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ORIGINAL ARTICLE

The role of ultrasonographic synovial assessment in rheumatoid arthritis patients with concomitant fibromyalgia

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ABSTRACT

Objectives: This study aimed to compare the prevalence and musculoskeletal ultrasonography (US) findings of rheumatoid arthritis (RA) patients with concomitant fibromyalgia (FM) according to the 1990 American College of Rheumatology (ACR) FM classification criteria or the 2016 ACR FM diagnostic criteria.

Patients and methods: This cross-sectional study included 63 patients (17 males, 46 females; mean age: 48.2±7.1 years; range, 18 to 62 years) with RA. Medical history and laboratory data were obtained from electronic records. Clinical examination, composite disease activity measures, functional status, and the German 7-joint ultrasound score were assessed to evaluate disease activity and synovial inflammation. The patients were divided into three groups: patients who met only the 2016 ACR criteria, patients who met only the 1990 ACR criteria, and patients who met both criteria.

Results: In patients with RA, concomitant FM prevalence was 34.9% according to the 2016 ACR FM diagnostic criteria versus 23.8% according to the 1990 ACR FM classification criteria. Rheumatoid arthritis patients with FM had high tender joint count and disease activity scores, while musculoskeletal US findings were similar. Patients who met only the 2016 ACR FM diagnostic criteria had significantly higher gray-scale US and power Doppler US synovitis scores than patients who satisfied only ACR 1990 FM classification criteria (p=0.03 and p=0.02, respectively).

Conclusion: Synovial inflammation is a prominent sign in RA patients diagnosed with FM according to the 2016 ACR FM diagnostic criteria. The higher disease activity seen in the presence of FM in RA patients is associated with FM rather than synovitis.

Keywords: Fibromyalgia, musculoskeletal ultrasonography, rheumatoid arthritis, subclinical inflammation.

Fibromyalgia (FM) presents with persistent generalized discomfort, cognitive impairment, disruption of sleeping, mood changes, and fatigue.[1] Although the pathophysiology of FM is not entirely clear, central sensitization is the most putative mechanism.[2-4] Central sensitization is the breakdown in the central nervous system's pain regulation and disproportion between inhibitory and excitatory neurotransmitters.[5]

The prevalence of FM in patients with rheumatoid arthritis (RA) differs between 4.9 and 52.4%, depending on the methodology.[6-16] The disruption of pain regulation in FM can affect composite disease activity scales, which leads to inaccurate treatment decisions in patients with RA.[12,15-17] In addition, a high level of inflammation in a patient with RA may lead to the concomitant presence of FM.[18]

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The inflammation in RA is evaluated by inflammatory markers and the disease activity scales.[19] However, these do not precisely reflect subclinical synovial inflammation, which is an important parameter in RA management.[19,20] Therefore, musculoskeletal ultrasonography (US) may help detect subclinical synovial inflammation.[21-24] However, the role of musculoskeletal US in patients with RA accompanied by fibromyalgia has not been studied in detail.

The 1990 American College of Rheumatology (ACR) FM classification criteria focus on widespread pain and the number of tender points, while 2010/2011 and 2016 ACR criteria focus on central pain perception and distress.[1,25,26] Previous studies have investigated the prevalence of FM according to different diagnostic criteria in RA patients and compared only the clinical findings without musculoskeletal US.[6-16] Additionally, there are few studies evaluating inflammation by musculoskeletal US in RA patients with and without FM, and these studies utilize a single diagnostic criterion for the diagnosis of FM.[17,27] The present study aimed to compare the prevalence and ultrasonographic findings of RA patients with concomitant FM according to two different ACR criteria.

PATIENTS AND METHODS

This cross-sectional study enrolled 63 RA patients (17 males, 46 females; mean age: 48.2±7.1 years; range, 18 to 62 years). Consecutive patients were included at the Gazi University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology until the estimated sample size was achieved. Patients with an arthritis onset age of ≥18 years and patients who fulfilled the 2010 ACR/The European Alliance of Associations for Rheumatology (EULAR) criteria were included in the study. Patients with concomitant systemic inflammatory disease, malignancies, infections, major kidney or liver disease, and endocrine system disorders, such as uncontrolled diabetes mellitus, hypothyroidism, and osteomalacia, were excluded.

Participants' demographic data included age, sex, body mass index, educational status, medical history (comorbidity, drugs, disease duration), and laboratory data obtained from electronic records. A rheumatologist performed a clinical examination by tender joint count, swollen joint count, disease activity score 28 with erythrocyte sedimentation rate (DAS28-ESR), and functional status.[28,29] Functional status was assessed with a validated Turkish version of the health assessment questionnaire (HAQ), which is a scale ranging from 0 to 3, with higher scores reflecting worse functional status.[30,31]

A physiatrist evaluated the patients for FM by the 1990 ACR FM classification criteria and 2016 ACR FM diagnostic criteria.[1,26] The 1990 ACR FM classification criteria require the presence of widespread pain for more than three months and having tenderness in at least 11 of 18 specific tender points. The term 'widespread pain' indicates axial, bilateral pain above and below the waistline.[26] However, the 2016 ACR FM diagnostic criteria require a Widespread Pain Index (WPI) score of 4-6, Symptom Severity Scale (SSS) score of ≥9, or a WPI score of ≥7 with an SSS score of ≥5, and generalized pain, which is defined as pain in at least four of five regions and the presence of symptoms at a similar level for at least three months.[1]

The SSS assesses the intensity of symptoms related to sleep quality, fatigue, and somatic and cognitive symptoms. The intensity of these symptoms in the previous week was graded on a scale of 0 to 3. The final SSS score is the sum of these symptoms' severity and varies from 0 to 12. The WPI displayed the number of uncomfortable body parts throughout the previous week (range, 0 to 19.[1]

A rheumatologist with a EULAR trainer certificate in musculoskeletal US blinded to the patients' clinical examination performed the synovial musculoskeletal US examination by MyLab 70 XV Machine® (Esaote, Genoa, Italy) equipped with a multifrequency (6-18 MHz) linear probe. The German 7-joint ultrasound (US7) score in the dominant side was used for the musculoskeletal US examination.[21]

Synovitis, paratenonitis/tenosynovitis, and erosion were assessed by gray-scale US mode. Synovitis was explored at the wrist (dorsal, palmar, and ulnar side), metacarpophalangeal (MCP) 2-3, proximal interphalangeal (PIP) 2-3 (palmar side), metatarsophalangeal (MTP) 2, and

MTP5 (dorsal side) joints. Paratenonitis and tenosynovitis were detected at the wrist (dorsal, palmar, and ulnar side) and MCP2-3 (dorsal side) joints. Erosion was explored at the MCP2 (dorsal, palmar, and radial side), MCP3 and PIP2-3 (the dorsal and palmar side), MTP2 (dorsal and plantar side), and MTP5 (dorsal, plantar, and lateral side) joints. For power Doppler US, all joints were examined at both dorsal and palmar sides, except for MTP joints, which were examined at the dorsal side only.[21]

Synovitis was analyzed by gray-scale US mode according to a semiquantitative scale as follows: normal = Grade 0; minimal hypoechoic or anechoic line under the joint capsule = Grade 1; the joint capsule is raised parallel to the joint region = Grade 2; a potent stretching of the joint capsule = Grade 3. Erosion and tenosynovitis/paratenonitis were recorded by the binary scoring system as 0 = absent or 1 = present.[22] The degree of power Doppler US activity for synovitis and tenosynovitis/paratenonitis were recorded according to the following semiquantitative scale: no intra-articular color signal = Grade 0; two single and one confluent signal or up to three color signals = Grade 1; color signal area covers between 1 and 50% of the intra-articular area = Grade 2; the color signal area covers more than 50% of the intra-articular area = Grade 3.[32]

The gray-scale US score was obtained by synovitis (0-27), tenosynovitis/paratenonitis (0-7), and erosion (0-14) scores. The power Doppler US scores were obtained from synovitis (0-39) and tenosynovitis/paratenonitis (0-21) scores.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA®). Normal distribution was tested visually (histograms, probability plots) and analytically (Kolmogorov-Smirnov/Shapiro-Wilk). Means and standard deviations were used for normally distributed variables, medians and minimum-maximum values for non-normally distributed variables, and frequencies for categorical data. Rheumatoid arthritis patients with FM were divided into subgroups: *(i)* RA patients with FM according to both 1990 and 2016 ACR criteria, *(ii)* RA patients with FM according to only 1990 ACR criteria, and *(iii)* RA patients with FM according to only 2016 ACR criteria.

Table 1. Demographic characteristics of the study population and subgroups

	RA patients (n=63)					RA patients with FM according to both 2016 ACR criteria and 1990 ACR criteria (n=9)				RA patients with FM only according to the 1990 ACR criteria (n=6)				RA patients with FM only according to the 2016 ACR criteria (n=13)						
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	p^a	p^b	p^c
Age (year)			48.2±7.1					49.1±3.8					48.1±4.4				47.5±6.2			0.59	0.31	0.59
Sex																						
Female	46	73				7	77.8				4	66.7				9	69.2			0.64	0.66	0.91
Educational level																						
≤High school	40	63.5				6	66.7				4	66.7				9	69.2			1	0.90	0.91
≥College degree	23	36.5				3	33.3				2	33.3				4	30.8					
Height (cm)				167	150-187				165	158-187				166	154-185				163	155-180	0.81	0.12	0.19
Weight (kg)				74	48-98				71	56-96				74	65-95				67	48-97	0.40	0.15	0.20
BMI (kg/m²)			27.9±5.6					27.5±4.1					25.2±2.4				26.7±5.7			0.19	0.43	0.62

RA: Rheumatoid arthritis; FM: Fibromyalgia; ACR: American College of Rheumatology; SD: Standard deviation; BMI: Body mass index; p^a: Result of statistical analysis between RA patients with FM according to both 2016 and 1990 ACR criteria, and RA patients with FM only according to the 1990 ACR criteria; p^b: Result of statistical analysis between RA patients with FM according to both 2016 ACR and 1990 ACR criteria, and RA patients with FM only according to the 2016 ACR criteria; p^c: Result of statistical analysis between RA patients with FM only according to the 2016 ACR criteria, and RA patients with FM only according to the 1990 ACR criteria

Demographic, clinical, and ultrasonographic data were compared between three subgroups. For categorical variables, the chi-square or Fisher exact test was employed, and for quantitative variables, the Mann-Whitney U test was used. The sample size was calculated according to the global prevalence of RA in the population (0.24%) and the frequency of FM in RA (16.7%) with a 95% confidence interval.[13] A *p* value of <0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the participants are displayed in Table 1. The mean disease duration was 119.2±17.4 months. Rheumatoid factor was positive in 68.3% of patients, and anti-CCP was positive in 54% of the patients. The mean DAS28-ESR was 3.01±0.67. The mean HAQ score of the patients was 0.81±0.27. Table 2 shows the clinical characteristics of the participants.

Fifteen patients satisfied the 1990 ACR FM criteria, 22 patients met the 2016 ACR FM criteria, and nine patients satisfied both criteria. Six patients who met the 1990 ACR FM criteria did not fulfill the 2016 ACR FM criteria. Additionally, 13 patients who met the 2016 ACR FM criteria did not meet the 1990 ACR FM criteria.

Table 2. Clinical evaluation, laboratory results, and ultrasonographic findings of study population

		According to the 1990 ACR FM criteria			According to the 2016 ACR FM criteria		
	RA patients (n=63)	Patients with FM (n=15)	Patients without FM (n=48)	*p*	Patients with FM (n=22)	Patients without FM (n=41)	*p*
Duration (month) (mean±SD)	119.2±17.4	118.4±15.3	121.2±18.2	0.98	117.2±18.4	120.2±17.1	0.45
Positive rheumatoid factor (n, %)	43 (68.3)	10 (66.7)	33 (68.8)	0.88	15 (68.2)	28 (68.3)	0.93
Positive anti-CCP (n, %)	34 (54)	8 (53.3)	26 (54.2)	0.95	13 (59.1)	21 (51.2)	0.55
Erythrocyte sedimentation rate (mm/h) (mean±SD)	12.2±5.2	10.2±4.1	12.8±5.3	0.16	11.4±5.5	12.6±5.0	0.25
C-reactive protein (mg/L) (mean±SD)	8.0±7.0	5.8 ±2.09	7.9±7.8	0.54	5.7±2.7	7.2±8.2	0.37
Drugs							
Conventional DMARD (n, %)	47 (74.6)	13 (86.7)	34 (70.8)	0.22	17 (77.3)	30 (73.2)	0.72
Biologic DMARD (n, %)	17 (27)	5 (33.3)	12 (25)	0.52	7 (31.8)	10 (24.4)	0.53
NSAID (n, %)	22 (34.9)	4 (26.7)	16 (33.3)	0.63	7 (31.8)	13 (31.7)	0.99
Prednisone dose (mg/day) (n, %)	2.7 (2.8)	2.76 (2.6)	2.79 (2.9)	0.94	2.5 (2.8)	2.8 (2.9)	0.71
Tricyclic antidepressants (n, %)	1 (1.5)	1 (6.7)	0 (0)	0.07	1 (4.5)	0 (0)	0.17
Duloxetine (n, %)	8 (12.6)	5 (33.3)	3 (6.3)	**0.006***	5 (22.7)	3 (7.3)	**0.03***
Pregabalin (n, %)	23 (34.9)	9 (60)	14 (29.2)	**0.03***	12 (54.5)	1 (26.8)	**0.03***
Comorbidity of patients (n, %)	25 (39.7)	8 (53.3)	17 (35.4)	0.21	9 (40.9)	16 (39)	0.88
Erosion on the radiograph of patients (n, %)	23 (46.5)	6 (40)	17 (35.4)	0.75	9 (40.9)	14 (34.1)	0.59
28-Tender joint count (median, min-max)	4 (0-17)	8 (5-17)	3 (0-13)	**<0.001***	8 (5-13)	2 (0-7)	**<0.001***
28-Swollen joint count (median, min-max)	1 (0-4)	1 (0-3)	1 (0-4)	0.71	1 (0-4)	1 (0-2)	0.42
DAS28-ESR (mean±SD)	3.01±0.67	3.4±0.56	2.9±0.66	**0.008***	3.5±0.45	2.8±0.64	**<0.001***
HAQ (mean±SD)	0.81±0.27	0.85±0.22	0.80±0.28	0.64	0.95±0.22	0.74±0.26	**0.004***
GSUS Synovitis score (median, min-max)	6 (2-14)	5 (2-14)	7 (2-12)	0.19	6 (3-14)	6 (2-11)	0.12
PDUS Synovitis score (median, min-max)	1 (0-3)	1 (0-3)	1 (0-3)	0.34	1 (0-3)	1 (0-3)	0.24
GSUS Tenosynovitis/paratenonitis score (median, min-max)	1 (0-3)	1 (0-2)	1 (0-3)	0.89	1 (0-3)	1 (0-3)	0.11
PDUS Tenosynovitis/paratenonitis score (median, min-max)	1 (0-3)	1 (0-2)	1 (0-2)	0.18	1 (0-2)	0 (0-2)	0.19
Erosion score (median, min-max)	1 (0-5)	3 (1-4)	2 (1-5)	0.43	2 (1-5)	2 (1-5)	0.96

ACR: American College of Rheumatology; FM: Fibromyalgia; RA: Rheumatoid arthritis; SD: Standard deviation; anti-CCP: Cyclic citrullinated peptide antibodies; DMARD: Disease-modifying anti-rheumatic drugs; NSAID: Non-steroidal anti-inflammatory drugs; DAS28-ESR: Disease Activity Score 28 with erythrocyte sedimentation rate; GSUS: Gray-scale US; HAQ: Health Assessment Questionnaire; PDUS: Power Doppler US; RA; Rheumatoid Arthritis; US: Ultrasound; significant differences between two FM groups were presented by * p<0.05.

According to the 1990 ACR FM criteria, patients with FM had a higher tender joint count and disease activity score compared to those without FM (p<0.001 and p=0.008, respectively). The musculoskeletal US findings did not differ between the two groups (Table 2).

According to the 2016 ACR FM criteria, patients with FM had a higher tender joint count, disease activity scores, and HAQ scores compared to those without FM (p<0.001, p<0.001, and p=0.004, respectively). The MSUS findings did not differ between the two groups (Table 2).

Ultrasonographic findings, disease duration, C-reactive protein (CRP) level, swollen joint counts, DAS28-ESR, and HAQ scores were similar between the patients who met only the 1990 ACR FM criteria and those who satisfied both the 1990 and 2016 ACR FM criteria (p=0.36, p=0.29, p=0.24, p=0.67, p=0.42, p=0.54, p=0.23, p=0.41, p=0.63, and p=0.90, respectively; Tables 3 and 4).

Ultrasonographic findings, disease duration, CRP level, swollen joint counts, DAS28-ESR, and HAQ scores were similar between the patients with FM only according to the 2016 ACR FM criteria and those who satisfied both the 1990 and 2016 ACR FM criteria (p=0.21, p=0.59, p=0.58, p=0.09, p=0.12, p=0.94, p=0.54, p=0.72, p=0.16, and p=0.12, respectively; Tables 3 and 4).

The mean disease duration and DAS28-ESR were similar in patients diagnosed with

Table 3. Analysis of clinical evaluation and laboratory findings of the FM subgroups

	RA patients with FM according to both 2016 ACR criteria and 1990 ACR criteria (n=9)	RA patients with FM only according to the 1990 ACR criteria (n=6)	RA patients with FM only according to the 2016 ACR criteria (n=13)	p^a	p^b	p^c
Duration (month) (mean±SD)	117.3±14.4	122±17.6	117.2±21.4	0.54	0.94	0.59
Positive rheumatoid factor (n, %)	6 (66.7)	4 (66.7)	9 (69.2)	1	0.90	0.91
Positive anti-CCP (n, %)	5 (55.6)	3 (50)	8 (61.5)	0.83	0.78	0.64
Erythrocyte sedimentation rate (mm/h) (mean±SD)	10.2±4.4	10.1±3.8	12.2±6.1	0.90	0.68	0.74
C-reactive protein (mg/L) (mean±SD)	6.3±2.5	4.9±0.68	5.3±2.8	0.23	0.54	0.86
Drugs						
Conventional DMARD use (n, %)	8 (88.9)	5 (83.3)	9 (69.2)	0.76	0.29	0.52
Biologic DMARD use (n, %)	3 (33.3)	2 (33.3)	4 (30.8)	1	0.90	0.91
NSAID use (n, %)	3 (33.3)	2 (33.3)	4 (30.8)	0.60	0.90	0.91
Prednisone dose (mg/day) (mean±SD)	2.7±2.6	2.8±2.9	2.5±3.1	0.69	0.75	0.78
Tricyclic antidepressants (n, %)	1 (11.1)	0 (0)	0 (0)	0.41	0.22	1
Duloxetine (n, %)	3 (33.3)	2 (33.3)	2 (15.4)	1	0.33	0.57
Pregabalin (n, %)	5 (55.6)	4 (66.7)	7 (53.8)	0.67	0.93	0.60
Comorbidity of patients (n, %)	5 (55.6)	3 (50)	4 (30.8)	0.83	0.25	0.43
Erosion on the radiograph of patients (n, %)	4 (44.4)	2 (33.3)	5 (38.5)	0.67	0.84	0.83
28-Tender joint count (median, min-max)	8 (5-10)	10 (6-17)	9 (6-13)	0.09	0.22	0.42
28-Swollen joint count (median, min-max)	1 (0-3)	1 (0-2)	1 (0-4)	0.41	0.72	0.24
Visual Analog Scale for pain (mean±SD)	4.8±1.2	5.5±1.2	5.4±1.2	0.31	0.27	0.92
DAS28-ESR (mean±SD)	3.3±0.5	3.6±0.64	3.6±0.36	0.63	0.16	0.63
HAQ (mean±SD)	0.86±0.26	0.83±0.17	1.01±0.16	0.90	0.12	0.06

FM: Fibromyalgia; RA: Rheumatoid arthritis; ACR: American College of Rheumatology; SD: Standard deviation; anti-CCP: Cyclic citrullinated peptide antibodies; DMARD: Disease-modifying anti-rheumatic drugs; NSAID: Non-steroidal anti-inflammatory drugs; DAS28-ESR: Disease Activity Score 28 with erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; p^a: Result of statistical analysis between RA patients with FM according to both 2016 and 1990 ACR criteria, and RA patients with FM only according to the 1990 ACR criteria; p^b: Result of statistical analysis between RA patients with FM according to both 2016 ACR and 1990 ACR criteria, and RA patients with FM only according to the 2016 ACR criteria; p^c: Result of statistical analysis between RA patients with FM only according to the 2016 ACR criteria, and RA patients with FM only according to the 1990 ACR criteria

Table 4. Ultrasound analysis of study population and subgroups

	RA patients with FM according to both 2016 ACR criteria and 1990 ACR criteria (n=9)		RA patients with FM only according to the 1990 ACR criteria (n=6)		RA patients with FM only according to the 2016 ACR criteria (n=13)				
	Median	Min-Max	Median	Min-Max	Median	Min-Max	p^a	p^b	p^c
GSUS Synovitis score	6	3-14	4.5	2-9	7	5-12	0.36	0.21	**0.03***
PDUS Synovitis score	1	0-3	0.5	0-2	2	1-2	0.29	0.59	**0.02***
GSUS Tenosynovitis/paratenonitis score	1	0-2	1	0-1	1	0-3	0.24	0.58	0.07
PDUS Tenosynovitis/paratenonitis score	0	0-1	0	0-1	1	0-2	0.67	0.09	0.06
Erosion score	3	2-4	2	1-4	2	1-5	0.42	0.12	0.91

RA: Rheumatoid arthritis; FM: Fibromyalgia; ACR: American College of Rheumatology; US: Ultrasound; GSUS: Gray-scale US; PDUS: Power Doppler US; p^a: Result of statistical analysis between RA patients with FM according to both 2016 and 1990 ACR criteria, and RA patients with FM only according to the 1990 ACR criteria; p^b: Result of statistical analysis between RA patients with FM according to both 2016 ACR and 1990 ACR criteria, and RA patients with FM only according to the 2016 ACR criteria; p^c: Result of statistical analysis between RA patients with FM only according to the 2016 ACR criteria, and RA patients with FM only according to the 1990 ACR criteria; Significant differences between two FM groups were presented by * $p<0.05$.

FM according to only 1990 or 2016 ACR FM criteria (p=0.59 and p=0.63, respectively). The majority of these patients were on conventional disease-modifying antirheumatic drugs than biological drugs. The mean HAQ score of patients who met only the 2016 ACR FM diagnostic criteria was slightly higher than patients who satisfied only the 1990 ACR FM classification criteria, but this finding was not statistically significant (Table 3).

Table 4 demonstrates the gray-scale and power Doppler US scores of patients who satisfied only the 1990 or 2016 ACR FM criteria. Gray-scale and power Doppler US synovitis score was significantly higher in patients who met only the 2016 ACR FM diagnostic criteria. Similarly, the gray-scale US tenosynovitis/paratenonitis score and power Doppler US tenosynovitis/paratenonitis score tended to be higher in RA patients with FM only according to the 2016 ACR FM diagnostic criteria, but this difference was not statistically significant. The erosion score did not differ between the groups.

DISCUSSION

In this cross-sectional study, we compared the clinical measurements and ultrasonographic findings of RA patients with FM according to the 1990 and 2016 ACR FM criteria and showed that the frequency of FM according to the 2016 ACR FM criteria was about 1.5 times higher compared to the 1990 ACR FM criteria in these patients. Although clinical assessments were similar, patients who met only the 2016 ACR FM criteria had significantly higher power Doppler and gray-scale US synovitis scores. To the best of our knowledge, this is the first study that compares ultrasonographic findings of RA patients with FM according to two different ACR criteria. In the literature, there are a limited number of studies in which RA patients with FM were evaluated by US.[17,27] However, these studies aimed to compare ultrasonographic findings in RA patients with or without FM.[17,27]

In our study, the frequency of concomitant FM was 34.9% for the 2016 ACR diagnostic criteria and 23.8% for the 1990 ACR classification criteria. Many investigations have found that FM was frequent among RA patients, with

a prevalence higher than that of the general population.[7,18,33] The prevalence of FM differs between 4.9 and 52.4%, according to different studies.[6-16,34] Some studies had similar results.[14,18] Shresher et al.[14] compared the 1990 and 2016 ACR FM criteria in RA patients and reported the prevalence of FM as 31.5% and 40%, respectively.

The 1990 ACR FM classification criteria focus on the widespread pain and the number of tender points.[26] The 1990 ACR FM criteria are limited since the tender point examination is operator-dependent, and it excludes nonpain symptoms.[1,35] For these reasons, 2010/2011 and 2016 ACR FM diagnostic criteria were designed with a more patient-centered questionnaire.[1] Moreover, the 2010/2011 and 2016 ACR criteria focus on central pain perception and distress, while the 1990 ACR criteria focus on peripheral allodynia.[1,25,26] Using different FM criteria and variations of demographic factors (e.g., age, sex, education level) might result in the variability of the prevalence of FM.[6,33] Additionally, different diagnostic criteria may detect different subgroups of FM.[25]

Widespread tenderness, which is one of the characteristic features of FM, may result in RA patients with FM having a higher number of tender joints, which may lead to a perception of higher disease activity.[6,8,10,11] Our results also support this finding. The presence of FM may lead to overtreatment of RA patients.[8] In this study, we also demonstrated a significant difference in power Doppler and gray-scale US synovitis scores between the FM patients who fulfilled only the 2016 ACR diagnostic criteria versus FM patients who met only the 1990 ACR criteria. However, there was no significant difference between the clinical and demographic data between these groups. Ultrasonography is a tool more useful and sensitive than the clinical examination for detecting subclinical inflammation.[23,24] Moreover, subclinical synovial inflammation may trigger the FM process by creating a central sensitization through the perception of central pain.[33,36] Nonpain symptoms, such as cognitive symptoms, waking unrefreshed, and fatigue, are the result of central pain perception and distress.[5,16,25] Subclinical inflammation may lead to the exacerbation of nonpain symptoms, which results in the overtreatment of patients with RA.

There are some limitations to this study. First, the duration of concomitant FM is unknown due to the lack of medical records. Nonetheless, it is not always easy to detect the onset of FM in RA patients. Another possible limitation is that we investigated subclinical inflammation using the German US7 scoring method. This scoring system involves only the hand, wrist, and foot joints on the dominant side. Ultrasonographic evaluations of other joints may provide additional information in further studies. The third limitation is that the number of patients in the FM groups is low for subgroup analysis. The sample size was calculated according to the frequency of FM in RA. However, due to statistical necessity, groups were formed with patients meeting only one criterion and patients meeting both criteria to avoid coparticipants in group comparisons. This limitation may affect the generalizability of the results. Lastly, although the participants' fatigue, depression, anxiety, and somatization levels were evaluated within the SSS, which is a part of the ACR FM 2016 criteria, a separate scale was not used to evaluate each of these symptoms as this study focused on musculoskeletal US findings.

In conclusion, this study showed that the prevalence of FM in RA patients was higher according to the 2016 ACR criteria compared to the 1990 ACR criteria. Furthermore, US-based subclinical inflammation was higher in RA patients who met the 2016 ACR FM criteria, although clinical features were similar in those who fulfilled the 1990 ACR FM criteria. The higher disease activity in the presence of FM in RA patients was due to FM rather than synovitis. Ultrasonographic assessment may help distinguish if the pain in RA patients is related to the presence of inflammation or FM.

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Ethics Committee Approval: The study protocol was approved by the Niğde Ömer Halisdemir University Non-Invasive Clinical Research Ethics Committee (no: 9586085-050.01.04-E26799/08). Reporting of this trial was conducted according to the STROBE (Strengthening the reporting of observational studies in epidemiology) checklist. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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