DOI: 10.24938/kutfd.1546206 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2025;27(2):120-126
Original Article *Özgün Araştırma*

THE FREQUENCY AND ASSOCIATED FACTORS OF CALCANEAL ENTHESITIS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Romatoid Artrit Hastalarında Kalkaneal Entezit Sıklığı ve İlişkili Faktörler

Zeynep FINDIKLI[1] **Mete PEKDİKER**[2]

[1] *Clinic of Internal Medicine, Dörtyol State Hospital, HATAY, TÜRKİYE*

[2] *Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Mustafa Kemal University, HATAY, TÜRKİYE*

ABSTRACT

Objective: Chronic synovitis in peripheral joints is the hallmark lesion but enthesal involvement is little known in patients with rheumatoid arthritis (RA). The aim of this study is to draw attention to this issue by defining the frequency, and associated factors of calcaneal enthesitis (CE) in patients with RA.

Material and Methods: This single-center study was conducted at our rheumatology outpatient clinic between July 2022 and December 2022. Electronic medical records was reviewed retrospectively. Patients with RA aged ≥18 years were included. Patients having any enthesitis-related non-rheumatic disorders were excluded. Calcaneal enthesitis was defined as the presence of heel pain accompanied by morning stiffness, and radiological evidence of calcaneal enthesitis (as irregular calcaneal spur).

Results: We examined totally 616 cases, and 75.8% of them were female. The mean age was 50.5±14.0 years, and the mean disease duration was 7.5±7.3 years. Rheumatoid arthritis-type joint involvement was present in 92.2% (n=568) of study population. Rheumatoid factor (RF) and anti-CCP positivity was 72.6% and 71.8%, respectively. Twenty-seven patients had CE; seven of them had spondyloarthritis (four had psoriasis, two ankylosing spondylitis, one ulcerative colitis). The 3.6% (n=20) of patients had RA-related CE. In univariate analysis, CE+ group had higher age at first symptom for RA (p=0.027), less severe radiographical joint involvement (p=0.016), less RF positivity (p<0.001), and less anti-CCP (p<0.001) positivity. Additionally, CE+ group had less biologic agent use (p<0.001). In multivariate analysis including age at first symptom, severe joint involvement, RF, and anti-CCP, there was no independent predictive factor for CE.

Conclusion: Enthesal sites may become a relevant domain of musculoskletal assessment of RA in future. Prospective studies using more sensitive imaging methods are needed to elucidate this issue.

Keywords: *Calcaneus, enthesopathy, rheumatoid arthritis, risk factor*

ÖZ

Amaç: Romatoid artrit (RA) olgularında periferik eklemlerdeki kronik sinovit temel lezyondur ancak entezal tutulum hakkında bilgi azdır. Bu çalışmanın amacı RA olgularında kalkaneal entezit (KE) sıklığını ve ilişkili faktörleri tanımlayarak bu konuya dikkat çekmektir.

Gereç ve Yöntemler: Tek merkezli çalışmamız Temmuz 2022-Aralık 2022 tarihleri arasında romatoloji kliniğimize ayaktan başvuran hastalarda yapıldı. Elektronik hasta dosyaları retrospektif olarak incelendi. On sekiz yaşından büyük RA olguları çalışmaya alındı. Entezit ilişkili non-romatolojik hastalığı olanlar çalışmadan çıkarıldı. Kalkaneal entezit, sabah tutukluğunun eşlik ettiği topuk ağrısı ve radyografik bulgunun (düzensiz spur) varlığı olarak tanımlandı.

Bulgular: Toplam 616 olguyu inceledik ve bunların %75,8'i kadındı. Ortalama yaş 50,5±14,0 ve ortalama hastalık süresi 7,5±7,3 yıldı. Romatoid artrit tipi eklem tutulumu çalışma grubunun %92,2'sinde (n=568) mevcuttu. Romatoid faktör (RF) ve anti-CCP antikor pozitifliği sırasıyla %72,6 ve %71,8 idi. Yirmi yedi hastada KE saptadık ve bunların yedisinde spondiloartrit (dört olguda sedef, ikisinde ankilozan spondilit, birinde ülseratif kolit) mevcuttu. Çalışma grubunun %3,6'sında (n=21) RA-ilişkili KE saptandı. Tek değişkenli analizde KE+ grup yüksek RA başlangıç yaşı (p=0,027), radyolojik olarak daha az ciddi eklem tutulumu (p=0,016), daha az RF pozitifliği (p<0,001) ve daha az anti-CCP pozitifliğine (p<0,001) sahipti. Ayrıca, KE+ grupta biyolojik ajan kullanımı daha azdı. Çok değişkenli analizde ise KE için bağımsız prediktif faktör saptanmadı.

Sonuç: Entezal bölgeler, gelecekte RA olgularında kas-iskelet sistemi değerlendirilmesinde yer alabilir. Bu konunun açıklanması için daha sensitif görüntüleme yöntemleri ile yapılan prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Topuk, entezopati, romatoid artrit, risk faktörü*

Correspondence / Yazışma Adresi: **Dr. Mete PEKDİKER**
Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Mustafa Kemal University, HATAY, TÜRKİYE
Phone / Tel: +905052003534 **E-mail** / E-posta: mete.pekdiker@hotmail.com
Received / Geliş Tarihi: 10.09.2024 **Accepted** / Kabul Tarihi: 17.06.2025

KÜ Tıp Fak Derg 2025;27(2):120-126
Doi: 10.24938/kutfd.1546206

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune and multisystemic rheumatic disease of unknown etiology. Its prevalence in Western countries is approximately 0.5-1% and the female to male ratio is 2-3:1. Rheumatoid arthritis leads to chronic and progressive inflammation in the peripheral joints, causing erosive arthritis. Loss of work capacity and increased morbidity are natural consequences of RA. Additionally, extra-articular complications that may occur in advanced stages of the disease are associated with an increased morbidity and mortality.[1] The prevalence of RA, its deformative and multisystemic course, and the need for lifelong treatment make it one of the highest-priority diseases in rheumatology practice The target tissue and the initial site of disease onset in RA is the synovium of the peripheral joints. Chronic erosive synovitis, which causes damage to bone and cartilage, is the fundamental histopathological finding in RA.[2] The disease typically begins insidiously in the small joints of the hands and feet. The most commonly affected initial joints are the wrists, metacarpophalangeal joints, proximal interphalangeal joints, and metatarsophalangeal joints. Large joints such as the shoulder, hip, knee, elbow, and ankle are generally affected in the later stages of the disease. Erosive arthritis, a result of chronic joint inflammation, can lead to deformities and restricted movement in some cases.[3]

Entheses are the sites where tendons and ligaments attach to bone. Enthesitis is a clinicopathological finding, particularly in the group of diseases known as seronegative spondyloarthritis (SpA); it occurs as a result of immune responses triggered by genetic predisposition, mechanical stress, and environmental factors. Inflammation initiated by the innate immune system, particularly through prostaglandin E2 mediation, leads to the activation of interleukin (IL)-23 receptor–positive(+) cells in the entheseal region. As a result, a chronic inflammatory response mediated by IL-17A, IL-22, and TNF develops. In the affected area, erosive changes and new bone formation occur concurrently; the net effect is generally in favor of osteoproliferation. There are distinct genetic, immunopathological, and clinical differences between diseases that involve enthesal involvement, such as-SpA, and diseases with synovial involvement like RA.[4]

Although enthesal involvement is not typically expected in in routine clinical practice, inflammatory enthesitis can develop in RA cases as a secondary condition resulting from chronic synovitis.[5] However, data related to enthesitis in cases of RA are very limited in the medical literature. In this study, we aimed to draw attention to extra-synovial musculoskeletal involvement in patients with RA by describing the frequency of inflammatory enthesitis and related factors in the calcaneal region, a site where enthesitis is commonly observed.

MATERIALS AND METHODS

This study was conducted through a retrospective analysis of patients with RA who presented to the rheumatology department of our tertiary university hospital between 07/01/2022 and 12/31/2022. Inclusion criteria for the study were being aged ≥18 years, fulfilling the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria, and having undergone an anteroposterior hand-wrist radiograph taken within the last year.[6] Exclusion criteria were having an enthesitis-related disorder such as Familial Mediterranean Fever, Behçet's disease, calcium pyrophosphate dihydrate arthropathy, diffuse idiopathic skeletal hyperostosis, SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) syndrome, morbid obesity (body mass index > 35kg/m^2), uncontrolled diabetes mellitus (HbA1c > 10g/dL), being a hemodialysis patient, familial hypercholesterolemia, celiac disease, hyperparathyroidism, hypoparathyroidism, acromegaly, hemochromatosis, ochronosis, tuberculosis, and X-linked hypophosphatemia.[4] Electronic patient records were scanned; demographic, laboratory, clinical, and treatment data were recorded.

Rheumatoid factor (RF) was measured using the nephelometric method and was considered positive if ≥14 IU/mL. Anti-cyclic citrullinated peptide 2 IgG antibodies (anti-CCP) were measured using the ELISA method and were considered positive if ≥5 U/mL. Radiographs (within the past year) were assessed by a rheumatologist (MP), and an experienced radiologist; the most recent hand/foot radiographs (within last year) were assessed. Rheumatoid arthritis-type erosive joint involvement (RJI) was defined as erosion or joint space narrowing in any joint according to the Modified Sharp Score (MSS).[7] Serious joint involvement (SJI) was defined as having any erosion score ≥ 3-5 points or joint space narrowing score ≥ 4-5 points according to the MSS. Lag time to diagnosis was defined as 'the time elapsed between the onset of arthritis and the diagnosis of RA'. Calcaneal enthesitis (CE) was defined as presence of inflammatory heel pain accompanied by morning stiffness (lasting longer than 30 minutes), and the presence of radiographic findings consistent with inflammatory enthesitis. According to the definition by Resnick et al., a calcaneal spur (CS: plantar), erosion, or irregularity was considered a positive radiographic finding for enthesitis.[8] Cases characterized by a large, well-defined, and regular bone cortex, indicative of a non-inflammatory spur, were not considered to be inflammatory enthesitis.[9] In the patient group of this study, all radiographs were evaluated by a

KÜ Tıp Fak Derg 2025;27(2):120-126
Doi: 10.24938/kutfd.1546206

rheumatologists (MP), and an experienced radiologist blinded to the patients and the radiographic assessments were concluded with full agreement. Patients, who were resistant to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and had high disease activity according to the DAS-28 scoring system, received biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).[10]

Statistical Analysis

In the evaluation of the findings obtained from the study, IBM SPSS for Windows version 22.0 software (IBM Corp, Armonk, NY, USA) and SPSS (Statistical Package for the Social Sciences) for Windows 20 package program were used for statistical analyses. The normality of distribution for numerical data was examined using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were summarized as mean, median, standard deviation, minimum, and maximum values; for categorical variables, they were summarized as number and percentage (%). The Pearson Chi-square analysis was used to examine the distribution of categorical variables between groups. The Independent Sample T-test was used for comparing data between two independent groups. Binary logistic regression analysis test was used to identify the independent predictors of CE, and was applied to estimate the dependent variable in terms of probabilities and to perform classification based on these probabilities. Results were evaluated at the 95% confidence interval, with significance considered at $p<0.05$ level. The study was approved by the ethical committee of university where the study was conducted (date: 07/26/2023, desicion number: 07). Written constent is obtained from participants.

RESULTS

We initially reviewed 642 patients with RA, and excluded 26 cases with enthesitis-related disorder other than SpA. Thus, this study included 616 RA patients, 75.8% of whom were women. The mean age was 50.5±14.0 years, and the mean duration of the disease was 7.5±7.3 years. Among the study population RF positivity was present in 72.6%, anti-CCP positivity in 71.8%, radiographic evidence of RJI in 92.2%, SJI in 30.2%, and 34.6% (n=213) of study population were receiving treatment with b/tsDMARDs. In our study population, the rate of CE was 4.4% (n=27). Seven of 27 patients were classified as SpA; four had psoriasis, two ankylosing spondylitis, one ulcerative colitis. Therefore, the rate of RA-related CE was 3.6% (n=20). Table 1 presents the demographic, clinical, laboratory, and treatment data of the patients. Figure 1 shows an example of CE in a patient with RA.

Table 1: Demographic, clinical, laboratory and treatment characteristics of study group.

Total patient, n	616
Age (mean±SD), years	50.5±14.0
Women, n (%)	467 (75.8)
Men, n (%)	149 (24.2)
Age at first symptom (mean±SD), years	42.9±14.6
Duration of disease (mean±SD), years	7.5±7.3
Smoking (active or ex), n (%)	208 (33.8)
Hypertension, n (%)	154 (25.0)
Diabetes Mellitus, n (%)	70 (11.4)
Coronary artery disease , n (%)	42 (6.8)
Chronic kidney disease, n (%)	10 (1.6)
Lag time to diagnosis (mean±SD), months	16.3±24.0
Rheumatoid factor positivity, n (%)	447 (72.6)
Anti-CCP positivity, n (%)	442 (71.8)
Rheumatoid arthritis-type joint involvement, n (%)	568 (92.2)
Serious joint involvement, n (%)	186 (30.2)
Calcaneal enthesitis, n (%)	27 (4.4)
Biological/targeted synthetic disease-modifying anti-rheumatic drugs, n (%)	210 (34.0)
-Etanercept, n (%)	8 (3.8)
-Infliximab, n (%)	2 (1)
-Adalimumab, n (%)	20 (9.6)
-Certolizumab pegol, n (%)	9 (4.3)
-Golimumab, n (%)	4 (1.9)
-Abatacept, n (%)	5 (2.4)
-Rituximab, n (%)	120 (57.1)
-Tocilizumab, n (%)	10 (4.7)
-Tofacitinib, n (%)	16 (7.6)
-Baricitinib, n (%)	16 (7.6)

SD: Standart Deviation, anti-CCP:anti- Cyclic Citrullinated Peptide Antibody

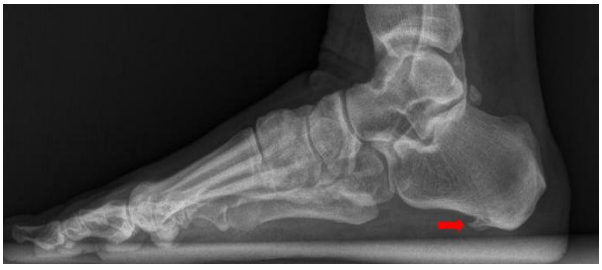

Figure 1: An example radiograph of patient with calcaneal enthesitis in rheumatoid arthritis cases.

In the CE+ group, all patients were female with a median age of 55 years (range=36-65 years), the mean age the onset of RA symptom was 48.8±8.4 years, and the mean duration of the disease was 4.3±4.0 years. Among patients with CE, 14.8% (n=4) had psoriasis (all four were positive for both RF and anti-CCP) and 3.7% (n=1) had ulcerative colitis; there were no reported cases of infectious gastroenteritis or urethritis within the past month. Five patients (four psoriasis and one ulcerative

KÜ Tıp Fak Derg 2025;27(2):120-126
Doi: 10.24938/kutfd.1546206

colitis) fulfilled the classification criteria for peripheral SpA.[11] In cases with a history of (suspected) inflammatory back pain, 7.4% (n=2) were found to have imaging evidence of bilateral stage-2 and unilateral stage-3 radiographic sacroiliitis, and these cases were classified as ankylosing spondylitis (AS) according to the Modified New York criteria.[12] In cases with CE, there was no history of chronic ankle arthritis, and no radiographic findings indicative of chronic arthritis (such as erosion or joint space narrowing) were detected in the ankle joints (including tibiotalar, subtalar, talonavicular, and midtarsal). Calcaneal enthesitis was present in 1.8% (n=8) of a total of 447 RF-positive RA cases, in 11.2% (n=19) of 169 RF-negative RA cases. While CE was present in 2% (n=9) of a total of 442 anti-CCP-positive RA cases, it was present in 10.3% (n=18) of 174 anti-CCP-negative RA cases.

We found no difference between the CE (+) and (-) groups in terms of age, smoking history, and RJI (respectively; p=0.291, p=0.315, p=0.115). The CE (+) group were observed a higher prevalence of female gender, earlier onset of symptoms, and longer lag time to diagnosis (p=0.002, p=0.027, p=0.018), respectively. In the CE (-) group, RF positivity, anti-CCP positivity, and SJI were significantly higher (p<0.001, p<0.001, p=0.007). In the CE (+) group, 3.6% (n=1) of patinets were using tsDMARD (Baricitinib), whereas 35.5% (n=209) of CE (-) group had a history of biological agent use (p<0.001). In the study group, 34% of the patients were using b/tsDMARDs (n=210). Rituximab was the most frequently chosen biologic agent, accounting for 57.1% (n=120), while Adalimumab was the second and Tofacitinib along with Baricitinib were the third in line. Table 2 shows the comparison of variables between the CE (+) and (-) group.

In univariate logistic regression analysis, we found that the age at first symptom (p=0.027), SJI (p= 0.016), RF (p<0.001), and anti-CCP (p<0.001) were each found to be predictors of the presence of CE (Table 3). In the multivariate logistic regression analysis including age at first symptom, SJI, RF, and anti-CCP, no independent predictive factor was identified.

Table 2: Comparison of variables between the calcaneal enthesitis (+) group and the calcaneal enthesitis (-) group.

Variables		Calcaneal enthesitis (+)	Calcaneal enthesitis (-)	p value
Gender, n, (%)	Woman	27 (100.0)	440 (74.7)	**0.002***
	Men	0 (0.0)	149 (25.3)	
Age, (mean±SD), year		53.2±6.69	50.3±14.3	0.291**
Age at first symptom, (mean±SD), years		48.8±8.4	42.6±14.7	**0.027****
Smoker, n (%)		7 (25.9)	201 (34.2)	0.315*
Lag time to diagnosis (mean±SD), months		26.9±27.8	15.8±23.8	**0.018****
Rheumatoid factor positivity, n (%)		8 (28.6)	439 (74.7)	**<0.001***
Anti-CCP positivity, n (%)		9 (32.1)	433 (73.6)	**<0.001***
RA-type joint involvement, n (%)		28 (100.0)	540 (91.8)	0.115*
Serious joint involvement, n (%)		2 (7.1)	184 (31.3)	**0.007***
b/tsDMARDs, n (%)		1 (3.6)	209 (35.5)	**<0.001***

SD: Standart Deviation, RA: Rheumatoid Arthritis, Anti-CCP: Anti-Cyclic Citrullinated Peptide Antibody, b/tsDMARDs:biological/targeted synthetic Disease-Modifying Anti-Rheumatic Drugs,
*Pearson Ki-kare Test, **Independent Sample T Test

Table 3: Results of univariate logistic regression analysis for the predictive factors in determining calcaneal enthesitis.

Variables	Beta Coefficient (95% Confidence Interval)	p value
Age	1.052 [-0.001-0.002]	0.291
Age at first symptom	2.213 [0.000-0.002]	**0.027**
Severe joint involvement	0.169 [0.040-0.719]	**0.016**
Rheumatoid factor	0.136 [0.059-0.315]	**<0.001**
Anti-cyclic citrullinated peptide antibody	0.170 [0.075-0.383]	**<0.001**

DISCUSSION

In this study, the frequency of radiographic calcaneal enthesitis and associated factors were investigated in a single-center cohort with the largest-sample size to date (n=616), and we found the frequency of CE to be 3.6%. In the CE (+) group, female patients, age at first symptom, and lag time to diagnosis were higher; whereas the rates of RF positivity, anti-CCP positivity, and use of biologic agents was lower compared to the CE (-) group. In the univariate logistic regression analysis, a higher age at first symptom, negativity for RF, negativity for anti-CCP, and the absence of SJI were identified as predictive factors for the development of CE. In 7 of 27 patients with CE, SpA features were present, while in the remaining 20 cases, no other disease associated with inflammatory enthesitis was detected. The fact that all cases with CE were female is a noteworthy finding. The low rate of RF and anti-CCP

KÜ Tıp Fak Derg 2025;27(2):120-126
Doi: 10.24938/kutfd.1546206

positivity in the CE (+) group was consistent with SpA. In the CE (+) group, the lower frequency of SJI and the less frequent use of b/tsDMARDs may be interpreted as indicative of lower disease activity in terms of RA. Again, the absence of clinical and radiographic findings of chronic arthritis in CE (+) cases was a significant and notable characteristic feature. This observation suggests that CE (+) in RA cases is not related to chronic synovitis, and may develop through unknown mechanisms.

There is very little literature on pathologies of the calcaneal region in cases of rheumatoid arthritis. Firstly, Bywaters GE pointed out that heel lesions in RA cases are often overlooked and drew attention to erosive changes in the subachilles bursa and plantar spurs in a series of 19 cases.[13] In the study comparing radiological findings among patients with RA (n=81), AS, (n=38), reactive arthritis (n=25), Mason et al. found that 15% of the patients with RA developed posterior spurs, and 39% developed plantar spurs. However, in this study, did not include any data related to inflammatory heel pain and spur formation in RA cases, and this study was designed solely as a radiographic analysis.[14] Bassiouni M. compared the frequency of CS in osteoarthritis, RA, and healthy controls using X-rays, and reported the frequency of CS as 81%, 21.7%, and 18%, respectively. In patients with RA, no gender difference was found in the frequency of CS and it was observed that the frequency of CS increased with age in the study population. Once again, this study evaluated CS rather than calcaneal enthesitis; no assessment was performed regarding inflammatory symptoms or spur radiographs.[15] Gerster et al. investigated the frequency of heel pain in patients with RA (n=100) and analyzed ankle radiographs. They reported that 20% of patients with RA developed simple CS, while 4% developed irregular CS (inflammatory spurs) with 2% located posteriorly and 2% plantarly. However, this study did not include radiographic analysis of the ankle in patients with inflammatory spurs.[16]

Resnick et al. retrospectively evaluated radiographic calcaneal abnormalities in patients with RA, AS, psoriasis, and reactive arthritis. In the RA subgroup (n=125), lateral heel radiographs were available for 64 individuals and radiographic calcaneal abnormalities were detected in 39% of these cases. Of these 25 patients, 24 were male (mean age 57 years), all were RF positive, and the average disease duration was 16 years. The high rate of RF positivity and male predominance was contrasted with the findings in our study. The incidence of patients presenting with both symptomatic and radiographic heel findings was determined to be 12%.[8] Bouysset et al. conducted a clinical and radiological study involving a total of 204 RA patients, with a mean age of 55.8 years and a mean disease duration of 8.2 years, aiming to highlight the association between specific heel lesions and midfoot involvement. They found the incidence of heel pain to be 3.8%, inferior CS to be 29.6%, and posterior CS to be 30.8%. It was reported that the frequency of CS increases with the patients' age and the duration of the disease. In this study, as in our study, inflammatory CS have been included in the results; however, despite this high rate of spur formation, the cases were analyzed for SpA.[17] In the multicenter prospective study by Helliwell et al., CE (erosion or new bone formation) was detected in 9.6% of RA cases; the definition of enthesitis included irregular bone tissue changes, however there was no data on inflammatory heel symptoms in the RA cases.[18]

Suzuki et al. found the frequency of Achilles tendon enthesitis as 22% using power Doppler ultrasonography (US) in RA cases.[19] Moreover, Falsetti et al. reported the frequencies of posteroinferior and inferior calcaneal enthesophytes to be 34% and 46%, respectively, using US.[20] Abdelzaher et al. compared ultrasonographic findings in the feet and ankles of 152 newly diagnosed RA patients, with a mean age of 43.2 years and 69.7% RF positivity, with those of healthy controls Pathologies involing the feet and ankles were significantly more frequent in RA patients compared to healthy controls. The most common soft tissue pathologies were tibialis posterior tenosynovitis (45.4%), peroneal tenosynovitis (39.1%), Achilles tendon enthesitis (37.8%); calcaneal erosion was 9.9% and plantar fasciitis was 18.1%. A notable result from this study is that Achilles enthesitis is an independent risk factor for functional disability, alongside tibiotalar synovitis, subtalar synovitis, and tibialis posterior tenosynovitis.[21] The discrepancy between previous studies and our study regarding calcaneal changes is undoubtedly due to the greater sensitivity of US compared to radiography in detecting enthesitis.[19-21]

An increase in data and awareness related to inflammatory enthesitis in RA cases is expected to positively contribute to the choice of treatment modalities in RA cases. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biological agents such as Rituximab, Abatacept, Tocilizumab, and Anakinra have not been shown to be effective in the treatment of enthesitis. In contrast, anti-TNF biological agents are effective in the treatment of enthesitis in SpA group diseases.[22] In addition, tsDMARDs that are Janus kinase inhibitors such as Tofacitinib, Upadacitinib, and Filgotinib are superior to placebo in the treatment of enthesitis.[23] In our study, the majority of cases undergoing biological therapy, comprising 87.1% were seropositive (RF+, anti-CCP+ or both RF+ and anti-CCP+), as a reflection of this, Rituximab was the most commonly chosen biological agent.

Our study had some limitations including retrospective design, the absence of a healthy control group, the lack of analysis of the patients' body mass indexes, the absence of using US or magnetic resonance imaging methods, which are more sensitive in detecting enthesitis, and the lack of the HLA-B27 test, which is included in both peripheral and axial Assessment of Spondyloarthritis International Society SpA classification criteria, in the CE (+) group.[11,24,25] However, it should be noted that the HLA-B27 positivity rate is 4.5% in the healthy Turkish population.[26] Furthermore, Vera-Marela et al. evaluated ankle enthesitis both HLA-B27 positive and negative RA cases and found no significant difference between the two groups.[27]

In conclusion, we conducted this study exclusively on symptomatic cases using an imaging method with low sensitivity for CE, and found a frequency of 4.4% in RA patients. The presence of SpA in approximately one-fourth of our cases, while absent in the remaining three-fourths, suggests that enthesitis in these cases may be secondary to RA. The absence of chronic ankle synovitis in the CE (+) group supports that enthesitis is not related to synovitis, but its mechanism remains unknown. Considering this, we believe that extra-synovial musculoskeletal involvement in RA patients should be assessed not only in terms of synovitis or tenosynovitis but also with regard to enthesitis. It appears that enthesitis studies have predominantly focused on SpA patient populations, while other inflammatory rheumatic diseases have been relatively neglected. However, growing evidence suggests that enthesitis can also coexist in RA. The studies conducted thus far do not provide an algorithm or treatment recommendations on this topic. Prospective, large-scale, randomized controlled trials utilizing high-sensitivity imaging techniques are needed in this regard.

Conflict of Interest: The authors have no conflicts of interest to declare.

Researchers' Contribution Rate Statement: Concept/Design: MP, ZF; Analysis/Interpretation: MP, ZF; Data Collection: MP, ZF; Writer:MP; Critical Review: MP, ZF; Approver: MP, ZF.

Support and Acknowledgment: No financial support received from any institution or person.

Ethical approval: The study was approved by the ethical committee of university where the study was conducted (date: 07/26/2023, decision number: 07).

REFERENCES

1. Smolen JS, Aletaha D, Barton A et al. Rheumatoid arthritis. *Nat Rev Dis Primers.* 2018;4:18001.
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;365(23):2205-2219.
3. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. *Eur J Radiol.* 1998;27(Suppl 1):18-24.
4. Schett G, Lories RJ, D'Agostino MA et al. Enthesitis: From pathophysiology to treatment. *Nat Rev Rheumatol.* 2017;13(12):731-741.
5. Slobodin G, Rimar D, Boulman N et al. Entheseal involvement in systemic disorders. *Clin Rheumatol.* 2015;34(12):2001-2010.
6. Neogi T, Aletaha D, Silman AJ et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. *Arthritis Rheum.* 2010;62(9):2582-2591.
7. Swinkels HL, Laan RF, van 't Hof MA, van der Heijde DM, de Vries N, van Riel PL. Modified sharp method: Factors influencing reproducibility and variability. Semin *Arthritis Rheum.* 2001;31(3):176-190.
8. Resnick D, Feingold ML, Curd J, Niwayama G, Goergen TG. Calcaneal abnormalities in articular disorders: Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Reiter syndrome. *Radiology.* 1997;125(2):355-366.
9. Sebes JI. The significance of calcaneal spurs in rheumatic diseases. *Arthritis Rheum.* 1989;32(3):338-340.
10. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum.* 1998;41(10):1845-1850.
11. Rudwaleit M, van der Heijde D, Landewé R et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011;70(1):25-31.
12. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27(4):361-368.
13. Bywaters EG. Heel lesions of rheumatoid arthritis. *Ann Rheum Dis.* 1954;13(1):42-51.
14. Mason RM, Murray RS, Oates JK, Young AC. A comparative radiological study of Reiter's disease, rheumatoid arthritis and ankylosing spondylitis. J Bone Joint Surg Br. 1959;41(1):137-148.
15. Bassiouni M. Incidence of calcaneal spurs in osteo-arthrosis and rheumatoid arthritis, and in control patients. *Ann Rheum Dis.* 1965;24(5):490-493.
16. Gerster JC, Vischer TL, Bennani A, Fallet GH. The painful heel. Comparative study in rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, and generalized osteoarthrosis. *Ann Rheum Dis.* 1977;36(4):343-348.
17. Bouysset M, Tebib J, Weil G et al. The rheumatoid heel: Its relationship to other disorders in the rheumatoid foot. *Clin Rheumatol.* 1989;8(2):208-214.
18. Helliwell PS, Porter G; CASPAR study group. Sensitivity and specificity of plain radiographic features of peripheral enthesopathy at major sites in psoriatic arthritis. *Skeletal Radiol.* 2007;36(11):1061-1066.
19. Suzuki T, Hidaka Y, Seri Y. Retrocalcaneal bursitis precedes or accompanies achilles tendon enthesitis in the early phase of rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord.* 2018;11:179544118781094.
20. Falsetti P, Frediani B, Fioravanti A et al. Sonographic study of calcaneal entheses in erosive osteoarthritis, nodal osteoarthritis, rheumatoid arthritis and psoriatic arthritis. *Scand J Rheumatol.* 2003;32(4):229-234.
21. Abdelzaher MG, Finzel S, Abdelsalam A, Enein AF, Abdelsalam N. Ankle and foot pathologies in early

KÜ Tıp Fak Derg 2025;27(2):120-126
Doi: 10.24938/kutfd.1546206

rheumatoid arthritis, what can ultrasound tell us? *Int J Rheum Dis.* 2022;25(11):1315-1323.
22. Ramiro S, Nikiphorou E, Sepriano A et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis.* 2023;82(1):19-34.
23. Jubber A, Tahir H, Moorthy A. Clinical efficacy of JAK inhibitors on enthesitis in spondyloarthropathy: A scoping literature review. *Musculoskeletal Care.* 2023;21(4):1195-1203.
24. Mandl P, Navarro-Compán V, Terslev L et al. European League Against Rheumatism (EULAR) recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis.* 2015;74(7):1327-1339.
25. Rudwaleit M, van der Heijde D, Landewe´ R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): Validation and final selection. *Ann Rheum Dis.* 2009;68(6):777-783.
26. Acar M, Cora T, Tunc R, Acar H. HLA-B27 subtypes in Turkish patients with ankylosing spondylitis and healthy controls. *Rheumatol Int.* 2012;32(10):3103-3105.
27. Mera-Varela A, Ferreiro-Iglesias A, Perez-Pampin E, Porto-Silva M, Gómez-Reino JJ, Gonzalez A. Ultrasonographic assessment of enthesitis in HLA-B27 positive patients with rheumatoid arthritis, a matched case-only study. *PLoS One.* 2013;8(3):e58616.