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Performance of 2016 revised fibromyalgia diagnostic criteria in patients with rheumatoid arthritis

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Abstract

Fibromyalgia (FM) is a common comorbidity in rheumatoid arthritis (RA). Recently, there were several updates for the American College of Rheumatology (ACR) FM criteria. To assess the performance of the 2016 revised ACR FM criteria in patients with RA in comparison to 1990 criteria and to study the relation to composite disease measures. This study included 130 adult RA patients fulfilling the 2010 ACR/EULAR classification criteria for RA. Patients were evaluated according to 2016 and 1990 ACR criteria for FM. Kappa agreement between the two criteria was determined. Spearman's correlation between the polysymptomatic distress scale (PSD) and selected variables including disease activity score-28 with erythrocyte sedimentation rate (DAS-28 ESR), clinical disease activity index (CDAI), patient global assessment (PGA), and visual analogue scale (VAS) for pain was evaluated. Of the 130 RA patients, 52 patients (40%) satisfied the 2016 criteria and 40 (31.5%) the 1990 criteria. The Kappa agreement between the two criteria was 0.733. RA patients with FM had higher DAS28-ESR, CDAI, PGA, and VAS compared with those without FM. A significant positive correlation was found between the polysymptomatic Distress scale (PSD) and DAS28-ESR, CDAI, and PGA (r_s 0.481, 0.516, 0.511, respectively, $P < 0.001$). FM coexists in a substantial number of RA patients according to the 2016 revised criteria and associated with high composite disease activity measures. Therefore, assessment of FM should be considered in RA patients with persistently high disease activity.

Keywords Fibromyalgia · Rheumatoid arthritis · Prevalence · Polysymptomatic distress

Introduction

Fibromyalgia (FM) is a common chronic pain syndrome, with a distinct clinical phenotype, that affects 2–8% of the general population [1]. The main symptoms are chronic widespread pain, fatigue, sleep disturbances, and cognitive changes. Many patients also have psychological distress and impaired function.

FM is common in rheumatoid arthritis (RA) patients, with an overall prevalence of FM to be 21% in RA (range 4.9–52.4%) [2]. The prevalence of FM in RA patients varies according to diagnostic criteria with a higher prevalence reported with the 2010/2011 American College of Rheumatology (ACR) criteria [3]. This may relate to the features of the 2010/2011 ACR criteria that take into consideration important non-pain characteristics of FM in RA such as fatigue, non-refreshing sleep, and cognitive impairment. Since these are common findings in RA patients, the prevalence of FM is higher in RA than in the general population.

Recently, there were several modifications to the American College of Rheumatology (ACR) 1990 criteria for the classification of fibromyalgia. The 1990 criteria required chronic widespread pain persisting for more than 3 months in combination with tenderness at 11 or more of the 18 specific tender point sites upon clinical examination [4]. In 2010 ACR preliminary diagnostic criteria for FM, the tender

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point count was abandoned in favor of widespread pain index (WPI) in addition to symptom severity scale (SSS) including other non-pain components of FM such as fatigue, non-refreshing sleep, cognitive impairment, and number of somatic symptoms. Symptoms have to be present at a similar level for at least 3 months and the patient does not have a disorder that would otherwise explain the pain. This modification makes it possible to use the FM criteria in primary care sitting [5]. The aim of 2011 revision was to develop an FM survey questionnaire for epidemiologic and clinical studies without the necessity of a physician examiner [6]. However, both the 2010 and 2011 modification criteria were criticized to allow for patients with regional pain conditions to be diagnosed with FM. To avoid such misclassification, the ACR launched the term "generalized pain criterion" as part of the 2016 modified criteria for FM: pain in four out of five bodily regions, relating to the four extremities and the axial region. In addition, the diagnosis of FM was considered valid irrespective of other diagnoses [7].

Therefore, the aim of this study was to determine the prevalence FM in a cohort of Egyptian patients with long-standing RA on conventional synthetic disease modifying antirheumatic drugs (csDMARDs) according to the 2016 revised FM diagnostic criteria and to assess the agreement between it and the 1990 criteria. Also, to evaluate the relationship between the polysymptomatic distress (PSD) scale, a measure of FM severity, and composite measures of disease activities of RA such as DAS28-ESR and CDAI, as well as other patients reported outcome (PROs) such as patient global assessment (PGA) and visual analogue scale (VAS) for pain.

Patients and methods

This prospective cross-sectional study was carried out at outpatient clinics of the Department of Physical Medicine, Rheumatology, and Rehabilitation, Suez Canal University Hospitals, Ismailia-Egypt. This is a teaching hospital with a referral from all Suez Canal Region. Patients were approached during their routine visit. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Suez Canal University (18/7/2018-3526). All patients provided written informed consent in accordance with the ethical standards of the 2013 version of the Declaration of Helsinki.

Patients

One-hundred and thirty consecutive RA patients aged 18 years or older from both genders fulfilling the 2010 American College of Rheumatology (ACR)–European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis were included in this study [8]. Patients were excluded if they had other causes of chronic widespread pain such as endocrinopathies (such as hypothyroidism), end-stage liver or kidney disease, malignancies, infections, major psychiatric disorders (such as major depressive disorders, and bipolar and personality disorders), metabolic bone disease, overlapping with other connective tissues diseases and refusal to sign the written informed consent.

Methods

All patients were subjected to full history taking and physical examination. In addition, appropriate laboratory evaluation was done including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Diagnosis of FM

FM symptoms and status were assessed using the 1990 ACR FM criteria and 2016 criteria [4, 7]. To fulfill the 1990 criteria, a positive chronic widespread pain criterion (pain bilaterally, above and below the waist and axially) for more than 3 months and a tender point count of 11 or more out of 18 upon physical examination were required [4]. The same examiner evaluated all patients for tender point counts of 1990 FM criteria.

To fulfill, the 2016 revised criteria, the patients should meet all the following, generalized pain, defined as pain in at least four of five regions; symptoms have been present at a similar level for at least 3 months; and Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9 [7].

For the WPI, patients indicated the number of painful bodily regions experienced during the previous 7 days (range 0–19): neck, upper back, lower back, abdomen, and the following left/right: jaw, shoulder, upper arm, lower arm, hip/buttocks, upper leg, and lower leg.

The SSS is based on the sum of severity of fatigue, unrefreshed sleep, and cognitive impairment (memory and concentration) (scores 0, "no problem" to 3, "severe problem") in the past 7 days, plus the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months: headaches (0–1), pain or cramps in lower abdomen (0–1), and depression (0–1). The final symptom severity score is between 0 and 12. PSD scale is a combination of the WPI and the SSS with a range of (0–31) [7].

RA disease characteristics

RA disease activity was assessed by both clinical disease activity index (CDAI) and disease activity score-28 with Erythrocyte Sedimentation Rate (DAS-28 ESR) [9, 10]. CDAI is a composite measure of patient global assessment (visual analogue scale (VAS) from 0 to 100 mm), evaluator global assessment (VAS from 0 to 100 mm), and 28 tender and swollen joint counts. Scores range from 0 to 76 with higher values reflecting more severe disease [9]. DAS28-ESR score is a composite score with its components, tender (TJC) and swollen joint counts (SJC), visual analogue scale for patients' global assessment of general health (VAS-GH scored 0–100 mm), and erythrocyte sedimentation rate (ESR in mm/first hour) [10]. The pain was assessed using VAS [11]. Functional status was assessed by a validated Arabic version of the health assessment questionnaire disability-index (HAQ-DI) [12]. The combined score ranges between 0 and 3, with higher scores indicating worse functional status [13].

Fibromyalgia impact questionnaire (FIQ)

A validated Arabic version of FIQ was used in our study [14]. The FIQ is an assessment tool developed to measure patient status, progress, and outcomes in FM. The FIQ is composed of ten items related to physical functioning, the number of days they felt well, and the number of days they were unable to work (including housework) because of fibromyalgia symptoms, how the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. The total maximum score is 100. Most of FM patients score around 50; severely affected patients have a score above 70 [15].

Statistical analysis

Collected data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corporation, Armonk, NY, USA) and MedCalc version 12.1.3.0 software for analysis (MedCalc Software, Ostend, Belgium). Categorical variables were presented as frequencies and percentages (%) and between variables difference was tested by Chi-squared test or Fisher's exact test when cell count < 5. Quantitative variables were statistically tested with the Shapiro–Wilk for normality of distribution. As our data were not normally distributed, quantitative variables were presented as the median (25th–75th percentiles), and the between-group comparisons were performed using the Mann–Whitney *U* test. Spearman's correlation coefficient was calculated to assess correlation between PSD scale and RA characteristics and interpreted according to Chan [16]. Agreement between FM diagnostic criteria was assessed using kappa statistics. Cohen's kappa coefficient was interpreted according to McHugh ML, with 0–0.20 = none, 0.21–0.39 = minimal, 0.40–0.59 = weak, 0.60–0.79 = moderate, 0.80–0.90 = strong, above 0.90 = almost perfect agreement. [17]. All statistical tests were two-tailed, and *P* values < 0.05 were considered significant.

Results

Socio-demographic and clinical characteristics

Most of our patients were females (87%), with a median (25–75 percentiles) age of 50.5 (40–60) years. Few patients had a college education (20%) and only 31.5% were working (Table 1). They had a longstanding disease with a median disease duration of 9 (5-15) years. Most of them had active disease as manifested by high 28TJC, 28-SJC, PGA, pain with VAS, ESR, and CRP (Table 2). Composite disease activity measures showed high disease activities with a median (IQR) of DAS28-ESR of 5.6 (4.8–6.3) and CDAI of 27.5 (21-33). Functional status was significantly impaired with median of HAQ score of 1.8 (1.6–2). 48 patients (36.9%) had at least one comorbidity. The most common associated comorbidities were HTN (30%), DM (24%), osteoporosis (21%), and peptic ulcer disease (18%). In our study, 114 (87%) patients were taking prednisolone ≤ 10 mg. All patients were taking one or more csDMARDs (e.g., methotrexate, leflunomide, sulfasalazine, and antimalarial agents). A total of 110 patients were taking methotrexate,

Table 1 Sociodemographic characteristics of the study population

Characteristics	Rheumatoid arthritis patients (*n* = 130)
Age, years, Median (25–75 percentiles)	50.5 (40–60)
Female, *n* (%)	113 (87)
Educational level	
≤ High school, *n* (%)	104 (80%)
College degree, *n* (%)	26 (20%)
Marital status	
Single, *n* (%)	7 (5.4%)
Married, *n* (%)	105 (80.8%)
Divorced, *n* (%)	6 (4.6%)
Widow, *n* (%)	12 (9.2%)
Occupation	
Housewife, *n* (%)	77 (59.2%)
Working, *n* (%)	41 (31.5%)
Retired, *n* (%)	12 (9.2%)
Smoking *n* (%)	3 (2.3%)

Table 2 Clinical and laboratory assessment of study population

Characteristics	Rheumatoid arthritis patients ($n=130$)
Disease duration, years	9 (5–15)
28-Tender joint count (0–28)	11 (8–15)
28-Swollen joint count (0–28)	4 (3–7)
Visual analogue scale for pain (0–10)	6 (4.7–7.0)
Patient global assessment (0–10)	6 (4.8–7.0)
Physician global assessment (0–10)	4 (3–6)
DAS28-ESR	5.6 (4.8–6.3)
CDAI (0–76)	27.5 (21–33)
HAQ-DI (0–3)	1.8 (1.6–2.0)
Comorbidity, *n* (%)	48 (36.9)
Positive rheumatoid factor, n (%)	89 (68.5)
ESR mm/h	40 (30–51.2)
CRP mg/dl	15 (10–23)
Methotrexate, *n* (%)	110 (84%)
Leflunomide, *n* (%)	46 (35.4%)
Hydroxychloroquine, *n* (%)	99 (76%)
Sulfasalazine, *n* (%)	9 (7%)
Prednisolone ≤ 10 mg *n* (%)	114 (87%)

Values are the median (25th–75th percentiles) unless otherwise indicated

CDAI clinical disease activity index; *DAS-28 ESR* disease activity measure 28 with erythrocyte sedimentation rate; *HAQ-DI* health assessment questionnaire, disability-index; *PGA* patient global assessment; *VAS* visual analogue scale

46 patients on leflunomide, 9 patients were on sulfasalazine, and 99 patients were using hydroxychloroquine.

Frequency of FM according to 1990 and 2016 ACR criteria

Of the 130 RA patients evaluated, 40 patients (31.5%) satisfied the 1990 ACR and 52 (40.0%) the 2016 revision. This resulted in moderate significant kappa agreement between 1990 criteria and 2016 criteria of 0.775 ($P<0.05$).

Comparison between RA patients with/without FM according to 2016 criteria

We further subdivided our sample into two groups: with and without FM. RA patients with FM were younger females and had higher VAS, ESR, PGA, and TJC (Table 3). Comparing RA patients with FM to those without FM showed a significantly higher median (IQR) of DAS28-ESR [6.1 (5.5–6.6) vs 5.2 (4.7–5.9), respectively, $P=0.002$] and CDAI [31 (25–37) vs 24 (19–30), respectively, $P<0.001$). Also, the median (IQR) of HAQ-DI was significantly higher in RA with FM versus those without FM (Table 3). The median of FIQ-A in RA patients with FM was 60 (58–61.3).

Fibromyalgia severity scale (PSD)

As expected, the prevalence of the most common clinical symptoms of FM such as fatigue, no-refreshing sleep, and headache was significantly higher in RA patients with FM compared to RA without FM. Also, the median (IQR) of PSD was significantly higher in patients with FM versus

Table 3 Disease characteristics among RA patients with and without FM according to 2016 criteria

Characteristics	RA with FM $n=52$	RA without FM $n=78$	*P* value**
Age, years	48 (35–58)	53 (43–63)	0.602
Female, *n* (%)	50 (96.2)	63 (80.8)	0.008[a]
RA disease duration, years	8.0 (3.0–15.0)	9 (6–15)	0.597
28-Tender joint count (0–28)	13 (10–16)	9 (7–12)	<0.001
28-Swollen joint count (0–28)	5 (3–8)	4 (3–7)	0.055
VAS for pain (0–10)	7 (6–7)	5 (4–6)	<0.001
Patient global assessment (0–10)	7 (6–7)	5 (4–6)	<0.001
Physician global assessment (0–10)	6 (4–7)	4 (3–5)	0.020
DAS28-ESR	6.1 (5.5–6.6)	5.2 (4.7–5.9)	0.002
CDAI (0–76)	31 (25–37)	24 (19–30)	<0.001
HAQ-DI (0–3)	1.8 (1.6–2)	1 (1.7–2)	0.039

Values are the median (25th–75th percentiles) unless otherwise indicated

**Mann–Whitney *U* test, except when mentioned otherwise

[a]Chi-squared test

CDAI clinical disease activity index; *DAS-28 ESR* disease activity measure 28 with erythrocyte sedimentation rate; *FM* fibromyalgia; *HAQ-DI* health assessment questionnaire, disability-index; *RA* rheumatoid arthritis; *VAS* visual analogue scale

those without FM (16 (14–18) vs 8 (7–10), $P < 0.001$) (Supplementary table S1).

Spearman's correlation between PSD scale and selected RA disease variables showed moderate significant correlation with several variables including PGA, VAS for pain, DAS-28 ESR, and CDAI score (r_s 0.511, 0.481, 0.516, 0.511, $P < 0.001$ for all). However, an only weak significant correlation was found between PSD and objective measures such as 28-SJC (r_s 0.237) (Table 4).

Discussion

Among our cohort of 130 Egyptian patients with longstanding RA, 52 patients (40%) satisfied the 2016 revised criteria for FM. Furthermore, significant moderate positive correlations of PSD score and several RA disease activity measures were demonstrated.

Our results support the notion that FM is common in RA, with prevalence up to 52% [2]. The prevalence of FM in RA varies widely. Fan et al. [18] reported a prevalence of 4.9% by 1990 ACR criteria in a sample of 325 RA patients. While, Gheita et al. [19], using 2010 ACR criteria reported a prevalence of (52.4%), among 63 RA patients. Duffield et al. [2] in a recent meta-analysis point out to the high heterogeneity of concomitant FM and chronic inflammatory arthritis. This was attributed to sample size, age, gender mix, classification criteria, and developed vs non-developed countries among others. Nonetheless, the prevalence among RA patients is still higher than the general population [20–23].

Table 4 Spearman's correlations between the polysymptomatic distress scale and selected variables in rheumatoid arthritis patients

Variables	Polysymptomatic distress scale	
	r_s	*P* value
DAS-28 ESR	0.481	< 0.001
CDAI score	0.516	< 0.001
Patient global assessment	0.511	< 0.001
Physician global assessment	0.474	< 0.001
28-Tender joint count	0.498	< 0.001
28-Swollen joint count	0.237	0.007
VAS for pain	0.511	< 0.001
HAQ-DI	0.153	0.082
Tender point (0–18)	0.747	< 0.001
FIQ	0.833	< 0.001

CDAI clinical disease activity index; *DAS-28 ESR* disease activity measure 28 with erythrocyte sedimentation rate; *FIQ* fibromyalgia impact questionnaire; *HAQ-DI* health assessment questionnaire, disability-index; *SSS* symptom severity score; *VAS* visual analogue scale; *WPI* widespread pain index

Several studies reported a range of FM in RA between 4.9 and 17% according to the 1990 ACR Classification criteria for FM [18, 24, 25]. More recent reports used the ACR 2010 and 2011 survey criteria reported a higher rate. Joharatnam et al. [26] using the 2010 criteria reported 48% to have FM among 50 RA patients. Most of these studies primarily came from North American, European, and Asian cohorts. We are aware of only a few studies reported from Egyptian RA patients [19, 27, 28].

We compared the revised 2016 FM criteria in RA patients with 1990 criteria. The estimated rate of FM was higher when assessed with the 2016 criteria (40%) versus 31.5% with the tender points 1990 ACR criteria. Similar studies looked at the performance of 2010/2011 criteria against 19990 criteria showed a similar result. In Australian RA patients, using 2010/2011 ACR FM survey criteria, 41.9% of RA patients were fibromyalgia compared to 33.3% of RA patients according to 1990 criteria [3]. In 636 patients in the observational Oslo RA register (ORAR), the prevalence of FM by 1990 Classification criteria was 8%, while 30% had FM by 2010/2011 ACR criteria [29].

The discordance between the 2010/2011 and later 2016 revised criteria and the 1990 ACR criteria may be related to the characteristics of these criteria that allow for exploration of other important characteristics of FM more than that found in ACR 1990 classification criteria such as fatigue, unrefreshed sleep, and cognitive dysfunction among other manifestations recorded through the symptom severity scale. Ahmed et al. [30] suggested that the 2016 revised criteria and 1990 criteria possibly pick up different subsets of FM patients with chronic widespread pain in a tertiary referral center.

Females constituted 96.3% of our RA patients with FM versus 80.3% of patients without FM. FM is known to be more prevalent among females. Jones et al. [21] reported higher prevalence of FM in female patients using 1990 criteria 13.7:1 versus 4.8:1, and 2.3:1 of those meeting 2010 and 2011 criteria. Wolfe et al. [31] reported that the female proportion of FM cases was ≤ 60% in the unbiased studies. However, in a large sample of Veterans with pain diagnoses, those who were diagnosed with FM were more likely women, with a female:male ratio of 4:1 [32]. Although, the underlying mechanism of this gender disparity is not fully elucidated, multiple ''biological'' and ''psychosocial'' mechanisms that may contribute to sex differences in pain and analgesic responses, including gonadal hormones, endogenous pain modulatory systems, gender roles, and cognitive/affective factors [33].

Our patients with RA associated with FM had longer disease duration, more severe pain by VAS, DAS28-ESR, CDAI, PGA, Physician Global Assessment, and TJC compared to RA patients without FM. These findings are consistent with several previous studies reporting higher disease

activity and TJC in RA patients with FM than patients with RA only [34–37]. No significant difference in SJC between the two groups was found.

The higher composite disease activity measures as determined by DAS28, and CDAI may be due to the influence of pain caused by FM as all these measures include pain assessment by the patient. In clinical settings, a patient could be doing quite well in terms of control of RA inflammation while still reporting high levels of pain and associated symptoms. Therefore, the scales could lead to an apparently paradoxical and "misleading" result [38–40].

In addition to the role of inflammation in the pathogenesis of FM, a recent neurobiological study using functional connectivity MRI (fcMRI) provided objective neuroimaging evidence that RA is a mixed pain state displaying characteristics of central sensitization. One of the main findings was that RA patients who reported high levels of fibromyalginess (PSD) demonstrated significantly higher functional connectivity between the Default Mode Network (DMN) and insula—a recognized neurobiological feature of 'primary' FM. They concluded that the ACR FM survey appears to be a strong surrogate for this neurobiological marker of central sensitization [41].

PSD scale, a combination of WPI and SSS, is the underlying metric of fibromyalgia (FM), and levels of PSD can identify criteria-positive FM with > 90% accuracy [42, 43]. Among our RA patients, PSD scale correlated significantly with most of RA-specific variables (DAS28-ESR, CDAI, PGA, VAS, and 28 TJC), except for weak correlation with 28 SJC. Most of these were moderate correlations, possibly due to the sample size. This is partially consistent with data from a validation study of the modified 2010 American College of Rheumatology diagnostic criteria for fibromyalgia in a Spanish population, which showed a strong correlation between tender points and PSD scale ($r = 0.71$, $P < 0.001$) [44]. In the current study, the correlation between tender points and PSD scale was significant ($r_s = 0.498$, P value < 0.001). Because of these correlations, and with the increasing use of composite (patient and physician items) questionnaires in daily clinical practice, assessment of RA disease activity in patients with concomitant FM might be misleading. Therefore, it is better to screen patients with persistently high disease activity for concomitant FM. Recently, ultrasound assessment of synovitis had shown less synovitis in RA patients with FM [45, 46].

Limitations of the study

There were a few limitations to our study. Most of our RA patients had moderate-to-severe disease activity; this is because our center is a referral hospital, which may have led to a biased exclusion of patients with milder disease. All study subjects were on conventional DMARDs due to economic constraints and lack of resources for biological therapy; this might explain the inadequacy of disease control in these patients. Finally, there is no consensus among researchers in the field upon a gold standard for classification of FM to test the revised 2016 criteria against it.

Conclusions

In conclusion, FM is common in patients with longstanding active RA on csDMARDs according to the 2016 revised FM criteria. Furthermore, the incidence of FM was associated with high disease activity score. Therefore, it is recommended RA patients with persistently active disease to be routinely assessed for the presence of concomitant secondary FM.

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Compliance with ethical standards

Conflict of interest All authors declare they have no conflict of interest.

Ethical approval The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Suez Canal University (18/7/2018-3526). All patients provided written informed consent in accordance with the ethical standards of the 2013 version of the Declaration of Helsinki.

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