

# Investigating Fibromyalgia in Sarcoidosis Patients

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**Cite this article as:** Atahan E, Çalışkaner Öztürk B, Yıldız P, Asaoğlu İ, Müsellim B. Investigating fibromyalgia in sarcoidosis patients. *Cerrahpaşa Med J.* 2023;47(1):14-18.

## Abstract

**Objective:** Sarcoidosis is a systemic inflammatory disease. Fibromyalgia is a chronic disease that is characterized by widespread musculoskeletal pain, muscle tenderness, fatigue, sleep disturbances, and depression. Fatigue is an integral part of the clinical picture of sarcoidosis. Fatigue and pain are the frequent symptoms in fibromyalgia patients as well as patients with sarcoidosis. This study seeks to determine the prevalence of fibromyalgia, pain, depression, and quality of life in patients with sarcoidosis.

**Methods:** Between January 2015 and June 2015, 39 sarcoidosis patients were included. Patients were evaluated using the Fatigue Severity Scale, fibromyalgia impact questionnaire, Beck's Depression Inventory, and visual analog scale. The groups with and without fibromyalgia were compared with each other.

**Results:** Fibromyalgia prevalence in sarcoidosis patients is determined to be 43.6% (17/39). Evaluation parameters such as Fatigue Severity Scale, fibromyalgia impact questionnaire, and Beck's Depression Inventory are statistically significant in fibromyalgia group.

**Conclusion:** The main reason of pain, fatigue, and depression in sarcoidosis patients might be fibromyalgia. If fibromyalgia is considered and diagnosed in the presence of these symptoms, this can help us manage our patients more successfully.

**Keywords:** Fibromyalgia, sarcoidosis, fatigue, pain, depression

## Introduction

Sarcoidosis is a systemic inflammatory disease of unknown cause that is characterized by the formation of immune granulomas in various organs, mainly the lungs and the lymphatic system.<sup>1</sup> Fatigue is one of the most important issues in the sarcoidosis patients.<sup>1</sup> Patients with sarcoidosis may also suffer from a wide spectrum of rather nonspecific disabling symptoms like arthralgia, muscle pain, general weakness, muscle weakness, exercise limitations, and cognitive failure.<sup>2</sup> Ultimately, quality of life might be impaired with fatigue, pain, sleep disturbances, and struggles with activities of daily living.<sup>1</sup>

Fibromyalgia (FM) is a chronic disease that is characterized by widespread musculoskeletal pain, muscle tenderness, fatigue, sleep disturbances, and depression.<sup>3</sup> Fibromyalgia prevalence is estimated to be around 2%-7% of the population.<sup>4</sup> Fibromyalgia is a prevalent but generally underdiagnosed disease that is related with multiple comorbidities. It is a potentially debilitating disorder that can have a devastating effect on the quality of life, impair patients' abilities, and result in economic and social burden. The pathophysiology of FM is still not completely understood.<sup>5</sup> Nevertheless, it is frequently associated with systemic inflammatory rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus, and ankylosing spondylitis (AS).<sup>4</sup>

Fatigue is an integral part of the clinical picture of sarcoidosis. Fatigue and pain are the frequent symptoms in FM patients as well as patients with sarcoidosis.<sup>6-8</sup> We hypothesized that FM may be a contributing factor to fatigue and pain in patients with sarcoidosis. There are no published data on the prevalence of FM in patients with sarcoidosis. This study seeks to determine the prevalence of FM, pain, depression, and quality of life in patients with sarcoidosis.

## Material and Method

The institutional review board (ethical committee) at medical faculty of a university of reviewed and approved all the procedures described in this protocol, and all subjects gave written informed consent prior to participating in the study (approval number: 309706).

Subjects were 39 consecutive outpatients admitted between January 2015 and June 2015. Diagnosis of sarcoidosis was based on consistent clinical features, together with biopsy-proven noncaseating epithelioid cell granulomas according to the international guidelines and excluding to other granulomatous diseases. Patient radiological stage (0, I, II, III, IV), duration of illness, spirometry and diffusion capacity of the lung for carbon monoxide (DLCO), 6 minute walking test (6MWT), serum angiotensin-converting enzyme (ACE), hemoglobin/hematocrit level, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the presence of extrathoracic involvement and treatments were recorded at the time of entry in the study. Smoking history and other medical illnesses were also recorded. All patients were questioned and none had a personal or family history of spondyloarthritis. They did not have an inflammatory back/low back pain. In addition, the range of motion examination of the spinal column showed no restriction

Received: December 19, 2022 Accepted: March 2, 2023

Publication Date: March 23, 2023

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DOI: 10.5152/cjm.2022.22124



in all directions. Therefore, we did not perform further investigations like imaging methods.

Data of 58 patients, 40 female and 18 male, were reviewed. In total, 19 patients (1 patient with malignancy, 2 patients with psychiatric disorders, 4 patients with stage 4 respiratory failure due to sarcoidosis, 5 patients with additional systemic disorders with the potential to affect pain and fatigue (eg, decreased or absent reflexes, muscle atrophy, muscle weakness), 7 patients with history of use of antidepressants) were excluded; 36 female and 3 male patients diagnosed with sarcoidosis were included. None of the sarcoidosis patients included in this study had musculoskeletal involvement. No patients were receiving treatment for sarcoidosis at the time of the study. The patients volunteered to participate in the study and gave their informed consent.

### Fibromyalgia Diagnosis

The Modified 2010 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia (ACR 2010) criteria questionnaire consists of 3 parts. The first part asks the subject to use a scale from 0 to 3 to rate the symptoms (in the last week) of fatigue, trouble thinking or remembering, and waking up tired (unrefreshed). The scores 0-3 correspond to no problem, slight or mild problems, moderate problems, and severe problems, respectively. The second part asks the subjects if, during the past 6 months, they have had any "pain or cramps in lower abdomen," "depression," or "headache." The options are "yes" or "no," scored as "1" or "0," respectively. The third part of the questionnaire asks the subject to indicate in a list of regions of the body where they have had pain or tenderness over the past week. A total of 19 body regions, if any, may be selected. First and second parts of questionnaire consist of Symptom Severity Score, although third part of questionnaire comprises widespread pain index. Combining these 3 parts, there can be a score range of 0-31 (maximum score of 9 from part 1, maximum score of 3 from part 2, and maximum score of 19 from part 3). The instrument is self-administered on paper.

Diagnosis of FM is made through the Modified 2010 ACR criteria if the widespread pain index is  $\geq 7$  and the Symptom Severity Score is  $\geq 5$  or the widespread pain index is 3-6 and the Symptom Severity Score is  $\geq 9$ .<sup>9</sup>

### Fatigue Severity Scale

Fatigue Severity Scale (FSS) contains 9 items that measure the severity of fatigue symptom of the subjects during the past week. Each item is scored from 1 to 7—"1" indicates strong disagreement with the statement, while "7" indicates strong agreement. Total score is calculated by deriving an arithmetic mean. A score of 4 or higher generally indicates severe fatigue.<sup>6</sup> The scale is also practical as it is brief and easy to administer and score.<sup>10</sup>

For physical functioning and health status of FM patients, fibromyalgia impact questionnaire (FIQ) was used. It is a 10-item, self-administered questionnaire. Because each item has a maximum possible score of 10, the maximum possible total score is 100. The high scores indicate high level of impaired daily activities.<sup>10</sup>

### Fibromyalgia Impact Questionnaire

The impact of FM on patients was measured by Turkish version of the FIQ.<sup>11</sup> Fibromyalgia impact questionnaire is a self-administered instrument with 3 main topics (function, overall effect of the disease, and symptoms) that assesses the physical function, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being. It assesses the impact of FM on patients for the last 7 days. The average FM patient scores about 50, and severely affected patients usually 70+. The FIQ takes approximately 5 minutes to

complete and has been extensively used as an outcome measure in FM-related studies.<sup>11</sup>

### Beck's Depression Inventory

The Beck's Depression Inventory (BDI) was used to assess depression severity of the sarcoidosis patients. This instrument has 4 choices for each of 21 symptom categories. Patients mark the most appropriate statement which represents how he/she has been feeling in the last week, including the testing day. It is composed of items relating to symptoms of depression such as hopelessness and irritability; cognition such as guilt and feelings of being punished; and physical symptoms such as fatigue, weight loss, and lack of interest in sex.<sup>12</sup> Each item is rated on a 4-point scale ranging from 0 to 3, and the maximum total score is 63. A cut-off score of  $>9$  is used to indicate at least minimal symptoms of depression. Higher total scores indicate more severe depressive symptoms.<sup>13</sup>

### Visual Analog Scale

All patients scored their pain severity on a 10-cm linear visual analog scale (VAS, from 0 "no pain" to 10 "worst possible pain").

### Statistical Analysis

Statistical procedures were performed using SPSS 20.0 software. Mann-Whitney *U*-test and Chi-Square tests were used to compare the groups. Correlation of normally distributed parameters was evaluated by Pearson test, and non-normally distributed parameters were evaluated by Spearman test. A *P* value of  $< .05$  was considered to be significant.

## Results

### Descriptive Data

Thirty-six female and 3 male patients with sarcoidosis are enrolled into the study. Mean age is  $44.7 \pm 11.0$  (minimum: 28 to maximum: 68) years. Duration of diagnosis is  $2.6 \pm 1.5$  years. Twenty-eight patients (71.8%) are housewives, 35 patients (90%) are married, 27 patients are nonsmokers, and 12 patients have smoking history—5 of them are smokers and 7 of them are ex-smokers. The mean cigarette use is  $11 \pm 05$  pack-years. The following extrapulmonary organs are involved: eye 23.1%, skin 10.3%, liver 5.1%, heart 2.6%, bone 2.6%, and kidney 2.6%; 10 (25.6%) patients are in stage I, 28 (71.9%) patients are in stage II, and only 1 (2.6%) patient is in stage III radiologically. Nineteen patients (48.7%) have used corticosteroids before. Two patients reported usage of methotrexate and azathiopurine. Eight patients (20.5%) had comorbidities. Of these 8 patients, 3 have arterial hypertension, 2 have obesity+hypertension+diabetes mellitus, 1 had obesity+hypertension, 1 had obesity+diabetes mellitus, and 1 had obstructive sleep apnea syndrome+obesity. Nineteen patients had used steroid therapy before and their therapy was discontinued more than 1 year ago. No patients were receiving treatment for sarcoidosis at the time of the study. Characteristics of the patients with sarcoidosis have been shown in Table 1.

Twenty-four sarcoidosis patients included in the study were under follow-up without any medication yet; 12 patients had used steroid therapy and their therapy was discontinued more than 1 year ago and 3 patients used steroid+methotrexate therapy and their treatment was discontinued more than 1 year ago.

### Outcome Data

Twenty-five patients (64.1%) described pain anywhere in the body. Twenty patients (51.3%) have headache. Frequency of back pain is 53.8%, neck pain is 51.3%, low back pain is 46.2%, and

**Table 1.** Demographic Characteristics of the Study Population

Study Population		
Number		39
Age (year)		45 ± 11.2
Female/male		36/3
Education (years)		10 ± 2
Married/single		35/4
Duration of diagnosis (years)		2.51 ± 1.55
BMI (kg/m <sup>2</sup> )		26.8 ± 2.48
Stages	Stage I	10 (25.6%)
	Stage II	28 (71.9%)
	Stage III	1 (2.6%)
Extrapulmonary involvement		16 (41%)
Sarcoidosis treatment (previous)		19 (48.7%)
Additional illness (n)		8 (20.5%)
Smoking history (n)		12 (30.8%)
BMI, body mass index.		

knee pain is 41%. Generalized body pain is 43.6%. Duration of pain is  $2.6 \pm 3$  years (median = 2 years). Average VAS score is  $3.6 \pm 3.1$  (median = 4.3 years).

Twenty-six patients (66.7%) reported fatigue. Duration of fatigue is  $3 \pm 3.31$  years (median = 2 years). Average fatigue score according to FSS is  $4.3 \pm 1.8$ .

Average FIQ score was  $39.6 \pm 27$ ; SF-12 physical and mental health subscores were  $33.8 \pm 7.9$  and  $41.7 \pm 9$ , respectively. Average BDI score is  $16.2 \pm 9.5$ . Twenty-one patients had a score lower than 16.

Of the 39 sarcoidosis patients, 17 were diagnosed with FM (43.6%). No FM was detected in 22 sarcoidosis patients.

Erythrocyte sedimentation rate values in FM and non-FM patients and being single rates are statistically significantly higher in FM group ( $P < .05$ ; Table 2).

Comparison of the characteristics, scores, and pain conditions of the groups with and without FM are given in Tables 3 and 4.

## Main Results

Relationship between FM score and evaluation parameters in FM group has been shown in Table 4. All evaluation parameters (duration of pain, duration of fatigue, FSS, FIQ, BDI, Short Form (SF)-12 physical, SF-12 mental, VAS, number of children) were statistically significant in FM group ( $P < .05$ ; Table 4).

## Discussion

In our study, FM prevalence in sarcoidosis patients was determined to be 43.6% (17/39). This rate is above the rate of the population, the prevalence of FM in the population is reported between 2% and 8%.<sup>14</sup> The explanation to this finding could be that sarcoidosis and FM can co-exist frequently or that the symptoms of sarcoidosis and FM are mixed up.

Pain (localized, multiple, or generalized), fatigue, and depression are symptoms of both sarcoidosis and FM. Therefore, the diagnosis of FM in sarcoidosis patients may not recur. These symptoms might

**Table 2.** Comparison of Characteristics of Groups With and Without FM

	FM (n = 17)	Not FM (n = 22)	P
Age	42.8 ± 10.9	46.8 ± 11.3	.24
Female/male	17/0	19/3	.057
BMI	27.3 ± 2.6	26.5 ± 2.3	.68
Married/single	13/4	22/0	.029*
Smoking history	3 (18%)	9 (40%)	.16
Additional illness	4 (23%)	4 (18%)	.79
Sarcoidosis stage (I/II/III)	5/12/0	5/16/1	.36
FVC (mL)	3079 ± 694	3047 ± 688	.88
FVC (%)	96.3 ± 12.1	97.3 ± 13.7	.32
DLCO	21.8 ± 5.1	20.7 ± 4.6	.80
DLCO (%)	86.7 ± 14.7	82.9 ± 9.4	.34
Plasma ACE (mg/dL)	78.2 ± 32.7	85.9 ± 37.1	.29
6MWT distance (m)	449.5 ± 55.9	449.2 ± 50.2	.98
Hemoglobin (mg/dL)	12.4 ± 0.8	12.6 ± 1.8	.61
CRP (mg/dL)	7.5 ± 9.3	6.2 ± 5.3	.57
ESR (mm/h)	27.1 ± 11.8	18.6 ± 10.6	.02*
Steroid usage (n)	6 (35%)	13 (59%)	.20
Extrapulmonary involvement	8 (53%)	8 (36%)	.84
6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; BMI, body mass index; CRP, C-reactive protein; DLCO, diffusing capacity of the lung for carbon monoxide; ESR, erythrocyte sedimentation rate; FM, fibromyalgia; FVC, forced vital capacity. * $P < .05$ .			

be due to the own pathophysiology of sarcoidosis as well as coexisting FM. However, the symptoms of sarcoidosis may also occur in the case of FM; so, it could be mistaken as FM. It is important to make this distinction in the clinic, in order to treat FM in sarcoidosis patients and control these symptoms.

Pain, according to its localization, was evaluated as headache, neck pain, back pain, lower back pain, knee pain, and generalized pain, and all were statistically significantly higher in FM group ( $P < .05$  Table 3). In the literature, among the pain types seen in FM, headache is the most prevalent (75.8%). Neck pain, back pain, lower back pain, knee pain, and generalized pain are other pain types that are in FM diagnostic criteria. When we look at the studies that question the relation of these symptoms with sarcoidosis, the studies about headache mostly compass neurosarcoidosis patients. In our study where there are no neurosarcoidosis patients, headache is seen in 51.3% (20/39) of the patients; 75% (15/20) of these are in the FM group. Although neck pain is not frequently encountered in sarcoidosis, some examples are seen as case reports.<sup>15-17</sup> In our study, neck pain is present in 88% of the FM group and 23% of non-FM group.

In the studies conducted until now, we see that back pain in sarcoidosis was linked to sacroiliitis and spondyloarthritis.<sup>18-20</sup> Our study is a first, as it links back pain in sarcoidosis to FM. It is presented in case reports that low back pain can be seen in

**Table 3.** Comparison of Pain Characteristics and Scores Between the 2 Groups

	FM (n = 17)	Not FM (n = 22)	P
Fatigue	17 (100%)	9 (40%)	<.001**
Duration of fatigue	4.5 ± 2.8	1.8 ± 3.2	.01*
Fatigue Severity Scale	5.5 ± 1.2	3.4 ± 1.6	<.001**
Pain	16 (94%)	9 (40%)	.001**
Headache	15 (88%)	5 (23%)	<.001***
Pain in neck	15 (88%)	5 (23%)	<.001***
Pain in back	14 (82%)	7 (32%)	.03*
Pain in low back	13 (76%)	5 (23%)	.001**
Pain in knee	12 (70%)	4 (18%)	<.001***
Diffuse pain	13 (76%)	4 (18%)	<.001***
Duration of pain (years)	3.94 ± 3	1.6 ± 2.6	.011*
Beck's Depression Inventory	16.2 ± 9.4	4.6 ± 6.5	<.001***
Depression	13 (76%)	7 (32%)	<.001***
Fibromyalgia impact questionnaire	61.9 ± 20.2	22.3 ± 17.2	<.001***
Visual analog scale	4.9 ± 3.2	2.1 ± 2.4	<.001***
Fibromyalgia score	18.1 ± 5.2	3.7 ± 4.0	<.001***

\*P < .05, \*\*P < .01, \*\*\*P < .001.  
FM, fibromyalgia.

sarcoidosis when it is accompanied by AS, multiple myeloma, or neurosarcoidosis.<sup>21-23</sup> In our study, when the comorbidities are excluded, the ratio of low back pain is 46.15% (18/39).

Musculoskeletal involvement due to sarcoidosis can present as knee pain.<sup>24-26</sup> However, our study has shown that even if there is no proven musculoskeletal involvement, if there is knee pain, the chances of accompanying FM are higher. Localized, multiple, or

generalized pain can be seen in sarcoidosis patients but they are seen more commonly in FM. When these symptoms are seen in sarcoidosis, accompanying FM should be taken into consideration.

Another shared symptom that is taken into consideration in our study was fatigue. Fatigue in sarcoidosis patients might be due to burden of granulomas, weight gain secondary to corticosteroid treatment, diabetes, depression, sleep disturbances, hypothyroidism, and other unknown factors.<sup>1,8</sup> This symptom is not related to disease activity and becomes worse with shortness of breath, 6 minute walk test shortening, and musculoskeletal pain.

In a previous study,<sup>27</sup> it was reported that fatigue is seen in 50%-70% of patients with sarcoidosis. Fatigue rates are reported to be more than 75% in FM patients in another study.<sup>28</sup> In our study, fatigue is seen among all sarcoidosis patients in the FM group and 40% of the sarcoidosis patients in the non-FM group. The results of our study support that high fatigue rates in sarcoidosis stated in the literature might actually be due to accompanying FM.<sup>27</sup>

Psychologic symptoms such as anxiety and depressive findings were reported in 17%-66% of sarcoidosis patients, and it is known that these rates are higher compared to the healthy population.<sup>2,29</sup> Depression, panic disorder, and anxiety can be seen in 50%-60% of FM patients.<sup>3</sup> In our study in FM and non-FM sarcoidosis patients, the rates are 76% and 32%, respectively.

In another study, the prevalence of FM comorbidity was found to be 18%-24%, 14%-16%, and 18% in patients with RA, axial spondyloarthritis, and psoriatic arthritis, respectively.<sup>30</sup> Prevalence of FM among patients with sarcoidosis is much higher than that reported for other rheumatic diseases such as RA, AS, and psoriatic arthritis.

Because of the fact that the clinical features of FM and sarcoidosis overlap, if accompanying FM is not considered and diagnosed, sarcoidosis patients might have to use higher doses of analgesics, nonsteroid anti-inflammatory drugs, and neurostimulants due to severe symptoms. Fibromyalgia in sarcoidosis patients can also aggravate the symptoms like fatigue and pain, therefore diminishing the quality of life.

We see in literature that the symptoms that we evaluated in our study could be seen in sarcoidosis. But, there is no other study that examines these symptoms that can be seen in FM and sarcoidosis one by one and that discusses the possibility of these symptoms being due to coexisting FM.

The limitations of our study are small sample size and sectional design. All the patients involved in the study were in stages 1, 2, and 3 of sarcoidosis; therefore, this study does not provide us data about FM prevalence stage 4 sarcoidosis patients. The other is; In our study, majority of the research population consists of women. We know that sarcoidosis is common in women; however, due to the limited number of male patients in the study, a gender analysis could not be performed for the frequency of FM in sarcoidosis patients.

## Conclusion

In conclusion, the main reason of pain, fatigue, and depression in sarcoidosis patients might be FM. If FM is considered and diagnosed in the presence of these symptoms, this can help us manage our patients more successfully.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of İstanbul University (Date: 06.10.2014, Number: 309706).

**Informed Consent:** Written informed consent was obtained from the participants who participated in this study.

**Table 4.** Relationships Between Fibromyalgia Score and Evaluation Parameters in Fibromyalgia Group

Correlations with fibromyalgia score	r	P
Duration of fatigue	<b>0.622</b>	<.001***
Duration of pain	<b>0.581</b>	<.001***
Fatigue Severity Scale	<b>0.595</b>	<.001***
Fibromyalgia impact questionnaire	<b>0.786</b>	<.001***
Beck's Depression Inventory	<b>0.634</b>	<.001***
Short form-12 physical	<b>-0.774</b>	<.001***
Short form-12 mental	<b>-0.391</b>	.014*
Visual analog scale	<b>0.843</b>	<.001***
Number of children (n)	<b>-0.409</b>	.01*

\*P < .05, \*\*P < .01, \*\*\*P < .001.



**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – E.A., B.M.; Design – E.A., P.Y.; Supervision – B.M.; Resources – P.Y., İ.A., B.Ç.Ö.; Materials – P.Y., B.Ç.Ö.; Data Collection and/or Processing – İ.A., B.Ç.Ö., E.A.; Analysis and/or Interpretation – E.A., İ.A.; Literature Review – E.A., B.Ç.Ö.; Writing – E.A., B.Ç.Ö., B.M.; Critical Review – B.M.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

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