Clinical significance of fibromyalgia syndrome in different rheumatic diseases: Relation to disease activity and quality of life

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ABSTRACT

Objective: To describe the frequencies of fibromyalgia syndrome (FMS) in various rheumatic diseases; rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Behçet disease (BD) patients and to study the relation to clinical manifestations and quality of life (QoL).

Patients and methods: 160 patients (50 RA, 50 SLE, 30 SSc and 30 BD) and matched corresponding healthy controls were included. Disease activity was assessed using disease activity score in 28 joints (DAS28) for RA, SLE Disease Activity index (SLEDAI), modified Rodnan skin score for SSc and BD Current Activity Form (BDCAF). The QoL was also recorded. Severity in FMS cases was estimated using the revised Fibromyalgia Impact Questionnaire score.

Results: In the RA, SLE, SSc and BD patients, FMS was found in 14%, 18%, 6.67% and 3.33% respectively compared to 2.1%, 3%, 3.3% and 0% in their corresponding controls. In RA patients, DAS28 was significantly higher in those with FMS (p = 0.009) and significantly correlated with both Widespread Pain Index (WPI) (p = 0.011) and Symptom Severity (SS) scale (p = 0.012). The QoL scale in those with FMS was significantly worse (62.3 ± 7.9) compared to those without (71.7 ± 14.4) (p = 0.023). In SLE patients, the WPI and SS both significantly correlated with the presence of thrombosis (r = 0.28, p = 0.049 and r = 0.43, p = 0.002 respectively). The SS scale tended to correlate with the SLEDAI (r = 0.28, p = 0.05). In BD patients, BDCAF and WPI significantly correlated (p = 0.03).

Conclusion: Fibromyalgia syndrome is more frequent in rheumatic diseases, could be related to the disease activity in RA and BD patients and to thrombosis in SLE and affected the QoL in RA.

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Significación clínica del síndrome de fibromialgia en diferentes enfermedades reumáticas: relación con la actividad de la enfermedad y la calidad de vida

RESUMEN

Objetivo: Describir las frecuencias del síndrome de fibromialgia (SFM) en los pacientes de diversas enfermedades reumáticas; artritis reumatoide (AR), lupus eritematoso sistémico (LES), esclerosis sistémica (ES) y enfermedad de Behçet (EB), y estudiar su relación con las manifestaciones clínicas y la calidad de vida (CV).

Pacientes y métodos: Se incluyó en el estudio a 160 pacientes (50 AR, 50 LES, 30 ES y 30 EB) y a los controles sanos emparejados. La actividad de la enfermedad se evaluó utilizando las escalas Disease Activity Score en 28 articulaciones (DAS28) para AR, SLE Disease Activity Index (SLEDAI), Rodnan modificada para ES y BD Current Activity Form (BDCAF). También se registró la CV. La severidad en los casos de SFM se estimó utilizando la escala Fibromyalgia Impact Questionnaire revisada.

Resultados: En los pacientes de AR, LES, ES y EB se encontró SFM en el 14%, el 18%, el 6.67% y el 3.33%, respectivamente, en comparación al 2.1%, el 3%, el 3.3% y el 0% en sus controles correspondientes. En los pacientes con AR, la clasificación DAS28 fue significativamente superior en aquellos con SFM (p = 0.009), guardando una correlación significativa con las escalas Widespread Pain Index (WPI) (p = 0.011) y Symptom Severity (SS) (p = 0.012). La escala CV en aquellos pacientes con SFM fue considerablemente peor (62.3 ± 7.9) en comparación con aquellos que no presentaban dicho síndrome (71.7 ± 14.4) (p = 0.023). En los pacientes

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Pain
There
As
In
Rheumatology/European
30%
In
the
SSc
and
BD.
A
SLE
of
DAS28
was
2.1%
and
RA
14%
and
corticosteroids
of
BD.
their
rheumatic
and
Fatigue
of
1/33
with
FMS
has
SLE
y
S.S.
career
were
seriously;
they
the
SSc
for
SSc
were
reported
and/and
the
SSc
of
80%
years)
for
0.049,
y
r =
0.002
respectively).
La
escalas
SSDAI
(r =
0.29,
p =
0.05).
En
los
pacientes
EB; las
escalas
BDCAF
y
WPI
guardaron
una
correlación
significativa
(p =
0.03).

Conclusion: El síndrome de fibromialgia es más frecuente en las enfermedades reumáticas y podría guardar
relación con la actividad de la enfermedad en los pacientes de AR y EB, y con la trombosis en los pacientes
de LES, afectando a la CV en la AR.

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Introduction
Fibromyalgia syndrome (FMS) is defined by the presence of
generalized pain, fatigue, unrefreshed sleep, multiple somatic
symptoms and cognitive problems.1 Pain and inflammation in
patients with inflammatory arthritis play a role in the development
and course of FMS.2 Perhaps the most important role of the rheuma-
tologist is to confirm the diagnosis and determine if the patient has
a co-morbid rheumatic condition that should be treated. If FMS is
complicating another rheumatic disease, specific management of
FMS may improve overall health outcomes.3

Rheumatic diseases are characterized by chronic pain and as
many as 15–30% of patients also have associated FMS.4 As these
rates are much higher 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.5 As concomi-
tant FMS is a common clinical problem in rheumatic diseases, its
recognition is important for their optimal management. Increased
pain, physical limitations, and fatigue may be interpreted as
increased activity of these diseases.6 The association of systemic
lupus erythematosus (SLE) and FMS may pose a clinical diagnostic
dilemma as both share many symptoms.7 The superimposed pain
of FMS may lead to the prescription of higher doses of corticosteroids
or biologic agents.8

In one study on systemic sclerosis (SSc) patients, the frequency
of FMS was reported to be 2%.8 There are little published data on
the relationship between FMS and Behçet's disease (BD); FMS is
a common and important clinical problem that may represent an
additional factor that worsens pain and physical limitations in BD
patients. An increased awareness of this possible coexistence may
contribute more accurate management of BD.9

The aim of the present work was to describe the frequencies of
FMS in various rheumatic diseases; rheumatoid arthritis (RA), SLE,
SSc and BD patients and to study the relation of FMS to the clinical
manifestations, laboratory features, disease activity and/or damage
as well as the quality of life (QoL).

Patients and methods
The study included 160 patients; 50 with RA, 50 with SLE,
30 with SSc and another 30 with BD. All patients were con-
sequently recruited from those attending the Rheumatology
outpatient clinic and department, Faculty of Medicine, Cairo
University Hospital. Patients were included when they fulfilled
their corresponding classification criteria: 2010 American Col-
lege of Rheumatology/European League Against Rheumatism
(ACR/EULAR) classification criteria10 for RA, Systemic Lupus Inter-
national Collaborating Clinics (SLICC) classification criteria11 for
SLE, 2013 ACR/EULAR classification criteria12 for SSc patients and
the International Study Group criteria for BD.13 Apparently healthy
volunteers (n = 141) were included as control groups who were age
and sex matched for each disease; they were 48 control for RA
patients, 33 for SLE, 30 for SSc and 30 for the BD patients. All controls
were recruited from the hospital staff members and employees
and relatives of the patients were not considered to avoid famil-
 iar aggregation. 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)14 and health
assessment questionnaire II (HAQII)15 for RA patients; SLE Disease
Activity index (SLEDAI)16 and SLICC/ACR damage index17 for SLE
patients, modified Rodnan skin score (mRSS)18 and systemic rhe-
mus disease severity19 for SSc patients and BD Current Activity
Form (BDCAF)20 for BD patients. The QoL scale21 was assessed for all
the patients. The 2010 ACR preliminary diagnostic criteria for FMS
was applied to all the patients and control22 and those with FMS
were assessed for severity using the revised Fibromyalgia Impact
Questionnaire (FIQR) score.23

Statistical analysis
Data were analyzed using the computer program, SPSS (Statis-
tical Package for the Social Science; SPSS Inc., Chicago, IL, USA)
version 15. 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 Mann Whitney U test for independent
samples. For comparing categorical data, Chi square (χ2) test was
performed. Comparison among more than 2 groups was by ANOVA.
Spearman's correlation analysis was used for detection of the rela-
tion between 2 variables. P-value <0.05 was considered statistically
significant.

Results
The characteristic features of the RA patients with and with-
out FMS are presented in Table 1. The controls were matched
in age (39.6 ± 14 years) (p = 0.1) and sex (F:M 7:1) (p = 0.7).
The frequency of FMS in the RA patients was 14% while in their corre-
spanding control was 2.1% (1/48 subjects). The mean FIQR score of
the 7 RA patients with FMS was 104.4 ± 23.9. The WPI component
of FMS significantly correlated with the DAS28 (r = 0.36, p = 0.01)
and negatively with the QoL scale (r = −0.39, p = 0.004) and the SS
correlated with the DAS28 (r = 0.35, p = 0.012), HAQII (r = 0.39,
p = 0.006) and negatively with the QoL (r = −0.36, p = 0.01).

The characteristic features of the SLE patients with and with-
out FMS are presented in Table 2. The controls were matched
in age (29.9 ± 7.1 years) and similarly were all females. The frequency
of FMS in the SLE patients was 18% while in their correspond-
ing control was 3% (1/33 subjects). The mean FIQR score of the 9
SLE patients with FMS was 94.2 ± 13.9. The WPI and SS scale both
significantly correlated with the presence of thrombosis (r = 0.28,

### Table 1

Demographic features, investigations, disease activity, functional status, quality of life and medications used in rheumatoid arthritis (RA) patients with and without fibromyalgia syndrome (FMS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA patients (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With FMS (No = 77)</td>
<td>Without FMS (No = 43)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.1 ± 8.9</td>
<td>43.9 ± 11.8</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>7 females</td>
<td>38.5</td>
</tr>
<tr>
<td>DD (years)</td>
<td>8.7 ± 8.4</td>
<td>8.3 ± 6.4</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>33.8 ± 11.1</td>
<td>41.9 ± 22.4</td>
</tr>
<tr>
<td>Positive RF</td>
<td>4 (57)</td>
<td>34 (79)</td>
</tr>
<tr>
<td>X-ray erosions</td>
<td>5 (71.4)</td>
<td>37 (86)</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.5 ± 0.9</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>HAQDI</td>
<td>7.6 ± 2.2</td>
<td>7.6 ± 6.4</td>
</tr>
<tr>
<td>QoL</td>
<td>62.3 ± 7.9</td>
<td>71.7 ± 14.4</td>
</tr>
<tr>
<td>SD scale</td>
<td>7 ± 1</td>
<td>1.1 ± 1.6</td>
</tr>
<tr>
<td>Steroids</td>
<td>2 (9)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>MTX</td>
<td>5 (71)</td>
<td>30 (70)</td>
</tr>
<tr>
<td>LFN</td>
<td>2 (29)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>HCQ</td>
<td>1 (14)</td>
<td>11 (26)</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis, FMS: fibromyalgia syndrome, DD: disease duration, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, DAS28: disease activity score 28, HAQDI: Health Assessment Questionnaire II, WPI: widespread pain index, SS: scale: symptoms severity scale, QoL: quality of life, MTX: methotrexate, LFN: leflunomide, HCQ: hydroxychloroquine. Results are either expressed as number (percent) or as mean ± SD. Bold values are significant at p < 0.05.

### Table 2

Demographic features, clinical manifestations, laboratory investigations, disease activity, damage, quality of life and medications used in systemic lupus erythematosus (SLE) patients with and without fibromyalgia syndrome (FMS).

<table>
<thead>
<tr>
<th>Variable mean ± SD or n (%)</th>
<th>SLE patients (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With FMS (n = 9)</td>
<td>Without FMS (n = 41)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.6 ± 10.6</td>
<td>29.5 ± 6.8</td>
</tr>
<tr>
<td>DD (years)</td>
<td>5.4 ± 3.7</td>
<td>4.8 ± 3.1</td>
</tr>
</tbody>
</table>

#### Clinical

- **Mucocutaneous**
  - Hematoxylin, incl. 8 (89) 34 (83) 0.56
- **Arthritis**
  - 8 (89) 22 (54) 0.052
- **Serositis**
  - 6 (67) 16 (39) 0.13
- **Nephritis**
  - 4 (44) 29 (71) 0.13
- **CNS affection**
  - 0 (0) 5 (12) 0.35
- **Vasculitis**
  - 1 (11) 12 (29) 0.52
- **Thrombosis**
  - 3 (33) 5 (12) 0.14
- **Leucopenia**
  - 6 (67) 18 (44) 0.19
- **Thrombocytopenia**
  - 3 (33) 11 (27) 0.49

**Laboratory**

- **Hb (g/dl)**
  - 11.6 ± 0.99 11 ± 1.6 0.17
- **WBC (× 10^9/mm^3)**
  - 8.8 ± 5.7 7 ± 2.8 0.37
- **PLT (× 10^9/mm^3)**
  - 234 ± 97.6 265 ± 91.6 0.39
- **ESR (mm/1st h)**
  - 38.4 ± 27.5 43.4 ± 21.4 0.62
- **Creatinine (mg/dl)**
  - 0.68 ± 0.18 0.96 ± 0.67 0.025
- **Proteinaemia (g/24h)**
  - 0.81 ± 1.4 0.88 ± 1.1 0.89
- **Positive ANA**
  - 9 (100) 41 (100) –
- **Positive anti-DNA**
  - 8 (89) 35 (85) 0.63
- **Positive APL**
  - 2 (22) 18 (44) 0.21

**Medications**

- **Steroids**
  - 9 (100) 41 (100) –
- **AZA**
  - 6 (67) 25 (61) 0.53
- **CYC**
  - 0 (0) 7 (17) 0.23
- **MMF**
  - 0 (0) 5 (12) 0.35
- **HCQ**
  - 9 (100) 37 (90) 0.44

**Scores**

- **SLEDAI**
  - 3 ± 1.8 2 ± 3.4 0.6
- **SLICC**
  - 1.9 ± 3.7 0.6 ± 8 0.32
- **QoL**
  - 77 ± 6.4 78.7 ± 10.7 0.54
- **WPI**
  - 8.1 ± 1.2 1 ± 1.7 0.0008

**SS scale**

- 6.7 ± 1.5 1.1 ± 1.6 0.0001


FMS. Both the WPI and SS scale significantly correlated with the BDCAF (r = 0.4, p = 0.03 and r = 0.48, p = 0.008 respectively).

The frequencies of FMS in the rheumatic diseases were as follows: 14% in RA, 18% in SLE, 6.67% in SSc and in 3.33% of the BD patients and all were higher than the frequencies in their corresponding control (2.1%, 3%, 3.33% and 0% respectively). On comparing the WPI among the rheumatic diseases patients, the mean was significantly higher in the SLE patients (2.3 ± 3.2) compared to that in the RA (1.96 ± 2.6), SSc (1.9 ± 2.2) and BD (0.7 ± 1.1) patients (p = 0.047 (Fig. 1), although the age and sex could not be unified among the diseases. The SS scale was comparable among the different rheumatic diseases (p = 0.43).

**Discussion**

In clinical practice, the co-expression of FMS and a rheumatologic disease deserves special attention as FMS may go unrecognized especially when it develops after the disease or more commonly when it is misdiagnosed as an autoimmune disorder. Concomitant FMS could influence the interpretation of the disease.
activity and QoL. Considerations of the FMS component in the management of rheumatologic diseases increase the likelihood of the success of the treatment.\(^5\)

In the present study, the frequency of FMS in the RA patients was 14%. Similarly, the prevalence of FMS in RA was reported to be 12–17%.\(^6\)\(^\text{25-28}\)

In the present study there was no significantly difference in the age or disease duration between RA patients with and without FMS. This is in agreement to the results of another study.\(^30\) In the present study, rheumatoid factor positivity was comparable between those with and without FMS. This result is similar to that of previous studies.\(^25,27,28,30,31\) Erode changes in x-rays occurred in 86% of RA patients without FMS as compared to 71.4% of those with and the difference was not significant. In accordance to the present results, articular erosions tended to occur more frequently in RA patients without FMS.\(^27\) It has been suggested that FMS may act as a protective trait in RA patients, possibly by alerting the physician more rapidly to onset of flare. Hence it was proposed that the association between RA and FMS does not appear to be a marker of worse prognosis, but rather an accidental relation that may provide these patients some protection against joint destruction.\(^31\) The DAS28 is a strong predictor of physical capacity and radiologic progression. Therefore, the possibility that FMS affects the interpretation of this score may have important implications and misclassification of disease activity may lead to an unnecessary change in the therapy of RA.\(^27\) In this study, the mean DAS28 was significantly higher in RA with FMS than those without. Similarly, DAS28 was significantly worse when FMS was associated to RA.\(^27,28\) Functional assessment in the current study using the HAQII score revealed a similar result in the RA with and without FMS. However, the QoL was significantly worse in RA with FMS. These results came in accordance with previous studies.\(^25,27-29,31\) The medications received by those with and without FMS were comparable, yet those with FMS tended to be less treated.

In this work, the frequency of FMS in SLE was 18%. Comparable frequencies were reported.\(^32-34\) A lower prevalence of FMS in SLE has been presented by others.\(^35-37\) Ethnic differences may contribute to the differences found in the co-existence of FMS and SLE.\(^36\)

Regarding the age and disease duration, comparison between the SLE patients with and without FMS yielded no significant difference. This was concomitant with the results of previous studies.\(^33,36,37\) In the present study, there was no statistical difference between those with and without FMS with respect to the clinical manifestations and disease activity or damage. The same finding was present in previous study.\(^36,37\) However, thrombosis tended to be increased in those with FMS and together with the significant correlation found between the WPI and SS scale with the presence of thrombosis throws light on the importance of considering subclinical thrombosis in this vulnerable subgroup of SLE patients. Interestingly, a hypercoagulable state has been reported in FMS patients demonstrated by increased markers of coagulation activation and increased blood viscosity due to the generation of soluble fibrin monomer. Moreover, in FMS patients an associated hereditary defect in coagulation regulatory proteins has been suggested.\(^38\) The QoL scale was not significantly different between the SLE patients with and without FMS. In contrast, impairment of health related QoL among SLE patients with FMS has been described.\(^36\) In terms of treatment, there were no significant differences between the SLE patients with and without FMS. Similar findings were reported.\(^33,37\)

The current study only 2 (6.67%) SSc patients had FMS. Similarly, FMS has been found in 2% of SSC patients and was not different from that in the healthy control.\(^8\)

Only one BD patients (3.33%) had FMS. The studies on the relationship between FMS and BD are limited. However, in a Turkish study\(^29\) FMS was reported in 9.2% of BD patients and was found to be 18% in another.\(^9\) This discrepancy from the current results could be attributed to using different classification criteria for diagnosis, ethnic differences and the female predominance of their study cohorts. Female predominance is a well-known feature of FMS possibly due to hormone-related mechanisms.\(^60\) Again, in disarray to the present findings, a Korean study revealed FMS in 37.1% of BD patients.\(^25\) In this study, the BDCAF score significantly correlated with WPI and SS scale. In disagreement, tender points did not correlate with the ESR or disease activity.\(^24\)

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 boosted by the fact that it was among the first to investigate the prevalence of FMS in patients with SSc. Also, adds to the limited insights on the relation of FMS to BD. The clinical significance of the association between FMS and the presence of thrombosis in SLE patients has to be considered. It is novel to present the relative prevalence of FMS in different Egyptian rheumatic diseases patients and to throw light on the association with disease activity in RA and BD as well as thrombosis in SLE. The impact of FMS on the QoL in RA patients requires special attention.

Ethical disclosures

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

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

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

None declared.

References


