Clinical research

Prevalence and impact of fibromyalgia on disease activity in a sample of Iraqi patients with rheumatoid arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease. Fibromyalgia (FM) is a common diffuse pain syndrome in several rheumatic diseases. This study aimed to find the prevalence of FM in RA patients and to explore its impact on the disease activity of RA patients.

Material and methods: A total of 170 RA patients diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA were enrolled in this cross-sectional study. Age, gender, body mass index, marital status, educational level, occupation, smoking history, disease duration, and medications used were reported. Fibromyalgia was diagnosed by using the fibromyalgia criteria 2016 revision. The disease activity of RA patients was measured by using the clinical disease activity index (CDAI) and disease activity score-28 (DAS28).

Results: The mean age of fibromyalgia syndrome (FMS) patients was 51.263 ±11.531 years, and for non-FMS patients it was 48.469 ±13.932 years. FM was present in 57 (42.7%) RA patients, among whom the prevalence of FMS among female patients was 36.4%, which was significantly higher than that among male patients, at 6.3% (p = 0.015). FM significantly increased the disease activity measured by DAS28 (β = 0.241, p = 0.001) and by CDAI (β = 0.359, p < 0.001). Female gender and functional class of patients with RA positively increase the disease activity DAS28 (β = 0.142, p = 0.032; β = 0.396, p > 0.001), while only functional class increased the disease activity measured by CDAI (β = 0.373, p > 0.001).

Conclusions: The occurrence of FM in RA patients was common, and there was significant positive correlation between FMS severity and RA disease activity.

Key words: fibromyalgia, rheumatoid arthritis, disease activity.

Introduction

Rheumatoid arthritis (RA) is the most common chronic autoimmune inflammatory disease, which leads to massive joint damage and deformity; it is also associated with extra articular and systemic effects that can lead to increased morbidity and premature mortality [1, 2].

The normally used disease activity indices are typically composite scores that can include the physician's assessment of symptoms, patient-reported measures, and laboratory measurements. The Disease

Activity Score (DAS), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI), for example, rely on joint counts, patient self-assessment and (with the exception of CDAI) laboratory tests. Although physician evaluation and patient self-reporting are critical components of patient assessment and management, they are influenced by intra- and inter-assessor variability and can be accompanied by comorbidities or joint damage resulting from long-standing disease [3]. The CDAI, which does include the C-reactive protein (CRP), is more widely used in typical clinical practice where a laboratory measure may not be available in a timely manner to make routine management decisions. The CDAI ranges in value from 0 to 76 and was examined as a continuous variable in our main analysis. We used the standard categories of the CDAI as a secondary definition, where a score of ≤ 2.8 indicates remission, 2.9–10.0 indicates a low level of disease activity, 10.1–22.0 indicates moderate activity, and above that indicates high activity [4].

Fibromyalgia (FM) is a chronic pain syndrome in multiple body regions leading to clinically significant impairment in everyday life. FM is characterized by diffuse and chronic musculoskeletal pain lasting at least 3 months [5]. Additional symptoms such as fatigue, lack of sleep, anxiety, and cognitive problems are also significant features of this syndrome [6].

Pain remains the most serious problem for people with RA. Active inflammation leads to pain, but pain due to non-inflammatory mechanisms can confound the assessment of disease activity. The presence of FM in several rheumatic diseases with a structural pathology is common [7].

The diagnosis of fibromyalgia syndrome (FMS) was made depending on the 1990 ACR criteria when the patients had characteristic symptoms of fibromyalgia as well as multiple tender points [8]. Secondary FM is common among patients with inflammatory arthritis, but little is known about its incidence and the factors leading to its development.

A study in Canada done by Lee *et al.* in 2012 on 1487 patients with inflammatory arthritis showed that the cumulative incidence rate was 6.77 cases (95% CI: 5.19–8.64) per 100 person-years during the first 12 months after inflammatory arthritis diagnosis, and decreased to 3.58 cases (95% CI: 1.86–6.17) per 100 person-years 12–24 months after arthritis diagnosis [9].

Another study to determine the prevalence of FM and to evaluate the possible relationship between the existence of FM and disease activity among rheumatic diseases was done in 2014 by Haliloglu *et al.* showed that the prevalence of FM in patients with rheumatologic diseases was 6.6% for RA, 13.4% for systemic lupus erythematosus (SLE), and 12.6% for AS. With the exception of SLE and FMF, disease activity scores were significantly higher in patients with FM than in patients without FM, and people with RA and FM show higher pain and higher measures of disease activity. The 28-joint disease activity score (DAS28), which combines 4 components into an overall measure of RA inflammatory disease activity; 28 swollen joint count, 28 tender-joint count, acute-phase response (ESR), and a general health assessment using a visual analogue score, is commonly used in RA as a clinical measure of inflammatory disease activity. It appears that higher pain levels contribute to higher DAS28 scores [10].

Up to our knowledge, there was no previous study on the impact of FM on disease activity in RA patients. This study aimed to find the prevalence of FMS in RA patients attending the Rheumatology Unit in Baghdad Teaching Hospital and to explore the impact of FMS on disease activity of RA patients

Material and methods

Study design

A cross-sectional study was conducted at outpatient clinics in Baghdad Teaching Hospital/Medical City Complex during the period from September 2019 to the end of April 2020.

Participants

A total of 170 Iraqi patients (16 males and 154 females) were included, who were known cases of RA diagnosed by rheumatologists according to the 2010 ACR/EULAR classification criteria for diagnosis of RA [11], with 1 year or more disease duration, and age > 18 years. Patients were excluded if they had overlapping inflammatory arthritis disease or systemic diseases like diabetes, liver/kidney failure, thyroid gland diseases, hyperparathyroidism, osteomalacia, or malignancy.

Data collection and measurements

The data were collected using a sheet containing a questionnaire for the patients. The questionnaire included general socio-demographic data: age, gender, body mass index (BMI), marital status, educational level, occupation, and smoking history (smoker, non-smoker).

BMI was calculated according to the following equation (weight in kilograms divided by the square of height in metres), divided into 5 categories: underweight if BMI < 18 kg/m^2, normal if 18.5–24.9 kg/m^2, overweight if 25–29.9 kg/m^2, and obesity if ≥ 30 kg/m^2, in accordance with the international classification system of the WHO [12].

The disease activity of the patients was measured by using the CDAI and DAS28 scores [13].

Diagnosis and assessment of fibromyalgia were done by using the fibromyalgia criteria 2016 revision [14].

Disease characteristics of RA were collected through the standardized questionnaire including time since diagnosis and type of drug treatment for RA (classified as use of non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, disease-modifying anti-rheumatic drugs (DMARDs), and biological treatment or combinations).

Presence of comorbidities was excluded by a full history, appropriate examination and doing a basic investigations including complete blood count, erythrocyte sedimentation rate, renal function test, liver function test, fasting blood sugar and thyroid function test (if needed).

Ethical approval

The study protocol was approved by the Department of medicine, College of medicine, University of Baghdad with the number 1319 and date 13.10.2019. Informed consent was obtained from patients who participated in the study. Data and information on the participants were kept confidential, and any personal or private information that identified the participants was kept secret.

Statistical analysis

The collected data were entered on a Microsoft excel 2016 spreadsheet and loaded into SPSS V26 statistical software. Descriptive statistics were presented using tables and graphs. The χ^2 test was used to find out the association between related categorical variables, 2 independent samples *t*-test was used to find out the significance of differences between the means of the numerical variables, Pearson's correlation was used to find the significance of correlation between related numerical variables, multiple regression was used to test the effect of FMS severity on RA disease activity, and *p*-values > 0.05 were considered statistically significant.

Results

The results of this cross-sectional study show that 170 (16 males, 154 females) RA patients were included in this study. The mean age of FMS patients was 51.263 ±11.531 years, and for non-FMS it was 48.469 ±13.932 years. There was no statistically significant difference between the mean age of FMS and non-FMS patients ($p = 0.167$). The prevalence of FMS among female patients (36.4%) was significantly higher than that among male patients (6.3%) ($p = 0.015$). There was no statistically significant difference between the mean BMI of FMS and non-FMS patients ($p = 0.324$), and no statistically significant association was found between marital status, education level, occupation, smoking status, and FMS proportion in RA patients ($p = 0.074$, $p = 0.311$, $p = 0.096$, and $p = 0.173$, respectively). There was no statistically significant association noticed between duration of disease in both FMS and non-FMS patients ($p = 0.232$). The disease activity according to CDAI was significantly higher among FMS patients, with mean 22.2 ±7.300, than among non-FMS patients, with mean 15.1 ±5.668 ($p = 0.001$). Disease activity according to DAS 28 score was also significantly higher in FMS patients than non-FMS patients. FMS prevalence was increased among higher functional class RA patients ($p = 0.001$). Regarding disease activity class, there was no significant correlation seen between active RA and inactive RA patients both with and without FMS ($p = 0.552$). Regarding drug use, it shows that patients with no FMS used NSAIDs more frequently than patients with FMS RA, while no statistical significant deference was noticed between use of steroids, DMARDs, and biological treatment in association with FMS and non-FMS RA patients ($p = 0.455$, $p = 0.297$, $p = 0.973$, respectively). There was no statistically significant difference between the mean level of ESR in FMS 40.965 ±26.415 and non-FMS RA patients 37.478 ±23.912 ($p = 0.388$). There was significant association found between positive CRP and FMS RA patients ($p = 0.002$), while there was no statistically significant association between positive RF or positive ACPA and the presence of FMS in RA patients ($p = 0.230$ and $p = 0.072$, respectively), as shown in Table I.

Table II shows the impact of fibromyalgia severity on disease activity measured by DAS28 score after multiple linear regression, which revealed that female gender, functional class, and fibromyalgia severity positively increase the disease activity ($\beta = 0.142$, $p = 0.032$; $\beta = 0.396$, $p > 0.001$; $\beta = 0.241$, $p = 0.001$, respectively).

Table III shows the impact of fibromyalgia severity on disease activity measured by CDAI, using multiple linear regression, which revealed that only functional class and fibromyalgia severity increase the disease activity ($\beta = 0.373$, $p > 0.001$; $\beta = 0.359$, $p > 0.001$, respectively).

Figure 1 shows the prevalence of FMS in both active and inactive RA patients, in whom it is present in 33.5% of active RA patients and in 0% of inactive RA patients

Discussion

This study aimed to show the prevalence of FMS in RA patients attending the Rheumatology Unit in Baghdad Teaching Hospital, by using the new 2016 criteria for diagnosis of FMS, as well as to explore

Table I. Baseline characteristics of RA patients according to the presence and absence of FMS

Variables	FMS	No FMS	*P*-value
Age [years] Mean ± SD	51.263 ±11.531	48.469 ±13.932	0.167
Gender, *n* (%):			0.015
Female	56 (36.4)	98 (63.6)	
Male	1 (6.3)	15 (93.7)	
BMI [kg/m^2] Mean ± SD	28.8 ±4.065	20.02 ±4.82	0.324
Smoking, *n* (%):			0.173
Non smoker	50 (32.1)	106 (67.9)	
Smoker	7 (50)	7 (50)	
Marital status, *n* (%):			0.074
Single	3 (13.0)	20 (87.0)	
Married	45 (36.0)	80 (64.0)	
Others	9 (40.9)	13 (59.1)	
Education, *n* (%):			0.311
Illiterate	15 (35.7)	27 (64.3)	
Primary	21 (36.8)	36 (63.2)	
Secondary	17 (36.2)	30 (63.8)	
University	4 (16.7)	20 (83.3)	
Disease duration [years] Mean ± SD	8.509 ±5.754	9.903 ±7.757	0.232
Disease activity, mean ± SD:			0.001
CDAI ()	22.2 ±7.300	15.1 ±5.668	
DAS28	5.2 ±0.971	4.3 ±0.969	
Occupation, *n* (%):			0.096
Not working	46 (37.4)	77 (62.6)	
Working	11 (26.8)	30 (73.2)	
Retired	0 (0.0)	6 (100.0)	
Disease activity class, *n* (%):			0.552
Active	57 (34.1)	110 (65.9)	
Inactive	0 (0)	3 (100)	
Functional class, *n* (%):			0.001
Class 1	18 (23.4)	59 (76.6)	
Class 2	13 (25.0)	39 (75.0)	
Class 3	14 (56.0)	11 (44.0)	
Class 4	12 (75.0)	4 (25.0)	
Medication, *n* (%):			
NSAIDS users	36 (43.4)	47 (56.6)	0.008
Steroids	23 (37.1)	39 (62.9)	0.455
DMARDS	46 (35.7)	83 (64.3)	0.297
Biologics	41 (33.6)	81 (66.4)	0.973
ESR [mm/h] Mean ± SD	40.965 ±26.415	37.478 ±23.912	0.388
CRP, *n* (%):			0.002
Negative	4 (11.4)	31 (88.6)	
Positive	53 (39.3)	82 (60.7)	
RF, *n* (%):			0.230
Negative	7 (24.1)	22 (75.9)	
Positive	50 (35.7)	90 (64.3)	
ACPA, *n* (%):			0.072
Negative	5 (26.3)	14 (73.7)	
Positive	20 (51.3)	19 (48.7)	

FMS – fibromyalgia syndrome, SD – standard deviation, n – number, % – percentage, BMI – body mass index, (kg/m^2) – kilogram per square meter, CDAI – clinical disease activity index, RF – rheumatoid factor, ACPA – anticitrullinated peptide antibody, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, DMARDs – disease-modifying anti-rheumatic drugs.

Table II. Multiple linear regression to assess the impact of FMS severity on disease activity measured by DAS28

Variables	Standardized coefficients β	*P*-value
Female gender	0.142	0.032
Functional class	0.396	> 0.001
NSAIDs	0.019	0.768
CRP	0.122	0.063
FMS severity	0.241	0.001

NSAIDs – non-steroidal anti-inflammatory drugs, CRP – C-reactive protein.

Table III. Multiple linear regression to assess the impact of FMS severity on disease activity measured by CDAI

Variables	Standardized coefficients β	*P*-value
Female gender	0.018	0.781
Functional class	0.373	> 0.001
NSAIDs	0.045	0.476
CRP	0.028	0.669
FMS severity	0.359	> 0.001

NSAIDs – non-steroidal anti-inflammatory drugs, CRP – C-reactive protein.

the impact of FMS on disease activity of RA patients and finally to find out the association between sociodemographic variables and FMS in RA patients.

The prevalence of fibromyalgia in this study was 33.5% in RA patients (170 participants were studied), in contrast to other studies in which the prevalence of fibromyalgia was 12% and 15.4% in patients with RA [15–17]. The possible explanation for this difference could be the high number of bad socioeconomic factors that people living in Iraq suffer from, and due to starting use of the new 2016 criteria for FMS diagnosis. Fibromyalgia prevalence is greater in rheumatic diseases and chronic illnesses compared to primary fibromyalgia, and the probable reason is that pain remains the most serious problem for people with RA, making their everyday life and work difficult, so any additional syndrome like FMS will make it worse by reducing the threshold to pain perception [8].

Disease activity according to CDAI and DAS28 in the present study was significantly higher among the fibromyalgia RA group than the non-FMS group. This is in agreement with a study performed in 2019, which revealed that fibromyalgia appears to affect and increase the disease severity in RA patients, particularly in terms of patient-reported outcome measures, and it confirms the results of previous studies showing an association between concomitant FM and a higher degree of disease activity [15–18].

The study also shows that fibromyalgia severity, functional class, and female gender significantly increase the disease activity measured by DAS28 while only fibromyalgia severity and functional class increase the disease activity when measured by CDAI, due to the lack of ESR measurement in the latter index. The mechanism that explains FMS impact on RA patients was attributed to the subjective measures of the score: the tender joint count and patient assessment of general health (VAS-GH), which were significantly higher in the fibromyalgia group [19–21].

Up to our knowledge, this is the first study to assess the impact of fibromyalgia on diseases activity for RA patients in Iraq.

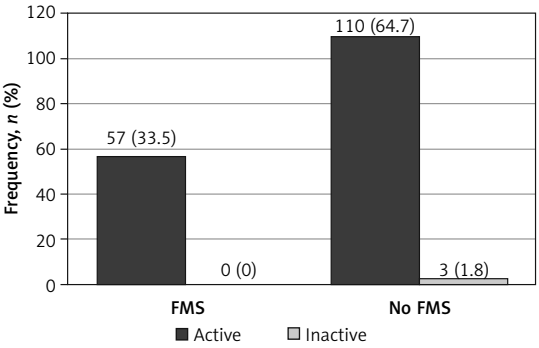

Figure 1. FMS prevalence in active and inactive RA patients

Another previous study that agrees with this one also showed the impact and severity of FMS on disease activity of RA patients using the DAS28 score index [22].

RA treatment requires accurate evaluation of disease activity in order to adapt the (DMARDs) regimen as closely as possible. Tools such as the Disease Activity Score (DAS) were used for this aim. This index is based in part on the patient's self-reported assessment, which is valuable in estimating the personal burden of the disease. However, if there is an associated illness, these subjective variables may be partially flawed by the patient's psychological condition, leading the physician to overestimate the patient's status [23].

Concerning the effect of gender, this study shows obvious differences between males and females regarding the prevalence of FMS, which was found to be significantly higher among females 36.4% than in males 6.3% ($p = 0.015$).

This finding is in agreement with 9 previous studies and with a one in 2017 for patients suffering from the same problem, in which the prevalence of FMS among women was 8–9-fold greater than that among men, and pain and disability were as high as in RA, which affects the personal activity and recreation, leading to occupational problems [24]. Also, it confirms another study on 124 participants done in the USA in 2015, in which the prevalence of fibromyalgia was 2.38% in women compared with 1.06% in men [21].

The study also did not reveal any significant difference in medications used by RA patients, except for NSAIDs, which were used more frequently in non-FMS patients than in patients with FMS.

Positive CRP showed a significant association with fibromyalgia in RA patients ($p = 0.002$), while there was no statistical significant association between ESR, positive RF, or positive ACPA and the presence of FMS in RA patients ($p = 0.388$, $p = 0.230$, $p = 0.072$, respectively), which is in agreement with a previous study in which ESR, RF, ACPA, and ANA, in addition to other markers, were not used to diagnose FMS but were obtained to evaluate other possible causes of symptoms or signs (diagnose other diseases), which means that these markers are not associated significantly with FMS [25].

The strength of this study comes from the fact that it is the first study in Iraq to assess the effect of FMS on disease activity and its outcomes in patients with RA, which is important, knowing that additional syndromes like (FMS) can lead to greater pain, impaired function, and worse general health, which can make it difficult to assess the response to medications that are used by RA patients. Some limitations of the study included being a cross-sectional study, and we cannot assess the causality. Also, there was some difficulty in performing some laboratory investigations because they were not available in the hospital and were costly. In addition, our diagnosis of FMS was dependent on a questionnaire, which is variable from one patient to another. Finally, there was no follow-up for these patients.

In conclusion, the occurrence of FM in RA patients was common. There was significant positive relation between FMS severity and disease activity in CDAI and DAS28. Female gender and functional class were significantly associated with FMS. This may suggest that early screening for FMS in patients with RA to obtain an early diagnosis and appropriate treatment will subsequently decrease the disease activity and subsequently improve the patient's quality of life. However, a multicentre study with larger sample size is important to obtain more representative and accurate results.

Conflict of interest

The authors declare no conflict of interest.

References

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011; 365: 2205-19.
2. Huizinga TW, Pincus T. Rheumatoid arthritis. Ann Inter Med 2010; 153: ITC1-1.
3. Centola M, Cavet G, Shen Y, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PLoS One 2013; 8: e60635.
4. Solomon DH, Reed GW, Kremer JM, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015; 67: 1449-55.
5. Zernikow B, Gerhold K, Bürk G, et al. Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents. Schmerz 2012; 26: 318.
6. Duffield SJ, Miller N, Zhao S, Goodson NJ. Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. Rheumatology 2018; 57: 1453-60.
7. Joharatnam N, McWilliams DF, Wilson D, et al. A cross-sectional study of pain sensitivity, disease-activity assessment, mental health, and fibromyalgia status in rheumatoid arthritis. Arthritis Res Therapy 2015; 17: 11.
8. Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat 2012; 2012: 584573.
9. Lee YC, Lu B, Boire G, et al. Incidence and predictors of secondary fibromyalgia in an early arthritis cohort. Ann Rheum Dis 2013; 72: 949-54.
10. Haliloglu S, Carlioglu A, Akdeniz D, et al. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int 2014; 34: 1275-80.
11. Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaboration initiative. Arthritis Rheum 2010; 62: 2569-81.
12. World Health Organization. Obesity: preventing and managing the global epidemic. World Health Organization 2000; 894(i–xii): 1-253.
13. Solomon DH, Reed GW, Kremer JM, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015; 67: 1449-55.
14. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016; 46: 319-29.
15. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology 2010; 49: 924-8.
16. Ranzolin A, Brenol JCT, Bredemeier M, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, Health Assessment Questionnaire, and short form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum 2009; 61: 794-800.
17. Wolfe F, Michaud K. Severe rheumatoid arthritis, worse outcomes, comorbid illness and sociodemographic disadvantage characterize RA patients with fibromyalgia. J Rheumatol 2004; 31: 695-700.
18. Zhao SS, Duffield SJ, Goodson NJ. The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. Best Pract Res Clin Rheumatol 2019; 17: 101423.
19. Ton E, Bakker MF, Verstappen S, et al. Look beyond the DAS28: tender points influence the DAS28 in patients with rheumatoid arthritis. J Rheumatol 2012; 39: 22-7.
20. Ranzolin A, Brenol JC, Bredemeier M, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum 2009; 61: 794-800.
21. Vilaseca DR, Otero CH. Effect of the coexistence of fibromyalgia in the DAS28 index in women with rheumatoid arthritis. Rheumatol Clin 2008; 40: 96-9.
22. Rehman AU, Rasheed A, Wagan AA, et al. impact of fibromyalgia on Das-28 score in rheumatoid arthritis. Pakistan Armed Forces Med J 2018; 68: 1210-4.

23. Coury F, Rossat A, Tebib A, et al. Rheumatoid arthritis and fibromyalgia: a frequent unrelated association complicating disease management. J Rheumatol 2009; 36: 58-62.
24. Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. Rheumatol Int 2017; 37: 1527-39.
25. Arnold LM, Clauw DJ, McCarberg BH. Improving the recognition and diagnosis of fibromyalgia. Mayo Clin Proc 2011; 86: 457-64.