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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

What Causes Joint Pain in Rheumatoid Arthritis Patients with Clinical Remission and Low Disease Activity according to DAS28?

DAS28'e göre Klinik Remisyon ve Düşük Hastalık Aktivitesi Olan Romatoid Artritli Hastalarda Eklem Ağrısına Ne Sebep Olur?

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ABSTRACT

Objective: The aim of this study was to evaluate synovial activity in patients with rheumatoid arthritis (RA) who were in remission or had low disease activity according to the DAS-28 (Disease activity scale-28) but complained of joint pain.

Material and Method: A retrospective review was made of the records and admission files of patients diagnosed with RA according to the American Rheumatism Association criteria between January 2016 and January 2018. The modified health assessment questionnaire (m-HAQ) and ultrasonographic evaluations of patients were recorded. Patients were compared in terms of demographic and disease characteristics according to the presence of synovitis detected with ultrasongraphy. Correlations between the presence of synovitis and demographic and disease characteristics were also evaluated.

Results: This trial included 53 patients with the diagnosis of RA who were in remission or had low disease activity (DAS-28 <3.2) for at least 6 months and had pain symptoms in at least one joint. Synovitis was detected on US in 23 (43.4%) patients, and in these patients, tenderness joint count (TJC) (p =0.03) and m-HAQ (p =0.019) were significantly higher. The presence of synovitis was associated with an increase in TJC (r: 0.518, p=0.001) and a deterioration in general health(r: 0.318, p=0.025). This relationship was shown to continue in the multivariate regression analysis

Conclusion: Even if patients show clinical remission or low disease activity, ultrasonographic evaluation should be performed in the presence of joint complaints. The use of US will continue to play an important role in the management of patients with RA, including in the assessment of disease activity when the disease activity status is not clinically apparent.

Keywords: Rheumatoid arthritis, ultrasonography, DAS28

ÖZ

Amaç: Bu makale, romatoid artritli (RA) remisyonda olan veya DAS-28'e (Hastalık Aktivite Skalası-28) göre hastalık aktivitesi düşük olan ancak eklem ağrısından yakınan hastalarda sinovyal aktiviteyi değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Ocak 2016-Ocak 2018 tarihleri arasında Amerikan Romatizma Derneği kriterlerine göre RA tanısı alan hastaların kayıt ve başvuru dosyaları geriye dönük olarak incelendi. Hastaların modifiye sağlık değerlendirme anketi (m-HAQ) ve ultrasonografik değerlendirmesi kaydedildi. Hastalar ultrasonografi ile saptanan sinovit varlığına göre demografik ve hastalık özellikleri açısından karşılaştırıldı. Ayrıca sinovit varlığı ile demografik ve hastalık özellikleri arasındaki korelasyonlar değerlendirildi.

Bulgular: Bu çalışmaya en az 6 aydır remisyonda olan veya hastalık aktivitesi düşük (DAS-28 <3.2) olan ve en az bir eklemde ağrı semptomları olan RA tanılı 53 hasta dahil edildi. Ultrasona göe 23 (%43,4) hastada sinovit mevcuttu, bu hastalarda hassas eklem sayısı (p=0,03) ve m-HAQ (p=0,019) anlamlı olarak yüksekti. Sinovit varlığı, hassas eklem sayısında bir artış (r: 0.518, p=0.001) ve genel sağlıkta bir bozulma (r: 0.318, p=0.025) ile ilişkili olarak bulundu. Bu ilişkinin çok değişkenli regresyon analizinde devam ettiği gösterildi.

Sonuç: Hastalar klinik remisyon veya düşük hastalık aktivitesi gösterse bile eklem şikayetlerinin varlığında ultrasonografik değerlendirme yapılmalıdır. Ultrason kullanımı, hastalık aktivite durumu klinik olarak belirgin olmadığında hastalık aktivitesinin değerlendirilmesi dahil, RA'lı hastaların yönetiminde önemli bir rol oynamaya devam edecektir.

Anahtar Kelimeler: Romatoid artrit, ultrasonografi, DAS28

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic connective tissue disease that causes symmetrical multiple joint damage through inflammation of the synovial membrane (1). The clinical evaluation of RA patients includes questionnaires that address history, physical examination, disease activity scores and quality of life (2). The European League Against Rheumatism (EULAR) recommended that the treatment of RA should target remission or low disease activity in each patient (3). The currently recommended RA management strategies are guided by close monitoring of disease activity using composite indices such as the disease activity score in 28 joints (DAS28), simplified disease activity index (SDAI) or clinical disease activity score (CDAI) (4). However, the clinical disease activity indexes have several limitations, as the clinical examination may not detect subclinical synovitis (5).

In recent years, musculoskeletal ultrasound (US) has been increasingly used in rheumatology practice worldwide, especially in cases with RA (6). One of the most common applications of US in RA is the evaluation of joint involvement for both diagnosis and follow-up after therapeutic procedures. Moreover, several studies have shown that US is more sensitive than clinical examination in the detection of synovitis (7, 8).

The aim of this study was to evaluate synovial activity in patients with RA who were in remission or had low disease activity according to the DAS-28 but complained of joint pain.

MATERIAL AND METHOD

A retrospective review was made of the medical charts of 53 patients diagnosed with RA according to the criteria of the American Rheumatism Association (ACR), who attended the outpatient clinic for follow-up visits between 2016 and 2018.

The study inclusion criteria were patients aged >18 years, who were in remission or had low disease activity (DAS-28 <3.2) for at least 6 months (9) and who had pain symptoms in at least one joint.

Exclusion criteria were defined as patients with moderate or severe disease activity, a history of trauma, surgery in the extremities, malignancy, other inflammatory and connective tissue disease, painful non-inflammatory diseases (such as fibromyalgia, osteoarthritis), progressive and non-progressive central and peripheral nervous disease, or known psychiatric and mood disorders.

Demographic and Disease Characteristics

The medical records of the patients included in the study were retrospectively evaluated. A record was made of demographic characteristics including age, gender, education status, employment status, comorbidities, and disease features including disease duration, used medication, and painful, tender and swollen joints (28 joints including bilateral shoulders, elbows, wrists, metacarpophalangeal 1-5, interphalangeal 1 and proximal interphalangeal 2-5). Disease-related laboratory parameters, including rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were recorded on the same day as the ultrasonographic evaluation.

The outcome measures included the following: patient global assessment (PGA), local pain level of painful joints measured with a visual analogue scale (VAS) of 100 mm, and the functional status of the patients evaluated using the modified Health Assessment Questionnaire (m-HAQ).

The m-HAQ consists of 8 items that evaluate the disability of the patients in daily activities. A high score indicates poor health status (10). The m-HAQ of patients was calculated using the number of tender and swollen joints, PGA and ESR level.

All US examinations were performed by a single experienced PMR specialist. The standard assessments of the joint began with the patient sitting or lying supine according to the joint region being examined. Optimal imaging was obtained with both longitudinal and transverse scanning using a 7-12 MHz linear array transducer (Logiq P5, GE, Medical Systems, USA). The painful joint was evaluated with gray-scale for synovitis (hypertrophy and/or effusion) and with power Doppler for synovial blood flow signals. The bone, muscle and tendons around the joint were also scanned. According to the results of the ultrasonographic evaluation, the presence or absence of synovitis in the painful joint was recorded.

Study Protocol

Clinical and US evaluations were performed by different specialists on the same day. Patients were compared in terms of demographic and disease characteristics according to the presence of synovitis evaluated on US. Correlations were investigated between synovitis presence and demographic and disease characteristics.

Statistical Analysis

Data obtained in the study were analyzed statistically using Statistical Package for the Social Sciences (SPSS 22.0 for Windows) software. The conformity of continuous variables to normal distribution was evaluated using the Kolmogorov-Smirnov test. In descriptive statistics, the data were expressed as median (minimum-maximum) for continuous variables, and as frequencies and percentages (%) for nominal variables. Statistically significant differences between the groups were analyzed with the Mann Whitney-U test. Spearman's rho correlation coefficient was performed to measure the relationship between synovitis and the evaluation parameters. For significant correlations, multivariate regression analysis was performed using the parameters in patients without synovitis as the dependent variable. A value of $p<0.05$ was considered statistically significant.

RESULTS

The 53 patients included in the study comprised 38 (71.7%) females and 15 (28.3%) males with a median age of 45.50 years (range, 27.0-63.0 years). Comorbidities were determined in 22 (41.5%) patients.

The demographic and disease characteristics of the patients are presented in **Tables 1** and **2.**

Table 1. Demographic characteristics of the patients

	n=53
Age (year) median (min-max)	45.50 (27.0-63.0)
Gender n (%)	
Female	38 (71.7)
Male	15 (28.3)
Education duration n (%)	
Illiterate	0
Just literate	4 (7.5)
5 years	29 (54.7)
8 years	10 (18.9)
11 years	10 (18.9)
>11 years	0
Job n (%)	
Housewife	31 (58.5)
Blue collar	6 (11.3)
White collar	0
Retired	16 (30.2)
Additional comorbidities n (%)	
Number of patients with comorbidity	22 (41.5)
HT	11 (20.8)
DM	3 (5.7)
Hyperlipidemia	6 (11.3)
Cardiac disease	2 (3.8)
Osteoporosis	1 (1.9)
Hypothyroidism	2 (3.8)
Peptic ulcer	4 (7.5)

Min-max: minimum-maximum; HT: hypertension, DM: diabetes mellitus.

The median disease duration was 15.0 years (range, 7.0-28.0 years) and the median DAS-28 score was 2.05 (range, 1.0-3.18). The most painful joints of the patients were the metacarpophalangeal joint (n=24, 45.3%), knee (n=16, 30.2%), wrist and ankle (n=9, 17%), metatarsophalangeal joint (n=5, 9.4%). and proximal interphalangeal joint (n=4, 7.5%), respectively. Joint pain was bilateral in 18 (34%) patients.

Synovitis was detected on US in 23 (43.4%) patients. The median local VAS for the painful joint was 50.0 (range, 25.0-75.0). The comparisons of demographic and disease characteristics of patients with (n=23) and without (n=30) synovitis are shown in **Table 3**.

In patients with synovitis, TJC and health disability were significantly higher (p=0.03, p=0.019, respectively). There was no difference in other parameters.

Table 2. The disease characteristics of the patients

Parameter	n=53
Disease duration (year) median (min-max)	15.0 (7.0-28.0)
Number of tender joints (0-28) median (min-max)	2.0 (0.0-8.0)
Number of swollen joints (0-28) median (min-max)	0.0 (0.0-0.0)
PGA (0-100 mm) median (min-max)	10.0 (0.0-25.0)
DAS 28 score median (min-max)	2.05 (1.0-3.18)
ESR level (mm/hour) (0-20) median (min-max)	13.0 (4.0-40.0)
CRP (µg/dl) (0-5) median (min-max)	4.10 (1.50-11.0)
RF (IU/mL) (0-20) median (min-max)	21.0 (5.0-87.0)
m-HAQ (0-3) median (min-max)	1.0 (0.50-1.75)
Used medication n (%)	
NSAID	42 (79.2)
Methotrexate	35 (66.0)
Sulphasalazine	37 (69.8)
Hydroxychloroquine	13 (24.5)
Leflunomide	11 (20.8)

Min-max: minimum-maximum, DAS 28: disease activity score 28, ESR: Erythrocyte sedimentation rate, CRP: C - reactive protein, RF: Rheumatoid factor, m-HAQ: modified health assessment questionnaire. PGA: patient general health assessment, NSAID: nonsteroidal anti-inflammatory drugs

Table 3. Comparison of evaluation parameters of patients with and without synovitis

Parameter	Patients with synovitis n=23	Patient without synovitis n=30	p
Age (year) median (min-max)	44.00 (29.0-63.0)	46.00 (27.0-58.0)	0.190
Gender			0.758
Female	17 (73.9)	21 (70.0)	
Male	6 (26.1)	9 (30.0)	
Presence of additional comorbidity n (%)	9 (39.1)	13 (43.3)	0.614
Disease duration (year) median (min-max)	15.0 (7.0-20.0)	12.0 (8.0-28.0)	0.209
Number of tender joints (0-28) median (min-max)	5.0 (0.0-10.0)	2.0 (0.0-5.0)	0.003
Number of swollen joints (0-28) median (min-max)	0 (0.0-0.0)	0.0 (0.0-0.0)	1.000
PGA (0-100 mm) median (min-max)	10.0 (10.0-25.0)	10.0 (0.0-25.0)	0.116
DAS 28 score median (min-max)	2.0 (1.0-3.18)	2.15 (1.65-3.07)	0.485
ESR level (mm/hour) (0-20) median (min-max)	14.0 (7.0-40.0)	13.0 (4.0-10.0)	0.102
CRP (µg/dl) (0-5) median (min-max)	4.05 (1.50-11.0)	4.10 (1.68-10.5)	0.930
RF (IU/mL) (0-20) median (min-max)	24.0 (19.0-87.0)	25.0 (5.0-78.0)	0.540
m-HAQ (0-3) median (min-max)	1.25 (0.50-1.75)	1.00 (0.50-1.25)	0.019
Local VAS for painful joint median (min-max)	50.0 (30.0-75.0)	50.0 (25.0-70.0)	0.114

Min-max: minimum-maximum, PGA: patient general health assessment, DAS 28: disease activity score 28, ESR: Erythrocyte sedimentation rate, CRP: C - reactive protein, RF: Rheumatoid factor, m-HAQ: modified health assessment questionnaire, VAS: visual analogue scale

The correlation analysis between the presence of synovitis and the demographic and disease characteristics of the patients is presented in **Table 4**.

Table 4. Correlation analysis between the presence of synovitis and demographic and disease characteristics

Parameter	r	p
Age	-0.232	0.094
Presence of additional comorbidity	0.043	0.760
Disease duration (year)	-0.128	0.362
Number of tender joints (0-28)	0.518	0.001
PGA (0-100 mm)	0.092	0.513
DAS 28 score	-0.040	0.776
ESR level (mm/hour) (0-20)	0.040	0.572
CRP (µg/dl) (0-5)	0.080	0.369
RF (IU/mL) (0-20)	0.143	0.308
m-HAQ (0-3)	0.318	0.025
Local VAS for painful joint (0-100 mm)	-0.157	0.262

r: correlation coefficient, PGA: patient general health assessment, DAS 28: disease activity score 28, ESR: Erythrocyte sedimentation rate, CRP: C - reactive protein, RF: Rheumatoid factor, m-HAQ: modified health assessment questionnaire, VAS: visual analogue scale

The presence of synovitis was found to be associated with an increase in TJC (r: 0.518, p=0.001) and a deterioration in general health (r: 0.318, p=0.025). This relationship was shown to continue in the multivariate regression analysis (**Table 5**).

Table 5. Multivariate regression analysis

	β	SE	P value	95 CI	
				lower bound	upper bound
Number of tender joint	0.107	0.030	0.003	-0.046	0.168
m-HAQ	0.104	0.212	0.037	-0.321	0.530

95% CI: 95% confidence interval; SE: standard error, m-HAQ: modified health assessment questionnaire

DISCUSSION

US is increasingly being used in both clinical practice and clinical trials to detect and monitor arthritis in RA (11). The examination of aching joints with US can help to identify the cause of pain, which may result from irreversible destructive changes or active inflammation of the synovial membrane (12). Ultrasound can evaluate the morphology and quantity of synovitis with gray scale (GS) and synovial vascularity with power Doppler (PD) (13). The combined use of PD and GS is an easy and non-invasive imaging modality in RA and has been shown to be an objective and sensitive tool for synovial inflammatory joint changes which cannot be detected in conventional clinical and radiographic examinations. (7,14,15).

GS and PD may show subclinical synovitis in patients with RA in remission achieved by the use of synthetic or biological disease-modifying antirheumatic drugs (DMARDs). Some studies have shown that US is superior to clinical examination in the detection of arthritis in RA (8).

In the current study, consistent with the literature, synovitis was detected in 43.4% of the patients in the US examination of the joints with pain despite clinical remission or low disease activity. In a study by Macchioni et al., it was reported that regardless of the specific criteria of remission used, when evaluated with US, synovitis activity is detected in 60–80% of patients (16). In another study, PD activity was found in 15–62% of patients in clinical remission according to the DAS28, ACR or SDAI remission criteria (17). In contrast, Ventura-Ríos et al reported a low percentage of active synovitis according to a score of 7 PD on US in RA patients with long remission (18).

The DAS28 has been used for the monitoring of RA activity for many years. It includes physical examination of tender and swollen joints, laboratory parameters, and an overall assessment of the patient's health status. DAS28 is used in both early and long-term RA patients. This may lead to conditions where pain is considered to be from destructive lesions rather than active inflammation or joint swelling from irreversible synovial hypertrophy due to prolonged inflammation. However, physical examination cannot determine subclinical synovitis (19). Therefore, the correlation between US findings and DAS28 scores tends to be weak. Nevertheless, it should be noted that this is due to differences in evaluation methods rather than the superiority of one method over another (20).

In a previous study which used SAS 1 score as a tool for RA activity assessment with US, this was seen to provide more objective results than the DAS28, which has subjective bias as it is a patient self-assessment of general health and evaluation of tender and swollen joint counts. The use of the SAS 1 score was also reported to provide results of remission more frequently than the DAS28 score, as synovitis collapse can be more easily evaluated on US, while in the same patient the DAS28 score may remain increased due to elevated ESR caused by old age or irreversibly damaged joints which remain tender [19]. DAS28 is less valid in cases where for example, a patient with concomitant fibromyalgia will have high TJC and VAS, or for obese patients in whom clinical joint examination may be difficult and who may have higher ESR without joint inflammation (21). In the APPRAISE study, it was shown that there was no exact correlation between disease activity assessments with PD and DAS28 (22). Some studies investigating US predictors for clinical remission have shown that US is not predictive of clinical remission (23, 24).

Another result of the current study was that in patients with synovitis, the TJC and HAQ scores were significantly higher. In a study by Zavada et al, PD and GS synovitis were found to be significantly positively correlated with the current HAQ score, similar to the finding of the current study (25).

This study had some limitations. Previous studies have reported a lack of complete overlap between ultrasound-assessed disease activity and clinical measures, with one study suggesting that the SDAI is more in line with US assessment of disease state than DAS28 (26). Furthermore, other studies have reported that PD results were more strongly correlated with the clinical assessment based on the SDAI (17, 22). A further limitation of the study was that although the DMARD used by the patient may affect the degree of synovitis, the relationship between DMARD and synovitis was not examined.

CONCLUSION

The disease activity scores used in daily practice for patients with RA may overlook the subclinical activity in these patients. Even if the patient shows clinical remission or low disease activity, ultrasonographic evaluation should be performed in the presence of joint complaints. Given the increased use of US in the evaluation of synovitis, this study is important in respect of further validating the role of US in the daily evaluation of clinical disease activity. Although both US and DAS28 have been shown to be valid indicators of patient health improvements, it would not be correct to seek a relationship between them as they reflect different aspects of the disease. Ultrasound will continue to play an important role in the management of patients with RA, including assessment of disease activity when the disease activity status is not clinically apparent..

ETHICAL DECLARATIONS

Ethics Committee Approval: In this research, the data before 2020 was used and the research was concluded before 2020. According to the Regulation on Clinical Researches published in the Official Gazette of the Republic of Turkey with the number 28617 dated 3 November 2015, the ethics committee approval was not obtained in accordance with the article "Retrospective studies are outside the scope of the regulation (article 2-(2))". This study was prepared in accordance with the Law on Protection of Personal Data, by anonymizing patient data and in accordance with the 2013 Brazil revision of the Helsinki Declaration and guidelines for Good Clinical Practice.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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