy control group. The bilateral foot AT and PF thicknesses of the patients were also found to be significantly increased than those of the control group. All patients had at least one pathological finding in the entheseal sites assessed using the GUESS scores. These results suggested that enthesopathy, a main characteristic of SpA, is common especially in the lower extremities of AS patients.

The study conducted by Spadaro et al. also did not demonstrate any correlation between the entheseal anomalies detected during clinical examination and the findings detected by ultrasonographic examination. This was thought to be due to the fact that enthesopathy is generally asymptomatic and that ultrasonographic evaluation is a far more sensitive and specific method to detect anomalies.[6] Entheseal involvement in SpA may not always be detected by clinical examination. US is more sensitive than clinical examination in the detection of entheseal abnormalities, and clinical examination may not always be consistent with ultrasonographic evaluation. Pathology may be detected by ultrasonographic examination even in clinically asymptomatic patients.[6]

Foot pain and functional limitation in patients with AS is a common and important condition that cause disability. Despite the variations among studies, the incidence rates of foot problems are 30-83% in the normal population and 30-100% in patients with SpA.[19] In such patients, while hindfoot involvement is more common, midfoot and forefoot problems may also be observed.[1,20,21] In a study conducted by Erdem et al. using MRI on SpA patients, Achilles and PF involvement were found in 33-58.3% of the patients.[21] Borman et al. reported pathological US abnormalities at insertions of the AT and PF on the calcaneum in 56.8% of 44 SpA patients, whereas 37% showed signs of entheseal involvement by clinical examination.[1] In the study conducted by Mesci et al. on 40 AS patients and 30 health individuals, clinical enthesitis findings were detected in 13 (32.5%) patients and at least one pathology was found in 30 (75%) patients by ultrasonographic examination. This study also showed that the mean FFI score of the AS group was higher, and their mean AT and PF thicknesses were increased compared to the control group.[22]

Our study demonstrated that foot disability determined by FFI score in the AS group was significantly higher compared to the control group, which supported the other studies. All these findings may suggest that AS also negatively affects foot functions.

Our study demonstrated no relationship between the GUESS and AFI scores. The GUESS system assesses only the Achilles and plantar entheseal sites. However, also midfood and forefoot problems are common in these patients, and pathologies such as joint effusion, bone marrow edema, soft tissue swelling, intraarticular narrowing, ankylosis, subchondral sclerosis, cysts or fissures.[21] Food disability seen in our patient group may have been not only by enthesitis but also by other pathologies associated with AS.

As in the other literature studies, our study did not demonstrate any correlation between the GUESS scores, and ESR and CRP that are inflammatory markers.[23,24] Laatiris et al. found a significant relationship between the Mander Enthesis Index and Masstrich AS Enthesis Index Score (enthesitis indices) and the BASDAI scores.[23] In the study conducted by Hamdi et al. on 60 AS patients, a relationship was found between the BASDAI, BASFI and VAS pain scores, and the ultrasonographic scores.[24] Also in our study, a correlation was found between the GUESS scores and the VAS pain, BASDAI, BASMI, disease duration and age parameters, which were consistent with the other literature studies.[25-27] These results suggested us that the presence of enthesitis in AS patients increases the disease activity. The correlation between the GUESS and BASMI scores may demonstrate that enthesitis may also contribute to the reduced flexibility in AS patients. According to the data of our study, entheseal pathologies increased with increasing disease duration and age.

We also found a significant relationship between the FFI and the VAS pain, BASDAI and BASFI scores. Also Mesci et al. demonstrated a marked relationship between the AFI and the BASDAI scores.[22] This result may suggest that foot disability may contribute to the disease activity.

The drugs used in the treatment of AS may cause changes in the ultrasonographic findings of the patients. NSAIDs usage may mask the ultrasonographic findings and result in lower soring.[2] Sulfasalazine is the best-studied DMARD in AS, but its efficacy remains unclear. In the study conducted by Genc et al, there was a significant improvement in clinical and laboratory activity parameters of the inflammatory rheumatologic diseases patients, a significant decrease was not observed in enthesal abnormalities and mean GUESS score after 1 year sulfasalazine trial.[5] Significant decreases in US scores have also been shown after TNF-alpha antagonist therapy and it has been suggested that US follow-up of enthesopathic findings should be used to monitor response to anti-TNF treatments.[8,22] In our study, the use of NSAIDs and anti-TNF was found to be significantly higher in the group with clinical pain and enthesitis. In this group, pain VAS and BASDAI, which are among the disease activity parameters, were significantly higher than the other group. Clinically high rate of pain and enthesitis, and a more active course of the disease may have caused the high drug use. However, it should not be forgotten that long follow-up periods are needed to evaluate the effects of drugs on enthesopathy.

The limitation of our study is that the study was conducted by only one researcher with a US machine, thus these findings need to be replicated by others. Another limitation is that GUESS was used for ultrasonographic enthesitis scoring. We did not use a clinical enthesitis score (e.g. Maastrich AS Enthesitis Score). There are limited number of studies that evaluate foot enthesitis with ultrasound and also clinically evaluate foot disability in patients with AS. Our study may contribute to the literature with this respect.

CONCLUSION

The severities of enthesitis and foot disability were higher in patients with AS. Foot involvement and disability should be evaluated either clinicaly or by US and managed properly in patients with AS. The presence of enthesitis and high level of foot disability negatively affect the disease activity and flexibility in patients with AS.

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