Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.373281.3898 Volume 31, Issue 5, May. 2025
Manuscript ID:ZUMJ-2504-3898 (R1)
DOI:10.21608/zumj.2025.373281.3898

ORIGINAL ARTICLE

Fibromyalgia and Its Relation with Quality of Life, Depression, and Anxiety among Hemodialysis Patients

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Submit Date 07-04-2025
Revise Date 24-04-2025
Accept Date 27-04-2025

ABSTRACT

Background& Aim: Various musculoskeletal disorders, including Fibromyalgia syndrome (FMS), are seen in most patients undergoing hemodialysis. This research aimed to assess the frequency of fibromyalgia among hemodialyzed patients and its relation to quality of life, depression, anxiety, and laboratory investigations.

Methods: A case-control study involved 131 hemodialysis patients and 131 healthy controls attending Rheumatology & Nephrology departments, Zagazig University Hospitals, Egypt. Demographic and clinical characteristics, including age, sex, body mass index, & dialysis duration, and laboratory investigations were recorded. FMS was diagnosed using the 2010 American College of Rheumatology diagnostic criteria. Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were applied.

Results: Fibromyalgia frequency was significantly higher among controls than hemodialyzed patients (76.3% versus 22.9%, respectively). Hemodialyzed patients with FMS revealed significant associations between fibromyalgia and (moderate & severe anxiety), (mild mood disturbance & depression), abnormal C-reactive protein (CRP), anemia, normal parathyroid hormone, normal bone turnover, normal calcium, and normal Vitamin D (P≤0.001**, ≤0.001**, 0.001*, ≤0.001**, ≤0.001**, ≤0.001**, 0.009*, & 0.001*, respectively). About two-thirds (60%) of hemodialyzed patients with fibromyalgia had impaired quality of life. Among the hemodialysis group, FMS showed significant positive correlations with FIQ (r=0.911, P≤0.001**) & BDI (r=0.268, P=0.002*) and insignificant positive correlation with BAI (r=0.153, P=0.080).

Conclusion: The frequency of fibromyalgia is higher in healthy controls than in hemodialyzed patients. FMS in hemodialyzed patients shows significant associations with depression, anxiety, abnormal CRP, anemia, and normal bone minerals. There are positive correlations between fibromyalgia and FIQ & BDI scores among hemodialyzed patients.

Keywords: Fibromyalgia, Hemodialysis, Depression, Anxiety, Quality of Life.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a common chronic musculoskeletal disease with widespread tender points. This multisystemic disorder is associated with extra-musculoskeletal manifestations like fatigue, headache, sleep disturbance, paresthesia, depressed mood, depression, anxiety, and irritable bowel syndrome [1].

According to the American Rheumatism Association, FMS is the 3rd most prevalent rheumatic condition, following rheumatoid arthritis and osteoarthritis [2]. Fibromyalgia

(FM) affects 3% to 10% of people in the general population [3]. Although fibromyalgia is typically thought to affect women between the ages of 20 and 50 years, it has also been reported in men, adolescents, children, and elderly people [4].

Primary fibromyalgia is idiopathic, while secondary fibromyalgia can develop after other medical conditions such as autoimmune diseases, stress, spinal injury, or surgery [5]. Even though the exact cause and pathophysiology of FMS remain unknown, recent theories rely on the central processes of pain modulation and amplification in its genesis, including central sensitization and dysregulation of the hypothalamic-pituitary-adrenal axis [6,7]. Environmental, genetic, and psychological aspects have been recognized as potential reasons [8].

The American College of Rheumatology (ACR) developed the most widely accepted criteria for diagnosing fibromyalgia in 1990. These criteria are based on a history of persistent, widespread pain in 11 or more of 18 tender points over three months [9]. In 2010, a multicenter study published by the American College of Rheumatology established easy, practical criteria to diagnose fibromyalgia clinically that don't need a tender point examination [10].

Chronic kidney disease (CKD) is one of the systemic illnesses that can exhibit rheumatic manifestations. These patients often have musculoskeletal complaints [11,12]. Musculoskeletal issues affect about two-thirds of patients with hemodialysis (HD). The incidence of rheumatic diseases rises with dialysis duration [13]. Consequently, in patients receiving hemodialysis, the differential diagnosis of fibromyalgia must be taken into consideration [14].

A review of the literature shows that there is little information available concerning fibromyalgia in particular populations, including those undergoing hemodialysis, peritoneal dialysis, and renal transplantation [4]. Studies investigating the associations between fibromyalgia and quality of life (QoL), anxiety, and depression in hemodialyzed patients are also limited [15,16].

Therefore, the purpose of this research was to assess the frequency of fibromyalgia among hemodialyzed patients and its relation to QoL, depression, anxiety, and laboratory investigations.

METHODS

Design of the study

A case-control study was organized in the outpatient clinics and inpatient wards at the Rheumatology & Rehabilitation Department and Nephrology Department, Zagazig University hospitals-Egypt, throughout one year from April 2023 to March 2024.

Study participants

The current study included 262 participants distributed into two equal groups: the hemodialysis and the control groups. The hemodialysis group involved 131 patients suffering from end-stage renal disease (ESRD) who received regular hemodialysis for at least six months at the rate of three sessions per week, four hours per session. All ESRD patients had adequate dialysis, confirmed by calculating urea kinetics (Kt /v), and patients' ages were above 16 years. On the other hand, HD patients with histories of other rheumatic diseases, chronic fatigue syndrome, limb ischemia after hemodialysis, malignancy, diabetic disease, thyroid disorders, severe bone disease, neuropathic diseases, immobilization, or co-existing liver disease were excluded from this study. The group of controls involved 131 healthy age & sex-matched individuals.

Sample size and patient selection

Based on the previous studies that reported the fibromyalgia prevalence in patients with hemodialysis was 14% versus 4% in the control group [4] by open epi program, power 80%, confidence interval (CI) 95%, the required sample was calculated to be 262 participants. Group I comprised 131 hemodialyzed patients and Group II comprised 131 healthy individuals.

A simple and systematic random sampling approach was employed to select participants.

Data was collected through clinical consultations including history taking, general, musculoskeletal, and systemic examinations. Demographic and clinical features comprising age, sex, body mass index (BMI), and dialysis duration were recorded.

All participants were evaluated for FMS through the 2010 ACR preliminary diagnostic criteria, including widespread pain index (WPI) and symptom severity scale (SSS). Accordingly, the WPI should be ≥7, the SSS score should be ≥5; or if the WPI is between three and six, the SSS should be ≥9. The patient's symptoms should have lasted over three months at the same degree and there should be no additional pain-causing conditions. The WPI measures the number of painful regions in the body from a specified list involving 19 areas. The SSS estimates the level of fatigue, unrefreshed waking, cognitive symptoms, and several somatic symptoms. The SSS can also be suitable for the assessment of patients with present and past fibromyalgia [10]

The translated Arabic version of the Fibromyalgia Impact Questionnaire (FIQ) was applied to evaluate the QoL [17].The FIQ is an assessment and evaluation tool for measuring FM patient status, progress, and outcomes. This scale consists of ten items to measure physical functioning, well-being, difficulty in work, missed work days, fatigue, pain, morning tiredness, stiffness, anxiety, and depression. The maximum possible score is 100, with 10 points for every subheading, the average FM patient scores about 50, and severely afflicted patients are usually 70 plus. A higher score reflects a greater influence of the syndrome on the person and a lower QoL [18].

All participants completed the translated Arabic version of the Beck Depression Inventory (BDI) to evaluate the symptoms of depression in adults [19]. There are 21 items in this questionnaire, and answers are graded using the following four options: 0, 1, 2, & 3. For each question, the lowest level of depression is represented by 0, while the highest level is represented by 3.The higher overall scores suggest a more severe level of depressive symptoms. The following are the standard cut-off scores: 0-10: These ups and downs are considered normal, 11-16: Mild mood disturbance, 17-20: Borderline clinical depression, 21-30: Moderate depression, 31-40: Severe depression, over 40: Extreme depression [20].

The translated Arabic version of the Beck Anxiety Inventory (BAI) was utilized to evaluate the degree of anxiety [21].There are 21 questions on the BAI, and each response is scored between 0 and 3. Higher total scores reflect higher severity of anxiety symptoms. The standardized cutoffs are 0–7: Minimal, 8-15: Mild, 16-25: Moderate, and 26-63: Severe anxiety [22].

Laboratory investigations were done for all participants including parathyroid hormone (PTH), phosphorus (P), calcium (Ca), bone turnover, Vitamin D, urea, creatinine, alkaline phosphatase (ALP), complete blood count, and C-reactive protein (CRP). Chronic kidney disease–mineral bone disorder (CKD-MBD) status was defined based on serum levels of PTH, ALP, and Ca and was classified into high, low, or normal bone turnover [23]. The hemodialysis adequacy could be determined by monitoring urea kinetics (Kt/V). Kt/V is the ratio of urea clearance (K) multiplied by dialysis time (t) to the volume of water in your body.

Ethical approval and Consent to participate:

The Institutional Review Board (IRB) gave approval to this work (ZU-IRB#10180/5-3-2023) at the Faculty of Medicine, Zagazig - University Hospitals in line with the 1964 Helsinki Declaration, which is The Code of Ethics of the World Medical Association for research involving people. All participants signed a written informed consent.

Statistical analysis

The Statistical Package for Social Science software (SPSS) (Version 20.0. Armonk, NY: IBM Corp.) was utilized to code, enter, present, and analyze the gathered data. The quantitative variables were presented as the mean ± standard

deviation (SD) (and median with range for data that was not normally distributed), whereas the qualitative factors were presented as a number and percentage. For quantitative data, an independent samples t-test (t) was applied for data with normal distribution, but non-parametric data was identified with the Mann-Whitney-U Test. The chi-square test ($\chi 2$) was employed for detecting the relationship between different qualitative data. Regression analysis was used to determine the independent factors affecting the development of fibromyalgia. Spearman correlation (r) was used to correlate fibromyalgia scores with FIQ, BAI, and BDI. If the significant probability (P value) was ≤ 0.05* and ≤ 0.001**, the results were defined as statistically significant and highly statistically significant, respectively.

RESULTS

This study comprised 262 participants subdivided into two equal groups: the hemodialyzed group and the control group. Regarding demographic features (age & sex), (Table 1) showed that there was no statistically significant difference between both groups; ensuring comparability of the groups. A highly statistically significant difference was noted between the hemodialyzed and the control groups regarding BMI (25.4±4.61 vs 27.8±3.37), respectively. On assessing the laboratory features, there were highly significant differences between both groups regarding all laboratory items where a higher percent of abnormal results was found in the hemodialyzed group. All patients undergoing hemodialysis displayed adequate Kt/V and the mean duration of dialysis was 3.67±4.8 years.

Fibromyalgia frequency was significantly higher among controls than in hemodialyzed patients (76.3% versus 22.9%, respectively) (Figure 1). In terms of WPI, SSS, FIQ, BAI, and BDI scores, a highly significant difference was observed between the hemodialyzed & control groups as regards WPI, SSS, and FIQ scores where the higher median and the higher percent of more severe scores were found in the control group with the following variations in the hemodialysis versus control groups (22.9% vs 53.4%), (36.6% vs 61.1%), and (60% vs 90%), respectively. Also, a significant difference was identified between the two groups as regards BAI and BDI where the higher median and the higher percent of more severe scores were found among the hemodialyzed group with the following variations (22.1% vs 7.6%) and (64.1% vs 62.6%), respectively (Table 2).

Patients undergoing hemodialysis were subdivided according to FMS into hemodialyzed patients with FMS and those without FMS. The associations between the independent factors and the development of fibromyalgia among the hemodialyzed group demonstrated a highly statistically significant association between normal PTH, normal bone turnover, anemia, WPI>7, SSS>4, higher BAI, & higher BDI and fibromyalgia, as well as significant associations were revealed between high CRP, normal Ca, & normal Vit D and fibromyalgia. Hemodialyzed patients with normal PTH, normal bone turnover, anemia, WPI>7, SSS>4, (moderate & severe) BAI, (mild mood disturbance & depression), abnormal CRP, normal Ca, and normal Vit D were (26, 14, 4.8, 63, 134, (7.0 & 2.4), (21 & 6.0), 12, 3.5, 13) times more likely to develop fibromyalgia, respectively. About two-thirds (60%) of hemodialyzed patients with fibromyalgia had impaired QoL. However, no significant association was found between FM and all remaining parameters (Table 3).

In addition, the control participants were subdivided according to FMS into controls with FMS and those without FMS. The associations between the independent factors and the development of fibromyalgia among the control group revealed highly statistically significant associations between WPI>7 & SSS>4 and fibromyalgia, as well as significant associations between female sex, & normal BMI and fibromyalgia. Controls with WPI>7, SSS>4, female sex, and normal weight were (72, 4.9, 3.4, 10) times more likely to develop fibromyalgia, respectively. Most (90%) of the controls with fibromyalgia had impaired QoL. However, there was no significant association

between FM and all remaining parameters (Table 4).

The correlation between fibromyalgia score and FIQ, BAI, and BDI showed that among the hemodialyzed group, a highly significant positive correlation was demonstrated between fibromyalgia score and FIQ (r=0.911, P≤0.001**). Furthermore, there was a significant positive correlation between fibromyalgia score and BDI (r=0.268, P=0.002*) and a positive correlation between fibromyalgia score & BAI (r=0.153, P=0.080), but still insignificant. In addition, among the control group, there were highly significant positive correlations between fibromyalgia score and FIQ (r=0.757, P≤0.001**) and with BAI (r=0.492, P P≤0.001**) & a significant positive correlation between fibromyalgia score & BDI (r=0.243, P=0.005*) (Table 5).

Table 1 Demographic, clinical, and laboratory features among the Hemodialyzed and Control groups (n=262).

Features	Hemodialyzed group (n=131) No (%)	Control group (n=131) No (%)	P value
Age (years)(mean ± SD) ≤ Median (37) > Median (37)	40.6±13.4 65(49.6%) 66(50.4%)	39.2±12.2 72(55%) 59(45%)	[a]0.383 [b]0.387
Sex Female Male	 52(39.7%) 79(60.3%)	 67(51.1%) 64(48.9%)	 [b]0.063
BMI, kg/m2 (mean ± SD) Underweight Normal weight Overweight Obese	25.4±4.61 24(18.3%) 27(20.6%) 57(43.5%) 23(17.6%)	27.8±3.37 0.0(00.0%) 20(15.3%) 51(38.9%) 60(45.8%)	**[a]≤0.001**** **[b]≤0.001****
Duration of dialysis (years) (mean ± SD) ≤ Median (1.5) > Median (1.5)	 3.67±4.8 74(56.5%) 57(43.5%)	 -	 -
Urea Normal Abnormal	 0.0(00.0%) 131(100%)	 131(100%) 0.0(00.0%)	 **[b]≤0.001****
Creatinine Normal Abnormal	 0.0(00.0%) 131(100%)	 131(100%) 0.0(00.0%)	 **[b]≤0.001****
CRP Normal Abnormal	 30(22.9%) 101(77.1%)	 131(100%) 0.0(00.0%)	 **[b]≤0.001****
ALP Normal Abnormal	 66(50.4%) 65(49.6%)	 131(100%) 0.0(00.0%)	 **[b]≤0.001****
Ca Normal Abnormal	 78(59.5%) 53(40.5%)	 131(100%) 0.0(00.0%)	 **[b]≤0.001****
P Normal Abnormal	 71(54.2%) 60(45.8%)	 131(100%) 0.0(00.0%)	 **[b]≤0.001****
PTH			

Features	Hemodialyzed group (n=131) No (%)	Control group (n=131) No (%)	P value
Normal	83(63.4%)	131(100%)	[b]**≤0.001****
Abnormal	48(36.6%)	0.0(00.0%)	
Bone turnover			
Low	24(18.3%)	0.0(00.0%)	[b]**≤0.001****
Normal	83(63.4%)	131(100%)	
High	24(18.3%)	0.0(00.0%)	
Vitamin D			
Optimal	101(77.1%)	131(100%)	[b]**≤0.001****
Low	30(22.9%)	0.0(00.0%)	
Kt/V			
Normal	131(100%)	-	-
Abnormal	0.0(00.0%)	-	-
Hb			
Normal	89(67.9%)	131(100%)	[b]**≤0.001****
Anemia	42(32.1%)	0.0(00.0%)	

SD: Standard deviation, BMI: Body Mass Index, CRP: C-reactive protein, ALP: Alkaline phosphatase, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, Kt/V: ureakinetics, Hb: Hemoglobin, [a]Independent samples t-test, [b]Chi square test, Statistically significant (P≤0.05*), Highly statistical significant (P≤0.001**).

Table 2 Fibromyalgia score, WPI, SSS, FIQ, BAI, and BDI among the Hemodialyzed and Control groups (n=262).

Variables	Hemodialyzed group (n=131) No (%)	Control group (n=131) No (%)	P value
WPI Median (range)	3(0.0-17)	8(0.0-13)	[a]**≤0.001****
Less severe (≤ Median7)	101(77.1%)	61(46.6%)	[b]**≤0.001****
More severe (>Median7)	30(22.9%)	70(53.4%)	
SSS Median (range)	3(0.0-9.0)	6(2.0-10)	[a]**≤0.001****
Less severe (≤ Median4)	83(63.4%)	51(38.9%)	[b]**≤0.001****
More severe (>Median4)	48(36.6%)	80(61.1%)	
Fibromyalgia score Median (range)	0.0(0.0-26)	14(0.0-22)	[a]**≤0.001****
Absent	101(77.1%)	31(23.7%)	[b]**≤0.001****
Present	30(22.9%)	100(76.3%)	
FIQ	**(n=30)**	**(n=100)**	
Median (range)	55(33.3-87)	64.5(32-92)	[a]0.406
Normal	12(40.0%)	10(10.0%)	[b]**≤0.001****
Impairment	18(60.0%)	90(90.0%)	
BAI Median (range)	22(4.0-63)	19(4.0-42)	[a]**0.006***
Low	60(45.8%)	81(61.8%)	[b]**0.002***
Moderate	42(32.1%)	40(30.5%)	
Severe	29(22.1%)	10(7.6%)	
BDI Median (range)	24(7.0-63)	19(5.0-34)	[a]**0.021***
Normal	23(17.6%)	11(8.4%)	[b]**0.024***
Mild mood disturbance	24(18.3%)	38(29.0%)	
Depression	84(64.1%)	82(62.6%)	

WPI: Widespread Pain Index, SSS: Symptom Severity Scale, FIQ: Fibromyalgia Impact Questionnaire, BAI: Beck AnxietyInventory, BDI: Beck Depression Inventory, [a]Mann-Whitney U Test, [b]Chi square test, Statistically significant (P≤0.05*), Highly statistical significant (P≤0.001**)

Table 3 Relationship between the independent factors and development of fibromyalgia among the Hemodialyzed group (n=131).

Factors	Hemodialyzed patients with fibromyalgia (n=30) No (%)	Hemodialyzed patients without fibromyalgia (n=101) No (%)	[a]P value	OR 95% CI
Age (years)				
≤ Median (37)(n=65)	15(23.1%)	50(76.9%)	0.962	1.1(0.45-2.31)
> Median(37)(n=66)	15(22.7%)	51(77.3%)		Ref
Sex				
Female(n=52)	15(28.8%)	37(71.2%)	0.189	1.7(0.76-3.94)
Male(n=79)	15(19.0%)	64(81.0%)		Ref
BMI, kg/m2				
Underweight(n=24)	4.0(16.7%)	20(83.3%)	0.678	Ref
Normal weight(n=27)	7.0(25.9%)	20(74.1%)		1.8(0.44-6.93)
Overweight(n=57)	12(21.1%)	45(78.9%)		1.3(0.39-4.65)
Obese(n=24)	7.0(30.4%)	16(69.6%)		2.2(0.54-8.81)
Duration of dialysis (years)				
≤ Median (1.5)(n=74)	18(24.3%)	56(75.7%)	0.659	1.2(0.45-2.31)
>Median(1.5)(n=57)	12(21.1%)	45(78.9%)		Ref
CRP				
Normal(n=30)	0.0(0.0%)	30(100%)	**0.001***	Ref
Abnormal(n=101)	30(29.7%)	71(70.3%)		12(1.60-94.1)
ALP				
Normal(n=66)	18(27.3%)	48(72.7%)	0.230	1.7(0.72-3.79)
Abnormal(n=65)	12(18.5%)	53(81.5%)		Ref
Ca				
Normal(n=78)	24(30.8%)	54(69.2%)	**0.009***	3.5(1.3-9.24)
Abnormal(n=53)	6.0(11.3%)	47(88.7%)		Ref
P				
Normal(n=71)	18(25.4%)	53(74.6%)	0.468	1.4(0.59-3.11)
Abnormal(n=60)	12(20.0%)	48(80.0%)		Ref
PTH				
Normal(n=83)	30(36.1%)	53(63.9%)	**≤0.001***	26(3.45-201)
Abnormal(n=48)	0.0(0.0%)	48(100%)		Ref
Bone turnover				
Low(n=24)	0.0(0.0%)	24(100%)	**≤0.001***	1(0.06-17.0)
Normal(n=83)	30(36.1%)	53(63.9%)		14(1.75-106)
High(n=24)	0.0(0.0%)	24(100%)		Ref
Vitamin D				
Optimal(n=101)	30(29.7%)	71(70.3%)	**0.001***	13(1.65-97.3)
Low(n=30)	0.0(0.0%)	30(100%)		Ref
Hb				
Normal(n=89)	12(13.5%)	77(86.5%)	**≤0.001***	Ref
Anemia(n=42)	18(42.9%)	24(57.1%)		4.8(2.04-11.4)
WPI				
Less severe ≤7 (n=101)	6.0(5.9%)	95(94.1%)	**≤0.001***	Ref
More severe >7 (n=30)	24(80.0%)	6.0(20.0%)		63(18.8-214)
SSS				
Less severe ≤4 (n=83)	0.0(0.0%)	83(100%)	**≤0.001***	Ref

Factors	Hemodialyzed patients with fibromyalgia (n=30) No (%)	Hemodialyzed patients without fibromyalgia (n=101) No (%)	[a]P value	OR 95% CI
More severe >4 (n=48)	30(62.5%)	18(37.5%)	*	134(17.1-1047)
FIQ				
Normal (n=12)	12(40.0%)	-	-	-
Impairment (n=18)	18(60.0%)			
BAI				
Low(n=60)	6.0(10.0%)	54(90.0%)	**≤0.001***	Ref
Moderate(n=42)	18(42.9%)	24(57.1%)	*	7.0(3.38-19.3)
Severe(n=29)	6.0(20.7%)	23(79.3%)		2.4(0.69-8.05)
BDI				
Normal(n=23)	0.0(0.0%)	23(100%)	**≤0.001***	Ref
Mild mood disturbance(n=24)	12(50.0%)	12(50.0%)	*	21(2.43-184)
Depression(n=84)	18(21.4%)	66(78.6%)		6.0(0.75-131)

BMI: Body Mass Index, CRP: C-reactive protein, ALP: Alkaline phosphatase, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, Kt/V: ureakinetics, Hb: Hemoglobin, WPI: Widespread Pain Index, SSS: Symptom Severity Scale, FIQ: Fibromyalgia Impact Questionnaire, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, [a]Chi square test, Statistically significant (P≤0.05*), Highly statistical significant (P≤0.001**), OR: Odds ratio, CI: Confidence interval

Table 4 Relationship between the independent factors and the development of fibromyalgia among the Control group (n=131).

Factors	Controls with fibromyalgia (n=100) No (%)	Controls without fibromyalgia (n=31) No (%)	[a]P value	OR 95% CI
Age (years)				
≤ Median (37)(n=72)	57(79.2%)	15(20.8%)	0.400	1.4(0.63-3.17)
> Median(37)(n=59)	43(72.9%)	16(27.1%)		Ref
Sex				
Female(n=67)	58(86.6%)	9.0(13.4%)	**0.005***	3.4(1.41-8.07)
Male(n=64)	42(65.6%)	22(34.4%)		Ref
BMI, kg/m2				
Normal weight(n=20)	20(100%)	0.0(0.0%)	**0.009***	10(1.25-80.0)
Overweight(n=51)	40(78.4%)	11(21.6%)		1.8(0.77-4.29)
Obese(n=60)	40(66.7%)	20(33.3%)		Ref
WPI				
Less severe ≤7(n=61)	30(49.2%)	31(50.8%)	**≤0.001***	Ref
More severe >7(n=70)	70(100%)	0.0(0.0%)	*	72(9.44-555)
SSS				
Less severe ≤4(n=51)	30(58.8%)	21(41.2%)	**≤0.001***	Ref
More severe >4 (n=80)	70(87.5%)	10(12.5%)	*	4.9(2.06-11.6)
FIQ				
Normal (n=10)	10(10.0%)	-	-	-
Impairment(n=90)	90(90.0%)			
BAI				
Low(n=81)	60(74.1%)	21(25.9%)	0.186	Ref
Moderate(n=40)	30(75.0%)	10(25.0%)		1.1(0.44-2.51)

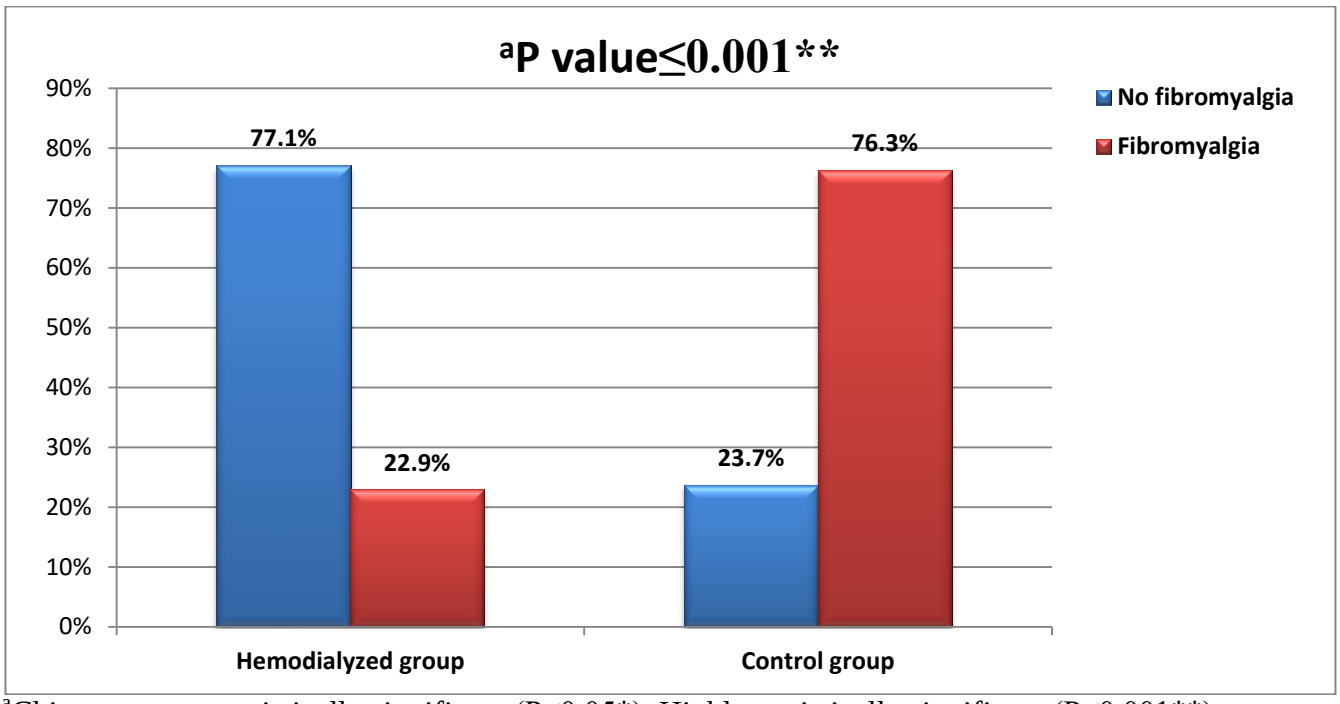
Factors	Controls with fibromyalgia (n=100) No (%)	Controls without fibromyalgia (n=31) No (%)	[a]P value	OR 95% CI
Severe(n=10)	10(100%)	0.0(0.0%)		3.5(0.42-29.1)
BDI				
Normal(n=11)	10(90.9%)	1.0(9.1%)	0.057	5.8(0.67-50.6)
Mild mood disturbance(n=38)	24(63.2%)	14(36.8%)		Ref
Depression(n=82)	66(80.5%)	16(19.5%)		2.4(1.02-5.67)

BMI: Body Mass Index, CRP: C-reactive protein, ALP: Alkaline phosphatase, Ca: Calcium, Ph: Phosphorus, PTH: Parathyroid hormone, Kt/V: ureakinetics, Hb: Hemoglobin, WPI: Widespread Pain Index, SSS: Symptom Severity Scale, FIQ: Fibromyalgia Impact Questionnaire, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, [a]Chi square test, Statistically significant (P≤0.05*), Highly statistical significant (P≤0.001**), OR: Odds ratio, CI: Confidence interval

Table 5 Correlation between fibromyalgia score and FIQ, BAI, and BDI among the Hemodialyzed and Control groups (n=262).

	Hemodialyzed group (n=131) Fibromyalgia	
	r	**P value**
FIQ	0.911	**≤0.001****
BAI	0.153	0.080
BDI	0.268	**0.002***
	Control group (n=131) Fibromyalgia	
	r	**P value**
FIQ	0.757	**≤0.001****
BAI	0.492	**≤0.001****
BDI	0.245	**0.005***

FIQ: Fibromyalgia Impact Questionnaire, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, Statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**)



[a]Chi square test, statistically significant (P≤0.05*), Highly statistically significant (P≤0.001**)

Figure 1 Multiple bar charts for comparing the frequency of fibromyalgia among the Hemodialyzed and Control groups (n=262).

DISCUSSION

Several widespread musculoskeletal disorders, including FM, have been identified in most patients receiving hemodialysis. However, the literature on fibromyalgia among patients with hemodialysis is still rather small [4]. Thus, this research aimed to assess the frequency of fibromyalgia among hemodialyzed patients and its relation to QoL, depression, anxiety, and laboratory investigations.

The current study included 262 participants subdivided into two equal groups: the hemodialyzed and the control groups. The fibromyalgia frequency and fibromyalgia scores among healthy controls were significantly higher than in patients with hemodialysis (76.3% versus 22.9%, respectively). Seyedmardani et al., [24] stated that the prevalence of fibromyalgia in patients suffering from severe renal failure and on regular hemodialysis was 44.4%.

Conversely, Çağlıyan Türk et al., [4] noted that the fibromyalgia prevalence in hemodialyzed patients was 14%, which was significantly higher than that of the controls. On the other hand, past studies assessing the fibromyalgia prevalence in patients with HD reported that it ranged from 3.9 to 12.2%, with these rates being comparable to those in the control group [11-13,25]. These different rates in the prevalence of fibromyalgia could be accounted for by the racial and geographic disparities in involved populations [13].

The present research detected a significant difference between the hemodialyzed and control groups regarding FIQ scores. Unexpectedly, higher median, higher percent of more severe scores, and lower QoL were found among the control group. These results agreed with Yonata et al., [26] who found that the majority of patients on HD had a good QoL. This was in contrast to other studies stating that the QoL was likely lower in patients on hemodialysis than in the general population due to HD inadequacy and malnutrition [12,13,15,16,27,28]. These disparate findings could be explained by the fact that the FIQ questionnaire was developed to evaluate the QoL among FM patients, so a higher FIQ score would be expected in the group

with a larger number of FM patients [11], which was the control group in our research.

This research also observed significant differences between hemodialyzed and healthy groups concerning bone minerals, bone turnover, renal function tests, and hemoglobin where a higher percentage of abnormal results were found among the HD group. These results were the same as in the study of Sargın et al., [16].

The study at hand compared depression and anxiety in hemodialysis and control groups. There were significant differences between the two groups regarding BAI & BDI where the higher median and the higher percent of more severe scores were present in the HD group. Similarly, Sargın et al., [16] concluded that patients with hemodialysis had more psychological issues related to neurological and metabolic conditions than healthy individuals.

In the current study, hemodialyzed patients were subdivided according to FMS into HD patients with FMS and those without FMS. We assessed the associations between the independent factors and developing fibromyalgia in the hemodialyzed group.

Similar to the literature [11], the present results didn't find associations between the development of fibromyalgia and age, gender, BMI, and dialysis duration among hemodialyzed patients. Also, Demirci et al., [6] found no differences between HD patients with and without FM according to their age, dialysis duration, or dialysis adequacy. Other studies showed that the average age of hemodialysis patients did not correlate with the incidence of fibromyalgia [11,12,16,25]. On the contrary, most of the studies evaluating FMS among hemodialyzed patients reported that the female sex was identified as a risk factor for developing FM in hemodialyzed patients [4,11,12,14,16,25]. Moreover, Seyedmardani et al., [24] concluded that gender and age would be the critical factors influencing fibromyalgia in patients with hemodialysis.

Additionally, the current results detected that WPI scores>7and SSS>4 were independent factors for developing fibromyalgia among hemodialyzed patients. Also, a highly significant positive correlation between fibromyalgia score and FIQ score was noted in the HD group. About two-thirds (60%) of hemodialyzed patients with fibromyalgia had impaired QoL

Similarly, hemodialyzed patients with fibromyalgia had lower QoL and higher FIQ scores than those without FM in other studies [4,11,25]. Demirci et al., [6] observed significantly higher WPI and SSS in HD patients with FMS. Sariyildiz et al., [29] confirmed a high frequency of central sensitization and its important negative effects on QoL in patients receiving hemodialysis. The prototype of central sensitization is fibromyalgia, which is characterized by generalized pain, impaired sleep and mental health, & several other somatic symptoms [30, 31]. Therefore, it can be speculated that fibromyalgia negatively impacts QoL through chronic pain and related symptoms in patients with ESRD [6, 25].

On studying the associations between laboratory investigations and the development of fibromyalgia among patients undergoing hemodialysis included in this study, normal PTH, normal bone turnover, normal Ca, normal Vitamin D, anemia, and abnormal CRP were related to the development of FMS among hemodialyzed patients. However, no significant association was detected between ALP, P, & dialysis duration and FMS. All included HD patients were with adequate kt/V.

Although fibromyalgia patients are not expected to undergo a change in these variables, they are typically assessed to aid in distinguishing other clinical conditions [12]. The majority of musculoskeletal issues in patients with ESRD are caused by the patient's altered metabolism, which is often brought on by calcium, phosphorus, or, frequently, by hyperparathyroidism, so they should be ruled out [13].

In accordance with the present results, Leblebici et al., [13] found no significant association between the duration of dialysis and FM in HD patients. This might explain the relationship

between the laboratory parameters and FMS in HD patients since a longer dialysis duration is associated with a higher frequency of bone and mineral problems [13]. Yao et al., [32] approved that iron is necessary for the synthesis of neurotransmitters, and low iron stores may result in less biogenic amine production, a phenomenon that was observed in patients suffering from FM. This explains the relationship between anemia and FM in the HD group in our study.

Moreover, Demirci et al., [6] stated that serum CRP levels were significantly higher in HD patients with fibromyalgia, as expected. Elevated serum CRP levels indicate the significance of inflammation in fibromyalgia patients in predicting the management approach [6]. Even though fibromyalgia is a neurogenic inflammatory response to infections, allergens, chemicals, or stress, it is still unclear what triggers the inflammation resulting in fibromyalgia [33].

On the other side, prior studies on hemodialyzed patients with fibromyalgia established no association between fibromyalgia and dialysis adequacy index, dialysis duration, Ca, P, PTH, ALP, CRP, or hemoglobin levels [4,6,13,16,24,25].

Nevertheless, Couto et al., [11] detected that only ionized calcium was significantly elevated in HD patients with FMS than those without FMS. Calcium ions play a key role in the physiology of muscle contraction and variations in the concentration of calcium ions may contribute to the pathophysiology of FMS [11]. In another study on hemodialyzed patients, the fibromyalgia group had higher PTH levels [12]. However, Sargın et al., [16] could not find a significant difference between fibromyalgia and secondary hyperparathyroidism in the HD group.

The present study observed highly significant associations between FM and BDI & BAI where hemodialyzed patients with mild mood disturbance & depression and hemodialyzed patients with moderate & severe anxiety were more likely to develop fibromyalgia. Also, there was a significant positive correlation between fibromyalgia score & BDI score, and a positive correlation between fibromyalgia score & BAI score, but still insignificant.

The previously mentioned findings agreed with numerous studies that compared hemodialyzed patients with and without fibromyalgia. They noticed higher levels of anxiety and depressive symptoms in hemodialyzed patients with fibromyalgia [4,11,13,25]. However, fibromyalgia was identified by Samimagham et al., [12] as a risk factor for depression, but it didn't influence anxiety levels.

FM symptomatology includes symptoms like weakness, disturbed sleep, and forgetfulness along with pain. From this viewpoint, co-morbid psychological disorders such as anxiety and depression that might impact all of these symptoms could result in more severe FM; for this reason, anxiety and depression should be taken into consideration while evaluating FM patients [34]. Moreover, chronic pain including FM might generate other adversities such as depression and anxiety symptoms. It might also contribute to decreased physical activity giving the apprehension of aggravating pain [11].

Regarding the control group, the present research showed significant associations between FMS and sex, BMI, WPI, and SSS where individuals with female sex, normal weight, WPI>7, and SSS>4 were more likely to develop fibromyalgia. Also, there were positive correlations between fibromyalgia scores and FIQ, BDI, and BAI scores. Fibromyalgia is mainly thought to affect women [25,35,36]. Age and weight have as well an impact on the clinical state of all chronic pain conditions, including fibromyalgia [37]. In addition, fibromyalgia is commonly known to be associated with lower QoL and several psychological problems including anxiety and depression in the general population [16, 34].

Overall, all these findings support that FMS is an essential differentiation for musculoskeletal disorders among hemodialyzed patients [4].

Strength and Limitation

This research assessed fibromyalgia as an essential differential diagnosis for musculoskeletal disorders among hemodialyzed patients and its relation to QoL, psychiatric disorders, and laboratory investigations since limited studies investigated this despite its importance. Furthermore, the design of this work was a case-control study, which is relatively inexpensive to conduct, suitable for diseases with long latent periods, and no loss of cases as no follow-up period in this type of study. However, this study was limited by single-center analysis and a relatively small sample size.

Conclusion and Recommendations

The frequency of fibromyalgia is higher in healthy controls than in hemodialysis patients. FMS in patients undergoing hemodialysis shows significant associations with depression, anxiety, abnormal CRP, anemia, and a normal bone mineral metabolism profile. About two-thirds (60%) of hemodialyzed patients with fibromyalgia had impaired QoL. There are positive correlations between fibromyalgia scores and FIQ & BDI scores among patients with HD. Therefore, we recommend that HD patients with musculoskeletal disorders should be evaluated for FMS. Patients with FMS receiving maintenance hemodialysis should be regularly monitored for psychiatric disorders and inflammation. Also, evaluation of inflammation in FMS with other inflammatory markers such as TNF-alpha, IL-6, and IL-8 is needed.

Acknowledgments: The authors extend their gratitude to all participants.

Conflict of interest: The authors declare that they have no conflict of interest.

Financial disclosures: The authors declare that they have no funding support.

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Citation

Abdelsalam, N., Taha, F., Abdelsalam, S., Hosseny, A. Fibromyalgia and Its Relation with Quality of Life, Depression, and Anxiety among Hemodialysis Patients. *Zagazig University Medical Journal*, 2025; (2082-2096): -. doi: 10.21608/zumj.2025.373281.3898