Secondary fibromyalgia in different rheumatic diseases

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Abstract: Objective: To assess for the presence of secondary fibromyalgia in some rheumatic diseases: Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) SLE, Primary knee osteoarthritis (OA) and Anklyosingspondyolitis (AS) in Egyptian patients. **Patients and methods:** The present cross sectional study included 56 patients; 20 with rheumatoid arthritis (RA), 15 with primary knee osteoarthritis (OA), 11 with systemic lupus erythematosus (SLE) and 10 with ankylosingspondoylitis (AS) patients. Disease activity was assessed using disease activity score in 28 joints (DAS28) for RA, SLE Disease Activity Index (SLEDAI), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for osteoarthritis patients and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS patients. Severity in FMS cases was estimated using the revised Fibromyalgia Impact Questionnaire score (FIQR). To diagnose fibromyalgia,2010 American College of Rheumatology (ACR 2010) had to be fullifiled. OA patients were subjected to Douleur Neuropathique 4 Questions (DN4) questionnaire. **Results:** In the RA, SLE, OA and AS patients, FMS was found in 25%, 18.2%, 20% and 30% respectively. In RA patients, DAS28 was significantly higher in those with FMS (p=0.001) and presence of x-ray erosions was significantly higher in those without FMS (p=0.05). In SLE patients, SLEDAI showed no significant difference between patients with FMS and those without (p=0.175). In OA patients, WOMAC was significantly higher in those with FMS (p=0.039) and DN4 was significantly higher in those with FMS (p=0.001). In AS patients, BASDAI was significantly higher in those with FMS (p=0.026). **Conclusion:** Some rheumatic disease including RA, SLE, OA and AS could be associated with FMS. FMS in RA, OA and AS could be related to higher disease activity. Recognition of secondary FMS is important for the optimal assessment and treatment of these diseases.
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1. Introduction:

Fibromyalgia is a syndrome of widespread pain, fatigue, sleep disturbance and cognitive problems that is assumed to originate from inappropriate pain processing in the central nervous system[1]. It is important to consider the frequency of concomitant fibromyalgia with other rheumatic diseases as most rheumatic diseases causes chronic pain, so treatment of fibromyalgia will decrease pain and improve the quality of life[2].

About 15–30% of rheumatic patients have associated FMS[2], which is more than the prevalence of FMS in the general population (2%), it seems that the pain accompanying chronic rheumatic diseases is also capable of triggering FMS.[3]Increased pain and fatigue with multiple tender points should not be automatically attributed to increased activity of these diseases and prescribe higher doses of a biologic agent or corticosteroids without proper examination and laboratory evaluation[4]. Presence of fibromyalgia with rheumatoid arthritis makes it difficult to assess rheumatoid arthritis activity as patient suffer from wide spread pain and disability even if the inflammation subside with higher DAS-28 at basline and FM should be considered in patients with RA not reaching remission.[5]It is important to rule out fibromyalgia with systemic lupus as sometimes fibromyalgia may be missed in lupus patient or fibromyalgia may be misdiagnosed as lupus[6]. About 22%of lupus patients have fibromyalgia[7]. There are little published data on the relationship between FMS and primary knee osteoarthritis. In one study on osteoarthritis (OA) patients, the frequency of FMS was reported to be 10%.[4]Other study found the frequency of FMS in patients with knee osteoarthritis scheduled to undergo knee arthroplasty to be 3.8%[8]. Patients with both AS and FMS, experience continuous pain, higher level of fatigue and higher intensity of pain than patients with AS alone[9]. FM was reported in up to 25% of the patients with AS[10].

The aim of the present work isto assess presence of secondary fibromyalgia in different rheumatic diseases: Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) SLE, Primary knee osteoarthritis (OA) and Anklyosingspondyolitis (AS) in Egyptian patients.

2. Patients and methods

The cross sectional study included 56 patients; 20 with RA, 11 with SLE, 15 with OA and another 10 with AS. All patients were consequently recruited from those attending the Rheumatology outpatient clinic of physical medicine, rheumatology and rehabilitation department, Faculty of Medicine, Ain-shams University Hospital. Patients were included when they fulfilled their corresponding classification criteria; 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria[11] for RA, Systemic Lupus Inter-national Collaborating Clinics (SLICC) classification criteria[12] for SLE, 1989 American College of Rheumatology (ACR) classification criteria[13] for OA patients and modified New York criteria for AS[14]. The study was performed in accordance with the Declaration of Helsinki, and all patients gave written consent for enrollment in the study.

All patients were subjected to full history taking and physical examination. Relevant laboratory and radiological investigations were done. The following disease activity indices and score were considered: disease activity score in 28 joints (DAS28)[15] for RA patients; SLE Disease Activity index (SLEDAI)[16] for SLE patients, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for OA patients[17] and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS patients[18]. The 2010 ACR preliminary diagnostic criteria for FMS was applied to all the patients[19] and those with FMS were assessed for severity using the revised Fibromyalgia Impact Questionnaire (FIQR) score.[20] Osteoarthritis patients subjected to Douleur Neuropathique 4 Questions (DN4) questionnaire[21].

Statistical analysis:

Data were analyzed using the computer program, Statistical Package for the Social Science; SPSS Inc., (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Data were described in terms of range, mean ± SD, median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Two sample t-test for independent samples. For comparing categorical data, Chi square test was performed. Comparison among more than 2 groups was done using ANOVA. McNemar testwas used to assess the statistical significance of the difference between a qualitative variable measured twice for the same study group. p-Value<0.05 was considered statistically significant, P > 0.05 was considered non-significant (NS) and P < 0.01 was considered highly significant (HS).

3. Results

The prevalence of fibromyalgia is presented in Table 1, where the prevelance in AS patients is 30%, in RA patients is 25%, in OA patients is 20% and in SLE patients is 18.2% respectively.

Table 1: FM percent in each group

			Fibromyalgia		No Fibromyalgia	
		Total NO.	Count	%	Count	%
Patient Group	Osteoarthritis	15	3	20.0%	12	80.0%
	Rheumatoid arthritis	20	5	25.0%	15	75.0%
	Ankylosingspondyolitis	10	3	30.0%	7	70.0%
	SLE	11	2	18.2%	9	81.8%

The characteristic features of the RA patients with and with-out FMS are presented in Table 2. The frequency of FMS in the RA patients was 25%. There was statistically significant difference between RA-FM group and RA-non FM group regarding activity score of the studied patients with P-value < 0.001. Erosive changes in x-ray occurred in 46.7% of RA patients without FMS and non of those with FMS had erosive changes in x-ray. When comparing RA patients with and without FMS, the ESR was not significantly higher in the RA patients with FMS than that in those without (p= 0.843). Regarding the medications, there was significant difference between the two groups regarding number of DMARDS used with p value (0.001).

The characteristic features of the SLE patients with and with-out FMS are presented in Table 3. The frequency of FMS in the SLE patients was 18.2%. All patients were females (100%). There was no significant difference regarding symptom severity scale and activity score (SLEDAI) with P-value 0.204 and 0.175 respectively. Regarding the medications, all patients (100%) received steroids.

Table 2: Comparison of demographic data, disease duration and different scores between RA patients with or without Fibromyalgia

Total N=20		Fibromyalgia N=5		No Fibromyalgia N=15		p-value
Age **(Mean±SD)**		48.20	11.05	48.87	15.24	0.930
sex **n (%)**	Female	4	80.0%	11	73.3%	0.766
	Male	1	20.0%	4	26.67%	
Duration of disease in years **(Mean±SD)**		3.50	1.87	8.43	7.01	0.24
WPI **(Mean±SD)**		7.80	1.48	4.40	1.59	**0.001**
SS scale **(Mean±SD)**		7.20	2.77	4.13	1.73	**0.008**
DAS28**(Mean±SD)**		6.44	.42	4.64	.92	**0.001**
ESR **(Mean±SD)**		38.00	7.58	40.00	21.41	0.843
Positive RF **n (%)**		5	100.0%	11	73.3%	0.197
x-ray erosions **n (%)**		0	0.0%	7	46.7%	**0.05**
NO.OF DMARDS **(Mean±SD)**		2.00	0	1.40	0.51	**0.001**
STEROIDS taken		4	80.0%	11	73.03%	---
Not taken		1	20.0%	4	26.7%	
MTX taken		5	100%	14	93.3%	---
Not taken		0	0%	1	6.7%	
Biologic drug taken		0	0%	1	6.7%	---
Not taken		5	100%	14	93.3%	
HCQ taken		5	100%	6	40%	---
Not taken		0	0%	9	60 %	

RA: Rheumatoid Arthritis, FMS: fibromyalgia syndrome, ESR: Erythrocyte Sedimentation Rate, RF: Rheumatoid Factor, DAS28: Disease Activity Score 28, WPI: Widespread pain Index, SS scale: Symptoms Severity scale, MTX: Methotrexate, HCQ: Hydroxychloroquine, DMARDs: Disease-modifying antirheumatic drugs.

Table 3: Comparison of demographic data, disease duration and different scores between SLE patients with or without Fibromyalgia

Total N=11		Fibromyalgia N=2		No Fibromyalgia N=9		p-value
Age **(Mean±SD)**		33.50	2.12	32.11	12.80	0.886
Sex **n (%)**	Female	2	100.0%	9	100.0%	
	Male	0	0.0%	0	00.0%	
Duration of disease in years **(Mean±SD)**		3.50	2.12	7.22	8.21	0.555
WPI **(Mean±SD)**		8.50	.71	3.67	1.32	**0.001**
SS scale **(Mean±SD)**		7.00	1.41	4.56	1.33	0.204
SLEDAI **(Mean±SD)**		10.00	2.83	14.44	3.97	0.175
STEROIDS taken		2	100.0%	9	100.0%	---
Hydroquinetaken		2	100.0%	8	88.89%	---
Not taken		0	0%	1	11.11%	
Azathioprine taken		0	0.0%	1	11.11%	---
Not taken		2	100%	8	88.89%	

SLE: s**ystemic** lupus erythematosus,, WPI: Widespread pain Index, SS scale: Symptoms Severity scale, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

The characteristic features of the OA patients with and with-out FMS are presented in Table 4. Total number of OA patients is 15, 11 patients were females: 3 of them have FM and 8 of them don't have FM. 4 patients were males and all of them don't have FM. The comparison yielded no statistical significance (p= 0.243). There was statistically significant difference between OA- FM group and OA-non FM group regarding wide pain index, symptom severity scale, activity score (WOMAC) and DN4 of the studied patients with P-value < 0.001, 0.001, 0.039 and 0.001 respectively. OA patients with

fibromyalgia: 2 (66.66%) of them were grade 1 and 1(33.33%) was grade 3 where as, OA patients without FM: 3 (20%) were grade 2, 6 (40%) of them were grade 3 and 3 (20%) of them were grade 4. Regarding the medications, all OA patients with FM were taking NSAIDs and pregabline.

Table 4: Comparison of demographic data, disease duration and different scores between OA patients with or without Fibromyalgia

Total N=15	Fibromyalgia N= 3			No Fibromyalgia N= 12		p-value
Age **(Mean±SD)**	45		18	56.42	8.72	0.109
Sex **n (%)**	Female	3	100.0%	8	66.7%	0.243
	Male	0	0.0%	4	33.3%	
Duration of disease in years **(Mean±SD)**	4.67		4.62	10.17	5.95	0.163
WPI **(Mean±SD)**	12.00		1.00	5.00	1.28	**< 0.001**
SS scale **(Mean±SD)**	9.67		1.53	3.33	1.30	**< 0.001**
WOMAC index **(Mean±SD)**	52.33		2.52	42.17	7.37	**0.039**
DN4 **(Mean±SD)**		4.67	0.58	0.83	0.83	**< 0.001**
Nodal OA **n (%)**	Yes	1	33.3%	5	41.7%	0.792
	No	2	66.7%	7	58.3%	
NSAIDs taken **n (%)**	3		100%	10	83.33%	---
NSAIDS not taken **n (%)**	0		0%	2	16.7%	
Local steroid injection done **n (%)**	0		0%	3	25 %	---
Not done **n (%)**	3		100%	9	75%	
Physiotherapy done **n (%)**	0		0 %	6	50%	---
Not done **n (%)**	3		100%	6	50%	
Pregabalin taken **n (%)**	3		100.0%	2	16.67 %	---
Not taken **n (%)**	0		0%	10	83.3%	
Grade 1 **n (%)**	2 (66.6%)			-------		---
Grade 2 **n (%)**	----------			3 (20%)		---
Grade 3 **n (%)**	1 (33.33%)			6 (40%)		---
Grade 4 **n (%)**	----------			3 (20%)		---

OA: primary knee osteoarthritis, WPI: Widespread pain index, SS scale: Symptoms Severity, WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index, DN4: Douleur Neuropathique 4 questionnaire. Grading, according to the **Kellgren and Lawrence system:** Comparison of osteoarthritis grades between OA patients with or without Fibromyalgia.

The characteristic features of the AS patients with and with-out FMS are presented in Table 5. All patients were males (100%). There was statistically significant difference between AS- FM group and AS-non FM group regarding wide pain index, symptom severity scale and activity score (BASDI) of the studied patients with P-value 0.089,0.000 and 0.026 respectively. There was no significant difference, regarding duration of disease and peripheral arthritis with P-value 0.331 and 0.49 respectively.

Table 6 shows that, on comparing the WPI among the rheumatic diseases patients, the mean was significantly higher in the OA patients (12 ± 1) compared to that in the SLE (8.5 ± 0.7), AS (8 ± 1.73) and RA (7.8 ± 1.48) but still yielded no statistically significant difference with P-value 0.297. Also, there was no statistically significant difference between OA, RA, SLE and AS groups regarding symptom severity scale and activity score of the studied patients with P-value 0.767 and 0.819 respectively.

Table 5: Comparison of demographic data, disease duration and different scores between AS patients with or without Fibromyalgia

Total N=10		Fibromyalgia N=3		No Fibromyalgia N=7		p-value
Age **(Mean±SD)**		31.00	3.61	28.71	9.66	0.709
Sex **n (%)**	Female	0	0.0%	0	00.0%	
	Male	3	100.0%	7	100.0%	
Duration of disease **(Mean±SD)**		8.33	4.73	5.43	3.82	0.331
peripheral arthritis		2	66.7%	3	420.9%	0.49
WPI **(Mean±SD)**		8.00	1.73	6.00	1.41	**0.089**
SS scale **(Mean±SD)**		9.00	.00	4.00	.82	**0.000**
BASDAI **(Mean±SD)**		7.88	1.66	4.44	1.89	**0.026**
NSAIDs taken	1	33.33%	4	57.14%	---	
Not taken	2	66.7%	3	42.9%	---	
Sulazopyrinetaken	1	33.33%	4	57.14%	---	
Not taken	2	66.7%	3	42.9%	---	
Anti- TNF taken	2	66.67%	3	42.86%	---	
Not taken	1	33.33%	4	57.14%	---	

AS: ankylosingspondylitis, WPI: Widespread pain Index, SS scale: Symptoms Severity scale, BASDI: Bath Ankylosing Spondylitis Disease Activity Index, NSAIDs: non steroidal anti inflammatory drugs, anti- TNF: inhibitors of tumor necrosis factor.

Table 6: Comparison between FM patients in each group as regard different Scores:

Patient groups	**RA**	**SLE**	**OA**	**AS**	**P-value**
WPI (Mean±SD)	7.8 ±1.48	8.5 ± 0.7	12 ± 1	8 ± 1.73	0.297
SS scale (Mean±SD)	7.20 ± 2.77	7 ± 1.41	9.67 ± 1.53	9 ± 0.0	0.767
Activity score (FIQR) (Mean±SD)	49.20 ± 7.69	57.00± 4.24	56.33± 8.02	58.00± 10.82	0.819

WPI: Widespread pain Index, SS scale: Symptoms Severity scale, FIQR: Fibromyalgia Impact Questionnaire.

4. Discussion

In clinical practice, special attention should be given to concomitant FMS and rheumatic diseases as FMS may be unrecognized, although its presence influence the interpretation of the disease[22]. Incidence of FM influenced by difference in nationality, race and the socioeconomic status.

In the current study, 5(25%) RA patients had FMS. Similarly, an Indian study in 2014, found that the prevalence of FMS in RA patients, was **(25.83%)**[23] and was found to be **30%** in another American study in 2019[5]. **Erosive changes** in x-rays of both hands, were found in 46.7% of RA patients without FMS and were absent in RA patients with FMS. This finding is similar to other previous studies[24,25]. These results showed that the association between RA and FMS, affords for these patients some protection against joint destruction.

Onlytwo of SLE patients **(18.2%)** had FMS. Similarly, an Egyptian study in 2017 showed that, 9**(18%)** out of 50 SLE patients had FMS[25]. Other Mexican study in 2017, found that **19.6%** of 138 women SLE patients had FMS[26].

In our study. 3 of OA patients **(20%)** had FMS. This result is similar to that of a Dutch study done in 2018, who found that **26%** of 842 generalized OA patients had concomitant FMS[27]. **DN4** questionnaire (which is an assessment of neuropathic pain) in **OA** patients, was significantly higher in OA with FMS than those without. Similarly, a study done in UK which showed that neuropathic knee pain is common with FMS[28]. The presence of osteoarthritis nodules **(nodal OA)** showed no significant differences between the OA patients with and without FMS. In contrast to a UK study done by Fernades in 2018, which showed significant difference between the OA patients with and without FMS, regarding osteoarthritis nodules.[28]This discrepancy from the current results could be attributed to the small number of patients conducted in our study and we recommend other studies to be performed on larger number of patients.

In the current study 3 of AS patients **(30%)** had FMS. Similarly, FMS has been found in **37.8%** (192/508 **)** of AS patients in a study done by Moltó in France in 2018[29] and **29%**of 100 AS patients in a study done by Xenofon in UK in 2018[30].

In the present study there was no significantly difference in the **age or disease duration** between **all** studied patients with and without FMS. This is came

in agreement with the results of previous studies done by EL-Rabbatin 2017 and Haliloglu in 2014 [25,31].

The **disease activity scores**, were significantly higher in RA (DAS28), OA (WOMAC) and AS (BASDAI) patients with FMS than those without but no significant difference was found in SLE (SLEDAI) patients with FMS and those without. This is in agreement to the results of previous studies25,31. These high scores are affected by fibromyalgia as they assesses the tender joint count and poor general health status in DAS28 and assess the pain and function scales in WOMAC and BASDAI, which are highly affected by FM presenceleading to misclassification of disease activity and unnecessary change in the therapy. On the other hand, SLEDAI score assessment is a combination of the clinical history, physical examination, organ specific functional tests, and serologic studies which are not affected by FMS.

In terms of treatment, there were no significant differences between all patients with and without FMS apart from the number of DMARDS used by RA patients and pregabalin which were consumed much more by OA-FM group than those without. The same finding was present in a previous study31,23,32.

In conclusion, concomitant FMS should be considered in the assessment of rheumatic disease and their management especially in RA, OA and AS patients with high disease activity as FMS leads to misclassification of disease activity due to exaggeration of pain and functional limitation which at last leads to unnecessary change in the therapy.

A larger scale longitudinal study is recommended to confirm the presented results and to detect the impact of treatment on the associated FMS. The significance of this study is to detect the prevalence of FMS in Egyptian patients with some rheumatic diseases and to throw light on the association with the disease activity. It also adds to the limited insights on the relation of FMS to these rheumatic disease.

Ethical disclosures

Protection of human and animal subjects. The authors declarethat no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have fol-lowed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare thatno patient data appear in this article.

Conflict of interest

None declared.

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