Factors Associated with Fibromyalgia Syndrome in Peritoneal Dialysis Patients

Ruya Ozelsancak, MD;[*] *Pınar Doruk Analan, MD;*[†] *Berrin Leblebici, MD*[†]

ABSTRACT

Purpose: We evaluated the prevalence of fibromyalgia syndrome (FMS) in peritoneal dialysis (PD) patients and whether this syndrome is associated with gender, age, duration of PD, or other laboratory parameters. ***Methods:*** A total of 60 chronic PD patients (26 women, 34 men) and 60 healthy controls (30 women, 30 men) were included. We recorded each participant's age, gender, cause of kidney failure, PD duration, laboratory parameters, education level, and symptoms related to FMS, diagnosed according to the 2010 American College of Rheumatology criteria. ***Results:*** Eleven patients (18%) in the PD group and nine (15%) in the control group met the diagnostic criteria for FMS. There were no statistically significant differences in age; gender; education level; PD duration; laboratory parameters; or sleepdisturbance, fatigue, or cognitive symptoms between the FMS and non-FMS groups among the PD patients. We next compared control and PD patients with FMS. Both groups were of a similar age and gender and had similar sleep disturbance and cognitive symptoms, but more patients had fatigue in the control group. ***Conclusions:*** The prevalence of FMS among PD patients was similar to that in the general population, and FMS was not associated with gender, age, duration of PD, or other laboratory parameters.

Key Words: fatigue; fibromyalgia; pain; peritoneal dialysis; sleep disturbance.

RÉSUMÉ

Objectif : les chercheurs ont évalué la prévalence du syndrome de fibromyalgie (SFM) chez les patients sous dialyse péritonéale (DP) et de son association avec le sexe, l'âge, la durée de la DP ou d'autres paramètres de laboratoire. ***Méthodologie :*** au total, 60 patients sous DP chronique (26 femmes et 34 hommes) et 60 sujets témoins en santé (30 femmes et 30 femmes) ont participé à l'étude. Les chercheurs ont consigné l'âge, le sexe, la cause de l'insuffisance rénale, la durée de la DP, les paramètres de laboratoire, le niveau de scolarité et les symptômes de chaque participant, liés au SFM diagnostiqués conformément aux critères de l'*American College of Rheumatology* établis en 2010. ***Résultats :*** onze patients (18 %) du groupe sous DP et neuf (15 %) du groupe témoin respectaient les critères diagnostiques de SFM. Ils ne présentaient pas de différence statistiquement significative sur le plan de l'âge, du genre, du niveau de scolarité, de la durée de la DP, des paramètres de laboratoire, des perturbations du sommeil, de la fatigue ou des symptômes cognitifs entre les groupes sous DP ayant un SFM et ceux n'en ayant pas. Les chercheurs ont ensuite comparé les sujets témoins et les patients sous DP ayant un SFM. Les deux groupes étaient d'âge et de sexe semblables et présentaient des perturbations du sommeil et des symptômes cognitifs analogues, mais plus de patients témoins ressentaient de la fatigue dans le groupe témoin. ***Conclusion :*** la prévalence de SFM chez les patients sous DP était semblable à celle de la population générale, et la SMF ne s'associait ni au sexe, ni à l'âge, ni à la durée de la DP ni à d'autres paramètres de laboratoire.

Fibromyalgia syndrome (FMS) is one of many central pain syndromes. It is a chronic musculoskeletal disorder characterized by persistent, widespread pain and abnormal pressure-pain sensitivity (i.e., tenderness) at multiple anatomical sites, including the tender points identified by the American College of Rheumatology (ACR) Multicenter Criteria Committee. Additional clinical manifestations include fatigue, sleep disturbance, impairment of attention and other cognitive functions, muscle and joint stiffness, subjective joint swelling, paresthesia, anxiety, headache, and irritable bowel and bladder syndromes.[1–3]

Several factors are associated with the pathophysiology of FMS, but causal relationships have yet to be documented. Environmental, psychological, and genetic factors have been suggested as possible causes, but these too have not been directly linked to FMS. Current theories on the etiology of FMS include alterations of central pain pathways, hypothalamic–pituitary–adrenal axis dysregulation, increased systemic pro-inflammatory and reduced anti-inflammatory cytokine profiles, and disturbances in the dopaminergic and serotonergic system.[3,4]

Population-based studies of chronic widespread pain in most industrialized countries have suggested that 10%–11% of the population have FMS at any given time.[5] Using the ACR criteria, the prevalence of this syndrome

From the: *Department of Nephrology; †Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Baskent University Adana Research and Education Center, Adana, Turkey.

Correspondence to: Ruya Ozelsancak, Department of Nephrology, Faculty of Medicine, Baskent University Adana Research and Education Center, Kazım Karabekir Cad. 4227, Sok. No 37 Yüreğir, Adana, Turkey; rusancak@hotmail.com.

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in the general population has been reported to be 0.5%–4.0%.[5] A study by Wolfe and colleagues found FMS rates to be 2.0% for both genders, but 3.4% for women and 0.5% for men; they also determined that FMS prevalence increases with age, with the highest rates seen in patients aged 60–79 years (> 7.0% in women of this demographic).[6] Few studies have focused on FMS among dialysis patients, and only one study has focused on FMS among peritoneal dialysis (PD) patients.[7–11] The frequency of FMS was found to be 9.7% in PD patients and 3.9%–12.2% in hemodialysis (HD) patients. Rheumatic disorders are a major complication of end-stage renal disease, and approximately 60% of HD patients develop musculoskeletal disorders.[12,13] Because of this, a differential diagnosis of FMS should be considered for this group of patients. The aim of our study was to evaluate the frequency of FMS in patients on PD and to assess whether this syndrome is associated with gender, age, duration of PD, or other laboratory parameters.

METHODS

This was a cross-sectional, single-centre, randomized controlled trial study. It was approved by the Baskent University Ethics Committee (Project Number KA15/165), and we obtained written, informed consent from all patients for their participation. We recruited PD patients being treated in a nephrology clinic who were referred to the Physical Medicine and Rehabilitation Outpatient Clinic, Baskent University Adana Teaching and Research Center (Adana, Turkey). Data were collected between January and June 2016.

We examined, consecutively, 60 PD patients: 26 women (aged 20–77 y; average age 56 y) and 34 men (aged 41–74 y; average age 59 y). We excluded from the study patients with liver disease, malignancies, and severe bone disease. We recorded the age; gender; education level; PD duration; fatigue, cognitive, and sleep disturbance symptoms; the number of tender points; and widespread pain index (WPI) and symptom severity (SS) scale scores of all patients. These measures were used to perform a differential diagnosis of FMS according to the 2010 ACR criteria: patients were diagnosed with FMS when the WPI scale score was 7 or more and the SS scale score was 5 or more, or when the WPI scale score was 3–6 and the SS scale score was 9 or more.[14] Additional criteria included symptoms present at a similar level for at least 3 months and that no other disorder could explain the pain. The control group was selected from among patients who were admitted to a physical therapy and rehabilitation outpatient clinic for general pain complaints. The control group consisted of 60 patients (30 women and men aged 27–83 y; average age 54 y), and the same clinical metrics were recorded for these participants as described for the PD patients.

Moreover, all FMS patients in the PD and control groups who received a diagnosis for the first time answered the Fibromyalgia Impact Questionnaire (FIQ) to assess their current health status. This questionnaire has been validated for use in Turkey with FMS patients.[15] It measures physical function, work status, and overall well-being, and it also contains six separate visual analogue scales (VASs) for pain, sleep, fatigue, morning stiffness, anxiety, and depression. After completing this questionnaire, a total score (0–100) was calculated for each responder by normalizing certain items and summing the VAS scores. The highest possible total score was 100, with a higher value indicating more severe adverse impacts on quality of life. In this patient population, the FIQ has been shown to be the most accurate way to measure the effects of pain on the daily activities of a patient.[16]

In addition to the FMS patients filling out the FIQ, we reviewed all patients' charts and recorded their laboratory parameters as follows: blood urea nitrogen (BUN), creatinine, hemoglobin, C-reactive protein (CRP), calcium, phosphorus, intact parathyroid hormone, albumin, ferritin, and serum-iron levels along with their iron-binding capacity and saturation index scores. Hemoglobin levels were determined using the Cell-Dyn 3700 (Abbott Laboratories, Abbott Park, IL), and intact parathyroid hormone levels were measured using an electrochemiluminescence immunoassay, Modular Analytics E170 (Roche Diagnostics, Indianapolis, IN). Serum levels of BUN, creatinine, calcium, phosphorus, albumin, ferritin, and CRP were assessed using standard laboratory methods using the Roche Hitachi 902 chemistry analyzer (Roche Diagnostics, Indianapolis, IN).

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 17.0 (IBM Corp., Armonk, NY). Continuous variables with normal distribution are presented as mean (SD) ($p > 0.05$ in the Kolmogorov–Smirnov or Shapiro-Wilk test [$n < 30$]) and variables that were not normally distributed are presented as median (range). Comparisons between the two groups were carried out using the Student *t*-test for normally distributed data and the Mann–Whitney *U* test for data that are not normally distributed. In addition, categorical variables between the groups were analyzed using either a χ^2 test or a Fisher's exact test. A $p < 0.05$ was considered statistically significant.

RESULTS

Demographic data for all 60 PD patients are shown in Table 1. There were no statistically significant differences with regard to age, gender, PD duration, or education level between PD patients with and without FMS. The etiology of kidney failure was hypertension ($n = 19$; 31.7%), diabetes mellitus ($n = 17$; 28.3%), various other causes

Table 1 Demographic Characteristics of PD Patients ($n = 60$)

Characteristic	PD patients, no. (%)*		
	With FMS	Without FMS	*p*-value
No. (%)	11 (18)	49 (82)	
Age, y; median (range, min–max)	59 (41–74)	56 (20–77)	0.33
Gender, male/female	5/6	29/20	
PD duration, mo; median (range, min–max)	29 (16–72)	21 (10–168)	0.28
Education level			0.78
No schooling	1 (9)	5 (10)	
Elementary school	6 (55)	15 (31)	
Middle school	1 (9)	7 (14)	
High school	1 (9)	8 (16)	
College	2 (18)	14 (29)	

* Unless otherwise indicated.
PD = peritoneal dialysis; FMS = fibromyalgia syndrome.

($n = 7$; 11.7%), unknown ($n = 7$; 11.7%), glomerulonephritis ($n = 6$; 10.0%), polycystic kidney disease ($n = 3$; 5.0%), and amyloidosis ($n = 1$; 1.7%). Eleven PD patients (18%) and 9 healthy controls (15%) met the diagnostic criteria for FMS. There were no statistically significant differences with regard to age, gender, or education level between FMS patients in the PD and control groups. In addition, the tender point count and WPI and SS scale scores were similar among FMS patients from the PD and control groups (see Table 2). There were no statistically significant differences in total FIQ score between FMS patients from the PD or control groups (see Table 2). Finally, there were no statistically significant differences related to sleep disturbance or cognitive symptoms between the FMS patients in the PD and control groups. Strangely, the number of FMS patients with fatigue was lower in the PD group than in the control group ($p = 0.018$; see Table 3).

Table 2 Demographic Characteristics of FMS Patients in the PD and Control Groups

Characteristic	FMS patients, median (range, min–max)*		
	PD ($n = 11$)	Control ($n = 9$)	*p*-value
Age, y	59 (41–74)	55 (44–70)	0.54
No. male/female	5/6	2/7	0.27
FIQ score	4 (0.00–81.34)	14.4 (0.00–82.79)	0.95
WPI	9 (6–17)	10 (6–18)	0.96
TP count	7 (1–12)	10 (6–16)	0.08
SS scale score	3 (1–8)	6 (4–10)	0.044
Education level; no. of patients			0.28
No schooling	1	3	
Elementary school	6	2	
Middle school	1	1	
High school	1	2	
College	2	1	

* Unless otherwise indicated.
FMS = fibromyalgia syndrome; PD = peritoneal dialysis; FIQ = Fibromyalgia Impact Questionnaire; WPI = widespread pain index; TP = tender point; SS = symptom severity.

Table 3 Comparison of the Clinical Features Associated with FMS in the PD and Control Groups

Feature	FMS patients, no. (%)		
	PD ($n = 11$)	Control ($n = 9$)	*p*-value
Sleep disturbance			0.08
None	7 (64)	1 (11)	
Mild	0	2 (22)	
Moderate	2 (18)	3 (33)	
Severe	2 (18)	3 (33)	
Cognitive symptoms			0.18
None	9 (82)	4 (44)	
Mild	2 (18)	4 (44)	
Moderate	0	1 (11)	
Severe	0	0	
Fatigue			0.013
None	4 (36)	0	
Mild	4 (36)	1 (11)	
Moderate	0	5 (56)	
Severe	3 (27)	3 (33)	

Note: Percentages may not total 100 because of rounding.
FMS = fibromyalgia syndrome; PD = peritoneal dialysis.

Clinical features of the PD patients with and without FMS were similar (see Table 4). Moreover, laboratory parameters were similar in PD patients with and without FMS (see Table 5).

DISCUSSION

Rheumatological disorders are very common in patients with chronic kidney disease, and a variety of widespread musculoskeletal discomforts, including FMS, are seen in most dialysis patients.[12,13] The reported incidence rates of FMS range from 0.5% to 4.0% in the general population, and women are affected more frequently than men.[5] However,in rheumatology clinics the frequency of FMS has been reported to be 3%–20%.[1]

Our study contributes to this field by providing the incidence rate of FMS in Turkish PD patients; our results show that 11 of 60 PD patients (18%) had FMS. Only one study has evaluated the frequency of FMS in PD patients; it found the frequency of FMS to be 9.7%.[11] A few studies have evaluated the frequency of FMS in HD patients; for example, Couto and colleagues found an FMS incidence rate of 3.9%, Yuceturk and colleagues determined that it was 7.4%, and Samimagham and colleagues identified it

Table 4 Comparison of the Clinical Features Associated with FMS in PD Patients

Feature	No. (%) of PD patients		*p*-value
	With FMS (n = 11)	Without FMS (n = 49)	
Sleep disturbance			0.15
None	7 (64)	36 (74)	
Mild	0 (0)	7 (14)	
Moderate	2 (18)	2 (4)	
Severe	2 (18)	4 (8)	
Cognitive symptoms			0.85
None	9 (82)	39 (80)	
Mild	2 (18)	7 (14)	
Moderate	0	2 (4)	
Severe	0	1 (2)	
Fatigue			0.51
None	4 (36)	20 (41)	
Mild	4 (36)	13 (27)	
Moderate	0	7 (14)	
Severe	3 (27)	9 (18)	

Note: Percentages may not total 100 because of rounding.
FMS = fibromyalgia syndrome; PD = peritoneal dialysis.

Table 5 Laboratory Results of PD Patients with and without FMS

Result	Median (range, min–max)		*p*-value
	Patients with FMS (n = 11)	Patients without FMS (n = 49)	
Hemoglobin, g/dL	10.7 (8.7–11.5)	10 (8.9–15.6)	0.43
Ferritin, ng/mL	615 (83–1,200)	380 (88–1,550)	0.26
Iron, µg/dL	56 (42–114)	62 (32–119)	0.51
C-reactive protein, mg/mL	8 (2–161)	9 (2–60)	0.59
Parathyroid hormone, pg/mL	466 (270–1,036)	567 (10–1,300)	0.93
Calcium, mg/dL	9.2 (8.2–9.7)	8.8 (6.5–10.7)	0.27
Phosphorus, mg/dL	4.6 (3.5–6.9)	4.8 (3.3–8.5)	0.33
Alkaline phosphatase, IU/L	120 (75–220)	110 (51–270)	0.65
Dialysis adequacy index, Kt/V	2.1 (1.3–3.3)	2.5 (1.1–5.4)	0.15
Uric acid, mg/dL	5.5 (4.5–6.1)	5.8 (3.8–9.2)	0.10
Albumin, g/dL	3.6 (2.8–3.9)	3.6 (3.3–4.4)	0.87

PD = peritoneal dialysis; FMS = fibromyalgia syndrome.

as 12.2%.[7–9] We have previously reported the incidence rate of FMS in Turkish HD patients to be 9.0%.[10] We postulate that these differences may be explained by racial or regional differences in the patient populations examined in these studies, but this is not certain.

In this study, we found no differences between FMS incidence rates in the PD or control patients; this accords with the findings of Okumus and colleagues.[11] An important note for this study is that the participants in the control group were taken from a physical therapy and rehabilitation clinic, and patients who are being evaluated at such clinics generally have pain. Therefore, it is possible that the frequency of FMS is high in this patient population; this is a limitation of our study.

It has previously been shown that FMS rates increase with age; for example, Wolfe and colleagues showed the highest rates of FMS in their patients aged 70–79 years.[6] We did not find any difference in the age of PD patients with and without FMS. However, the number of participants in the different age groups was low, and the small groups make it difficult to compare rates between groups.

In our study, the diagnostic rates of FMS in male and female PD patients were similar, and they agree with the results of Okumus and colleagues.[11] These results are surprising because, in both HD patients and the general population, the prevalence of FMS is higher among women.[6–9]

Consistent with other studies, we found that diabetes mellitus and high blood pressure were the main causes of end-stage renal disease, and we also determined that there was no link between the duration of dialysis or dialysis adequacy index and the prevalence of FMS.[7–9] Although duration of dialysis is another important factor that could affect the prevalence rate of this syndrome, in accordance with the literature, we found no statistically significant difference in PD duration between PD patients with or without FMS. This might explain why the laboratory parameters were similar in these two groups because the frequency of bone and mineral disorders is related to a longer duration of HD.

All participants with FMS, from either the PD or the control group, completed the FIQ. We found no statistically significant differences in FIQ scores between FMS patients in the PD and control groups. The FIQ reflects general health status and factors that affect daily activity. We conclude that PD does not cause additional functional disability or negative effects on general health among FMS patients.

Education level may reflect the socioeconomic status of a population, which, in turn, may play a role in a patient's quality of life. Generally, more educated patients accept PD treatment because patients must adhere to clinical instructions while undergoing PD treatment (e.g., washing hands, cleaning rooms, weighing drainage bags to calculate ultrafiltration, and being aware of ultrafiltration failures or peritonitis symptoms). However, in our study the education level of the PD and control group FMS patients and of the PD patients with and without FMS was similar.

FMS is a central sensitivity syndrome, and it overlaps with a similar group of syndromes that cause dysregulated activity in the central nervous system. Central sensitivity syndromes have several common features, such as pain, fatigue, poor sleep, sensitivity to noxious and non-

noxious stimuli, and psychosocial difficulties. In FMS, the presence of sleep disturbance, fatigue, and cognitive symptoms is a result of the common mechanisms of central sensitization.[17,18] Okumus and colleagues determined that fatigue, morning stiffness, headache, and symptoms of restless leg syndrome were more frequent among the PD patients with FMS than among those without FMS.[11] However, in our study, we found no statistically significant differences related to sleep disturbance or cognitive symptoms in either the PD and the control group FMS patients or the PD patients with and without FMS. In addition, fewer PD FMS patients than control FMS patients had fatigue. It is common among HD patients for uremia to cause fatigue and weakness. Over time, PD patients may have learned to ignore, or become accustomed to, fatigue symptoms, thereby causing them to report such symptoms less frequently than do FMS patients from the general population.

Yuceturk and colleagues and Samimagham and colleagues showed that there were no significant differences in calcium, phosphorus, alkaline phosphatase, alanine aminotransferase, albumin, hemoglobin, ferritin, or CRP levels between HD patients with and without FMS.[8,9] Okumus and colleagues showed that there were no significant differences in the calcium, phosphorus, alkaline phosphatase, ferritin, uric acid, or CRP levels between PD patients with and without FMS.[11] These results were consistent with our study'sresults, which showed that chronic inflammatory state, bone and mineral metabolism, and malnutrition were not correlated with FMS in the PD patient group.

This study had a few limitations. First are the control group's features, the small sample size, and that the study participants were drawn from a singlecentre. Second, the control group was selected from among patients who had been admitted to a physical therapy and rehabilitation clinic; this may be the cause of the high prevalence of FMS in the control group. Finally, the number of participants in the different age groups was low, and the small groups make it difficult to compare the rates between groups.

To the best of our knowledge, this is the first study to use the 2010 ACR criteria to evaluate FMS in a Turkish PD population, and the results show that the FMS incidence rate for that group was 18%. The laboratory parameters were similar between the PD patients with and without FMS. Chronic inflammatory illness, malnutrition, and any disorders related to calcium or phosphorus metabolism were not connected with FMS. Ultimately, our results show that neither the duration nor the adequacy of PD can identify comorbid FMS among PD patients. Because of the limitations of our study, we recommend a new study using a larger sample size and a healthy control group.

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