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Assessment of disease activity with simplified joint ultrasonography method in rheumatoid arthritis patients

Nurdan Orucoglu [1], Alev Alp [2], Deniz Merih Yurtkuran [2]

[1] Department of Internal Medicine, Division of Rheumatology, Medical Faculty of Mersin University, Mersin, Turkey
[2] Department of Physical Therapy and Rehabilitation, Medical Faculty of Uludag University, Bursa, Turkey

ORCID ID of the author(s)
NO: 0000-0002-8613-5373
AA: 0000-0002-3904-5463
DMY: 0000-0003-0325-1924

Corresponding Author
Nurdan Orucoglu
Department of Internal Medicine, Division of Rheumatology, Mersin University Faculty of Medicine, Mersin, TR-33343, Turkey
E-mail: nurdanorucoglu@yahoo.com

Ethics Committee Approval
The study was approved by ethics committee of Uludag University Faculty of Medicine, Turkey (Approval date and Decision no: 19/12/2013: 2013-19/12).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Ultrasound (US) is a highly useful tool for assessing the disease activity of rheumatoid arthritis (RA). On the other hand, examining all joints could be time-consuming and unfeasible. Defining the number of joints and which joints should be tested is essential to accurately measuring RA activity. Several simplified US methods are undergoing development for this purpose. The aim of this study was to assess the correlation between simplified 12-joint US findings and physical examination findings/disease activity in RA patients.

Methods: This cohort study included 62 RA patients who had been undergoing treatment for at least three months. Multiplanar grayscale images and power Doppler (PD) of the 12 joints (bilateral elbow, wrist, second and third metacarpophalangeal [MCP] joints, knee, and ankle) were acquired and compared with clinical assessments. Disease activity was assessed using the clinical disease activity and simplified disease activity indices and disease activity score-28 (CDAI, SDAI, and DAS28, respectively). Synovial effusion, synovial proliferation, and PD US scores were calculated for 12 joints. Correlations between US scores and disease activity, clinical examination, and acute phase reactants were assessed.

Results: The number of joints with PD activity and US total and US synovial proliferation scores showed weak correlations with clinical activity scores (r = 0.25, r = 0.26, and r = 0.28 for SDAI and r = 0.23, r = 0.26, and r = 0.28 for DAS28, respectively). The CDAI did not present any statistically significant correlations. The agreement between US findings and clinical joint examination was generally weak. PD activities of the second MCP joints (r = 0.84, $P < 0.01$) and knees (r = 0.42, $P < 0.01$) mostly correlated with clinical examination although it was weakly correlated at the third MCP (r = 0.152) and wrist (r = 0.148), and not correlated at the elbow (r = 0.125).

Conclusion: The weak correlation between US findings and clinical examination/disease activity suggests that clinical examination alone may not be sufficient to determine joint inflammation and disease activity. US could provide a more accurate assessment of RA patients and aid in medication selection.

Keywords: Disease activity, Rheumatoid arthritis, Ultrasound

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Introduction

Rheumatoid arthritis (RA) can cause erosive joint destruction and severe loss of joint function if not treated properly [1]. Early diagnosis and treatment of the disease is important because greater inflammatory activity is observed during the first years of RA [2]. Disease remission is now an achievable target due to advances in biological treatments and tight control strategies [3]. Regular and sensitive disease monitoring is required to effectively control symptoms and accurately assess synovial inflammation to attain this goal [4]. Currently, in terms of disease activity and treatment response evaluations in RA patients, composite clinical disease activity indices are used, which include some subjective clinical variables, such as joint tenderness and patient and physician global assessments of the disease [5–7]. In general, these indices are useful in assessing patients' global disease activity, but assessment of joint tenderness and swelling based on clinical examination may not be sensitive enough to accurately guide anti-rheumatic treatments because they cannot directly measure inflammation [8].

With recent advancements in medical treatment for RA and changes in treatment goals, a greater need for more reliable monitoring methods exists, and ultrasound (US) appears to be a promising monitoring tool for addressing this need [9–11]. Evaluation with US is more time-consuming than clinical joint examination. This process makes it more difficult for every patient to routinely obtain an US scan in clinical settings. In clinical practice, evaluating all accessible joints could take a long time, making it difficult to administer. As a result, many researchers have developed a simplified US score to expedite US evaluation and improve reliability and validity during treatment follow-up [12–14]. Simplified US procedures have been shown to be valid and reliable for assessing disease activity and inflammation [12–15]. However, no agreement on which joints should be assessed in RA imaging and how many joints should be tested to correctly define disease activity can be found [13, 16–18].

This study aimed to assess the correlation between clinical joint examination, disease activity indices, and US findings in RA patients and determine the degree of correlation between different joints based on the simplified 12-joint scoring method described by Naredo et al. [13].

Materials and methods

Study protocol

The study included 62 patients who presented to the Uludag University Rheumatology outpatient clinic between December 2013 and April 2014 and were diagnosed with RA according to the 1987 American Rheumatism Association and 2010 American Rheumatism Association criteria. Patients must have been receiving medication for at least three months. The study was approved by the local Ethics Committee of Uludag University, Turkey (Approval date and Decision no: 19/12/2013: 2013-19/12). The purpose and scope of the study were explained to participants, and the informed consent form was signed.

Clinical and laboratory evaluation

Demographic and clinical patient data, such as gender, age, disease duration, duration of morning stiffness, and medications used to treat rheumatoid arthritis were collected. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values over the last week were recorded. Swelling and tenderness in 28 joints (bilateral elbow, shoulder, wrist, metacarpophalangeal [MCP] and proximal interphalangeal joints, and knees) were identified after clinical examination. The disease activity was measured using the clinical disease activity and simplified disease activity indices and disease activity score 28 (CDAI, SDAI, and DAS28, respectively). Health assessment questionnaire (HAQ) scores of the patients were also calculated.

Ultrasonographic evaluation

The US evaluations were performed by a single investigator blinded to the clinical and laboratory findings of the patients. Following the clinical examination and evaluation of the patients, grayscale and power Doppler (PD) US evaluation of 12 joints (bilateral second and third MCP joints, wrist, elbow, knees, and ankles) were performed on the same day. Ultrasound was performed with the MyLab60 (Esaote, Genova, Italy) US device with a 6–18 MHz multi-frequency linear probe. Multiplanar grayscale (B-Mode) and PD images of 744 joints were obtained. US evaluation was based on the simplified 12-joint scoring method described by Naredo et al. [13] and 24 synovial areas in 12 joints, including anterior and posterior recesses of the elbow, dorsal carpal recess of the wrist, dorsal and palmar sides of the second and third MCP joints, suprapatellar and lateral parapatellar recess of the knee, anterior tibiotalar recess of the ankle, and medial and lateral tendon sheaths, were evaluated.

The Outcome Measures in Rheumatology (OMERACT) definitions were used to assess synovial hypertrophy, effusion, joint erosion, and the presence of PD signals in each joint [19]. The highest score (from 0 to 3) for effusion, synovial hypertrophy, and/or PD in any synovial area of each joint was accepted as the joint's synovial effusion/proliferation and PD score. For 12 joints, the US-synovial effusion score (US-SE), US-synovial proliferation score (US-SP), and US-power Doppler score (US-PD) ranging from 0 to 36 were calculated. The total US score (USTotal) was calculated by adding the effusion, synovial proliferation, and PD US scores from 12 joints (ranging from 0 to 108). For each patient, the number of joints with synovial effusion (SE-JC), synovial proliferation (SP-JC), and PD signal (PD-JC) were counted. Pathological synovitis was defined as a grayscale and/or a PD US signal score ≥ 1.

Statistical analysis

A Kendall's W value of < 0.40 was considered a weak correlation, 0.40–0.69 a moderate correlation, 0.70–0.89 a high correlation, and 0.90–1.00 a very strong correlation. As a result, correlation coefficients of at least ≥ 0.4 in US parameters were considered significant. The sample size was at least 47 when the Type I error was set at 0.05, and the confidence interval was 80%. Sixty-two patients were enrolled in this study.

Statistical analysis was performed with SPPS version 22.0 (Chicago, IL, USA) software. Quantitative variables, such as gender, age, disease duration, DAS28, SDAI, and CDAI were given as descriptive statistics (mean, standard deviation,

maximum–minimum values). The Kolmogorov–Smirnov test was used to assess the normality of variable distribution. Pearson's correlation analysis was used to determine the correlation between disease activity scores and US parameters with a normal distribution, and the Spearman's correlation analysis was used to determine the correlation between parameters with a non-normal distribution and ordinal variables. The Cohen's kappa (κ) statistic was used to test the agreement between clinical examination and US findings.

Results

Patient Characteristics

Of the patients included in the study, 91.9% (n = 57) were female and 8.1% (n = 5) were male. The mean age of the patients was 51.82 (11.71), and the mean disease duration was 117.94 (99.96) months. The clinical characteristics of the patients are presented in Table 1. Sixty patients were using at least one disease-modifying anti-rheumatic drug (DMARDs) either synthetic or biological or in some cases, both. Forty-three of these patients were using synthetic DMARDs, and 17 were using biological DMARDs whether in monotherapy or in combination.

Table 1: Demographic and clinical characteristics of the patients

	Mean (SD)
Age (years) (Min–Max)	51.82 (11.71) (24–77)
Disease duration (months) (Min–Max)	117.94 (99.96) (5–408)
ESR (mm/h)	22.13 (13.65)
CRP (mg/dl)	0.95 (1.00)
Swollen joint count (28 joints)	2.15 (2.73)
Tender joint count (28 joints)	5.65 (6.69)
HAQ	0.63 (0.52)
Morning stiffness (minutes)	49.68 (109.09)
Patients' global disease assessment score	4.48 (2.48)
Physicians' global disease assessment score	4.2 (2.12)
DAS28-ESR	4.04 (1.41)
DAS28-CRP	3.71 (1.24)
SDAI	17.29 (11.53)
CDAI	16.11 (11.30)
Mean US time (minutes)	24.8 (4.8)

SD: standard deviation, ESR: erythrocyte sedimentation rate, CRP: C-Reactive protein, HAQ: Health assessment questionnaire, DAS28: 28 joint disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index

Correlation between clinical, laboratory and ultrasonographic parameters

A significant correlation was found between the physician' global disease score and all US parameters except the number of joints with effusion and the effusion US score. No correlation between the global disease evaluation of the patient and any US parameters was found. No correlation was found with any US parameters between the patients' global disease scores and health assessment questionnaire (HAQ) as shown in Table 2.

No significant correlation between CRP and PD US findings and the number of joints with erosion was found, while weak correlations between CRP and other US parameters were detected. Significant correlations between ESR and all US parameters were found (Table 2).

No significant correlations between swollen joint count, joints with effusion count, and the effusion US score were noted, but a moderate correlation was found in terms of other parameters. Good correlation (r = 0.59, $P < 0.01$) between joints with erosion and swollen joints was found. A weak correlation between tender joint counts and the joints with erosion was found, but no significant correlation was found between other US parameters (Table 3).

Table 2: Correlation of clinical, laboratory, and ultrasonographic variables

	ESR	CRP	PtGDA	PhGDA	HAQ
SJC	0.27†	0.11	0.34*	0.59*	0.28†
TJC	0.26†	0.16	0.50*	0.68*	0.56*
US-SE	0.44*	0.46*	0.18	0.22	0.11
US-SP	0.38*	0.38*	0.23	0.34*	0.13
PDUS	0.30†	0.20	0.16	0.29†	0.20
PD-JC	0.26†	0.15	0.17	0.29†	0.24
SP-JC	0.27†	0.36*	0.21	0.31†	0.17
SE-JC	0.39*	0.44*	0.19	0.21	0.13
Synovitis	0.29†	0.27*	0.18	0.28†	0.19
US-Total	0.38*	0.35*	0.17	0.30†	0.16
Erosion-JC	0.26†	0.04	0.24	0.44*	0.16
PD ≥ 2	0.31†	0.32†	0.18	0.31†	0.18

* $P < 0.01$, † $P < 0.05$, US: ultrasound ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PtGDA: Patient's global disease assessment, PhGDA: Physician's global disease assessment, HAQ: Health assessment questionnaire, SJC: Swollen joint count, TJC: Tender joint count, US-SE: Synovial effusion US score, US-SP: Synovial proliferation US score, PDUS: Power Doppler US score, PD-JC: Joint count with Power Doppler activity, SP-JC: Joint count with synovial proliferation, SE-JC: Joint count with synovial effusion, US-Total: Total US score, PD ≥ 2: Presence of at least 2nd degree PD signal

Table 3: Correlation of swollen and tender joint count, disease duration, morning stiffness, and ultrasonographic parameters

	SJC	TJC	Disease duration	Morning stiffness
US-SE	0.21	0.01	-0.02	0.11
US-SP	0.39*	0.06	0.11	0.15
PDUS	0.32†	0.04	0.11	0.13
PD-JC	0.30†	0.05	0.10	0.13
SP-JC	0.37*	0.04	0.03	0.12
SE-JC	0.19	0.06	-0.04	0.13
Synovitis	0.34*	0.01	0.08	0.96
US-Total	0.34*	0.05	0.06	0.13
Erosion-JC	0.59*	0.32†	0.45*	0.05
PD ≥ 2	0.29†	0.05	0.45*	0.21

*$P < 0.01$, † $P < 0.05$, SJC: Swollen joint count, TJC: Tender joint count, US-SE: Synovial effusion US score, US-SP: Synovial proliferation US score, PDUS: Power Doppler US score, PD-JC: Joint count with Power Doppler activity, SP-JC: Joint count with synovial proliferation, SE-JC: Joint count with synovial effusion, US-Total: Total US score, PD ≥ 2: Presence of at least 2nd degree PD signal

Correlations between clinical disease activity and US scores

No correlations between CDAI and US parameters, except the eroded joint count, were found. The eroded joint count correlated moderately with DAS28-ESR (r = 0.41; $P < 0.01$), DAS28-CRP (r = 0.42; $P < 0.01$), CDAI (r = 0.49; $P < 0.01$), and SDAI (r = 0.46; $P < 0.01$). The count of joints with synovial proliferation, synovitis, and PD signals, synovial proliferation US scores, and total US scores weakly correlated with DAS28-CRP, DAS28-ESR, and SDAI scores. No correlations between the synovial effusion US score, joint count with synovial effusion, and disease clinical activity scores were found (Table 4).

Table 4: Correlation of the disease activity scores and ultrasonographic parameters

	DAS28-CRP	DAS28-ESR	SDAI	CDAI
US-SE	0.21	0.25†	0.20	0.14
US-SP	0.28†	0.29†	0.28†	0.24
PDUS	0.23	0.23	0.25†	0.18
PD-JC	0.24	0.24	0.27†	0.20
SP-JC	0.28†	0.25†	0.26†	0.21
SE-JC	0.22	0.24	0.20	0.16
Synovitis	0.31†	0.30†	0.25†	0.19
US-Total	0.26†	0.27†	0.26†	0.20
Erosion-JC	0.42*	0.41*	0.46*	0.49*
PD≥2	0.24	0.23	0.26†	0.18

* $P < 0.01$, † $P < 0.05$, DAS28: 28 joint disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index

Correlations between clinical examination and US scores

In general, the correlation between clinical joint examination and US findings was weak (Table 5). A weak correlation between only swollen joints and B-mode (κ = 0.29) and PD-US when PD2 was used (κ = 0.31) was found, but no correlation between tender joints and US findings were noted (Table 5). When clinical examination of joints and the compatibility of the US were evaluated separately on a joint basis (Table 6), no correlation between clinical examination of the elbow with B-mode and PD-US was detected. While a

significant but weak correlation between B-mode and PD ≥ 2 tender and swollen joints at the wrist was found, no significant correlation between PD-US ≥ 1 was observed. A good/excellent significant correlation with swollen and both tender-swollen joints for PD ≥ 2 in the second MCP joint was found.

A weak correlation between joint tenderness in the second MCP joint and PD US score only was noted. A significant correlation between swollen joint and B-mode/PD-US was found, while a correlation between tender joint and US findings only for PD-US ≥ 1 in the third MCP joint was observed. The highest correlation between clinical and US findings was found in terms of the second MCP joint and knees, while the correlation of the wrist and third MCP joint was weak. In the elbow, no correlation between clinical and US findings was noted (Table 6).

Table 5: Agreement between clinical examination and ultrasonographic findings

		Swollen Joint	Tender Joint	Both Swollen and Tender Joint
Gray scale ≥ 1	%	77.9	64.2	75.3
	κ	0.295	0.069	0.146
PD ≥ 1	%	71.9	66.3	70.6
	κ	0.216	0.182	0.135
PD ≥ 2	%	84.8	72.7	86.1
	κ	0.313	0.167	0.246

κ: Kappa coefficient, %: percentage of concordance, Gray scale: Presence of at least grade 1 synovial effusion and/or synovial proliferation, PD ≥ 1: Presence of at least grade 1 and higher power Doppler signal, PD ≥ 2: Grade 2 and higher power Doppler signal

Table 6: Correlation of individual joints with the presence of gray scale and power Doppler (k values)

		Gray scale	PD ≥ 1	PD ≥ 2
Elbow	Tender	0.068	0.100	0.125
	Swollen	0.154	0.036	-0.016
	Swollen and tender	-	-	-
Wrist	Tender	0.270	0.051	0.223
	Swollen	0.270	0.049	0.208
	Swollen and tender	0.154	0.035	0.148
2nd MCP	Tender	0.106	0.241	0.247
	Swollen	0.375	0.415	0.568
	Swollen and tender	0.282	0.418	0.849
3rd MCP	Tender	0.028	0.219	0.012
	Swollen	0.227	0.243	0.349
	Swollen and tender	0.017	0.079	0.152
Knee	Tender	0.038	0.270	0.129
	Swollen	0.232	0.524	0.427
	Swollen and tender	0.101	0.337	0.307

MCP: Metacarpophalangeal joint, power Doppler (PD) ≥ 1: Presence of at least grade 1 and higher PD signal, PD ≥ 2: Grade 2 and higher PD signal

Discussion

In recent years, musculoskeletal US has frequently been used for early diagnosis of RA, assessment of disease activity and treatment response, and prediction of prognosis [20-22]. The goal of US use is to accurately determine disease activity and thus provide tight control of RA [23]. In the assessment of disease activity in RA, combined clinical activity indices, such as SDAI, CDAI, and DAS28, are traditionally used, and treatment decisions are based on these indices [5, 24, 25]. However, due to their subjective nature, these evaluation indices cannot directly measure inflammation at the primary site of pathology [26] and may be misleading about the actual disease activity [27]. This study was designed to assess the degree of correlation between disease activity indices, laboratory markers, clinical joint examination, and US findings in patients with RA, in addition to determining the degree of correlation between different joints. The number of joints with PD activity, total US scores, and synovial proliferation US scores all showed a weak correlation with clinical activity scores (SDAI and DAS28). No significant correlations with CDAI were found. In general, agreement between clinical joint examination and US findings was also weak.

Since the US can detect changes in the synovium directly, evaluation based on US is expected to be more accurate and more sensitive than clinical disease activity indices [28]. However, studies have shown different results about the degree of correlation between current disease activity indices and US findings [29, 30]. Compared with clinical examination, both grayscale and PD US have been found to be more sensitive for detecting synovitis [10, 16, 31, 32]. It has been suggested that the weak correlation between US findings and clinical joint examination can be explained by the high sensitivity of US [33]. Another theory may be that the correlation between clinical and US findings varies between different joints, and this finding may explain why a better correlation with clinical joint examination in studies conducted with a small number of joints exists [30].

One of the most important explanations for the discrepancy between the presence of a tender joint and US findings could be the presence of a PD signal on US even though no tender joint was found in the clinical evaluation. This difference could indicate the presence of ongoing subclinical joint inflammation, which is not detectable on clinical examination. Subclinical synovitis was identified in half of the patients who were assumed to be in remission based on clinical indices as reported in various studies [33, 34]. Subclinical synovitis is suggested to be the cause of persistent erosive damage in patients whose disease activity seems to be under control clinically [3, 35]. Despite low disease activity, persistent subclinical inflammation may explain the increasing erosion and destruction of joints in some RA patients [26].

The DAS28 score is one of the disease activity measurements used in RA and is frequently used in clinical practice for initiating and maintaining biological treatment. The DAS28 score multiplies the number of tender joints by a 2-times higher coefficient than the number of swollen joints. In the evaluation of disease activity, the number of clinically tender joints is assigned more weight than the number of swollen joints [3]. The fact that the number of tender joints rather than swollen joints have a greater effect on the DAS28 total score and the lack of correlation between tender joints and US findings may explain the discrepancy observed between disease activity scores and US findings. Fibromyalgia and degenerative pathologies that often accompany rheumatic diseases can cause widespread pain. Pain is frequently associated with RA by patients and may cause overestimated disease activity scores [36, 37].

The joints selected in studies with simplified joint scores are generally selected from those that correlate well with clinical joint examinations [12, 13, 38]. It has been shown that US using grayscale and PD-US is more sensitive than clinical joint examination for detecting synovitis and can reflect inflammation better than disease activity indices in patients with RA; thus a weak correlation exists between them [39, 40]. Naredo et al. [13] stated that the simplified 12-joint US evaluation is a valid, reliable, sensitive, and applicable method compared to the 44-joint US evaluation for the evaluation of joint inflammation in RA patients. It has been shown that a simplified 12-joint PD-US evaluation can identify 100% of patients with synovitis and 91% of patients with PD signals. In a

recent multicenter study, it was also reported that 22- and 6-joint US showed a strong correlation with each other, but a weak correlation with DAS28 scores was noted [41].

In this study, the existence of PD-US findings in joints with no clinical evidence of inflammation and no symptoms suggests subclinical synovitis, which has been linked to radiographic damage and clinical exacerbations. The absence of correlation between disease activity indexes, clinical joint examination, and US findings supports the view that clinical examination alone may not always be adequate for measuring disease and joint activities and that using US may lead to a significant improvement in the assessment. It has been shown that patients whose disease activity is monitored with US need less medication modification in the long-term, and their disease activity is more stable. [17]. A weak correlation between CRP and US parameters in our study may support the fact that acute phase reactants do not always accurately reflect subclinical inflammation. Additionally, if not combined with PD, the changes due to chronic joint degeneration in joints assessed using a grayscale alone may not yield adequate information regarding whether inflammation is present or not.

Limitations

This study has some limitations. The study was a single-center study. Other limitations include patients seen only at a single visit, changes in time were not observed, and the effect on the prediction of exacerbations could not be evaluated. Since US is a user-dependent subjective method, the operator's experience in US can be regarded as a limitation. The fact that the US operator may have noticed the symptoms of inflammation, such as joint swelling and warmth in addition to structural damage, such as deformities and synovial hypertrophy, may have generated a bias.

Conclusion

Accurate evaluation of joint inflammation via US may contribute to the opportunity for early diagnosis and lead to a better prognosis. It may be beneficial to add US to the existing RA disease activity indices and remission criteria to improve disease activity assessments and treatment outcomes. US may be a better tool than clinical evaluations to more accurately assess disease status, prevent exacerbations, and is applicable in the new definition of remission. Further studies with the simplified US methods are needed to determine the minimum number of joints to be evaluated and which joints should be selected for imaging to reduce examination time.

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