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Frequency of fibromyalgia and its associated factors among patients with renal transplantation

Renal transplantasyon hastalarında Fibromiyalji sıklığı ve seyri

Firdevs Tuğba Bozkurt,[1] Oytun Derya Tunç,[2] Turan Çolak[3]

[1]Intensive Care Unit, Mehmet Akif Inan Research and Training Hospital, Şanlıurfa, Turkey
[2]Department of Orthopedics and Traumatology, Pendik Training and Research Hospital, İstanbul, Turkey
[3]Department of Nephrology, Başkent University Hospital of Medicine, Ankara, Turkey

Abstract

Introduction: Musculoskeletal complications such as fibromyalgia syndrome may occur following renal transplantation. However, frequency and the course of this condition have not been deeply assessed in this group of patients. This study aimed to investigate the frequency of fibromyalgia syndrome and identify the factors associated with its occurrence in patients who underwent renal transplantation for end-stage renal disease.

Methods: The demographic, clinical, and laboratory characteristics of the patients were recorded in this observational study. All patients were assessed in outpatient setting for the presence of fibromyalgia and classified into three groups in the following order: Group 1, normal patients; Group 2, possible fibromyalgia; Group 3, fibromyalgia syndrome. In addition, Fibromyalgia Impact Questionnaire was administered.

Results: A total of 128 patients who underwent renal transplantation were included. Three groups did not differ with regard to the age, marital status, smoking history, etiology of the renal failure and laboratory findings (p>0.05). However, female gender was more frequent among patients with fibromyalgia. Fatigue, sleep disturbance, irritable colon syndrome, depression and antidepressant use were also more common and Fibromyalgia Impact Questionnaire score was higher in patients with fibromyalgia. A multivariate logistic regression analysis identified Fibromyalgia Impact Questionnaire score and antidepressant use as significant independent predictors of fibromyalgia syndrome and possible fibromyalgia (OR 1.2 [95% CI 1.1–1.3], p<0.001; OR 21.0 [95% CI 1.2–357.2], p=0.035).

Discussion and Conclusion: Fibromyalgia syndrome shows a tendency to occur more commonly in renal transplant patients than in normal population, where depression is accompanied by these conditions. The treatment strategy could be established on the relief of sleep disturbance, fatigue, and irritable colon syndrome, which are more frequently observed in patients with fibromyalgia syndrome.

Keywords: End-stage renal disease, fibromyalgia; musculoskeletal system; observational study; renal transplantation.

Özet

Amaç: Fibromyalji sendromu gibi kas-iskelet sistemi komplikasyonları renal transplantayondan sonra görülebilir. Ancak, bu durumun sıklığı ve seyri bu grup hastalarda derinlemesine incelenmemiştir. Bu çalışmada, fibromyalji sendromunun sıklığının araştırılması ve son dönem böbrek hastalığı nedeniyle renal transplantasyon yapılan hastalarda fibromyalji görülmesi ile ilişkili faktörlerin belirlenmesi amaçlandı.

Gereç ve Yöntem: Gözlemsel çalışmamızda hastaların demografik, klinik ve laboratuvar özellikleri kayıt edildi. Tüm hastalar fibromiyalji varlığı açısından poliklinikte değerlendirildi ve sırasıyla üç gruba ayrıldı: Grup 1, normal hastalar; Grup 2, olası fibromiyalji; Grup 3, fibromiyalji sendromu. Ek olarak, Fibromiyalji Etki Anketi doldurduldu.

Bulgular: Renal transplantasyon yapılan toplam 128 hasta çalışmaya dahil edildi. Yaş, medeni hal, sigara kullanımı, böbrek yetmezliği etyolojisi ve laboratuvar bulguları açısından üç grup arasında fark yoktu (p>0.05). Ancak, fibromiyalji sıklığı kadınlarda daha fazlaydı. Fibromiyaljili hastalarda, halsizlik, uyku bozukluğu, irritable bağırsak hastalığı, depresyon ve antidepresan kullanımı daha fazla ve aynı zamanda Fibromiyalji Etki Anketi skoru daha yüksekti. Çoklu lojistik regresyon analizi sonucunda Fibromiyalji Etki Anketi skorunun ve antidepresan kullanımının fibromiyalji sendromu ve olası fibromiyalji için anlamlı bağımsız belirteçler olduğu saptandı (OR 1.2 [95% CI 1.1–1.3], p<0.001; OR 21.0 [95% CI 1.2–357.2], p=0.035).

Sonuç: Depresyonun da eşlik ettiği fibromiyalji sendromu normal popülasyona göre renal transplant hastalarında görülme eğilimi göstermektedir. Tedavi stratejisi uyku bozuklukları, yorgunluk ve irritable kolon sendromu daha yüksek oranda Fibromiyalji sendromlu hastalarda görüldüğünden bunları düzeltmeye yönelik oluşturulmalıdır.

Anahtar Sözcükler: Son dönem böbrek hastalığı; fibromiyalji; kas iskelet sistemi; gözlemsel çalışma; renal transplantasyon.

Corresponding *(İletişim)*: Firdevs Tuğba Bozkurt, Mehmet Akif İnan Eğitim ve Araştırma Hastanesi, Yoğun Bakım Ünitesi, Şanlıurfa, Turkey
E-mail *(E-posta)*: drtugbaicu@gmail.com

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Fibromyalgia syndrome (FMS) is a noninflammatory condition characterized by the presence of widespread bodily pain and multiple tender points on physical examination.[1] Other than the pervasive pain, comorbidities those may impair the quality of life in these patients include fatigue, sleep disturbance, stiffness, depression, anxiety as well as the cognitive dysfunction, which undermine the individuals' ability to cope with the life events and ability to communicate with others.[2] In this regard, FMS represents a major health problem.

The reported prevalence for FMS in the general population ranges between 0.5% and 5.8% increasing with age and reaching a peak between ages 40 and 60; and female to male ratio is 4 to 9:1.[3,4] In addition, 10% to 20% of the patients admitting to rheumatology outpatient units have been diagnosed with this condition.[5] Despite its common occurrence, the underlying etiopathogenesis of FMS has not been clearly identified in which is suggested to be a complex interplay between genetic and environmental factors.[6,7]

Chronic renal failure is characterized by the development of uremia due to chronic, progressive, and irreversible impairment of kidney function.[8] Obviously, renal transplantation represents a superior therapeutic modality as compared to dialysis for the treatment of chronic renal failure and it is associated with improved quality of life and survival in patients with end stage renal failure.[9] Recent advances in the field of kidney transplantation have provided significant improvement in success rate in patients undergoing this procedure.[10]

Musculoskeletal including other organ system complications might occur after renal transplantation. Most of these complications lead to bone and joint pain, those generally does not differ from FMS in spite of the findings obtained from physical examination and laboratory analysis. However, presence of such findings does not confirm the diagnosis of FMS, which could be accompanied by other pathologies of the musculoskeletal system. To our knowledge, no previous studies have assessed the incidence and clinical progress of FMS in renal transplant patients.

The purpose of the present study was to determine the frequency of FMS, and assess the factors associated with the occurrence of this condition, in patients after renal transplantation.

Materials and Method

Patients

An observational and cross-sectional design was selected. A total of 128 patients who underwent renal transplantation between January 1998 and December 2013, admitted to regular follow-up outpatient visits between December 2013 and December 2014, and patients with a serum creatinine level below 3 mg/dl as well as the absence of transplant rejection, osteoporosis, active infection, or elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were included in this study. The demographic, clinical, and laboratory characteristics of the patients were recorded. In addition, laboratory data within the past 6-month period prior to study inclusion were also obtained from the hospital database and recorded. Patient without any of the data mentioned above were excluded from the study. All patient data were recorded and analysed anonymously. This study was conducted in accordance with the principles of Helsinki Declaration as well as national human research legistation. Ethics Committee of Baskent University Hospital reviewed and approved this study protocol.

Diagnostic criteria

All patients were assessed in outpatient settings with physical examination, family and medical history of all patients were completed in outpatient unit. The diagnosis of fibromyalgia was made based on the American College of Rheumatology (ACR) classification.[11] Patients were inquired about elicited pain at previously described points of tenderness by the ACR. A pressure of four kg per square centimeter with one kg per square centimeter increment per second using the pulp of the thumb was exerted at each of the points. Oral expression of pain and tenderness by the patient was considered an indication of a positive test result. Patients were separated into three groups as follows: Patients with a history of widespread pain for more than three months and the presence of tender points more than 11 on examination were diagnosed as FMS and enrolled in Group III. Patients with a pain history more than three months and the presence of tender points between six and 10 on examination were diagnosed as possible fibromyalgia and included in Group II. Other patients with normal physical examination findings were considered as control and enrolled in Group I.

Fibromyalgia Impact Questionnaire

In order to assess the effect of pain on activities of daily living, the Fibromyalgia Impact Questionnaire (FIQ) with a total score between 0 and 100 was administered to all patients. A higher score indicates more severe restriction of the activities of daily living. The FIQ was originally developed by Burchardt et al., and the validity and reliability of the Turkish version were established by Sarmer et al.[12,13]

Statistical analysis

The normality of the variables was assessed using Kolmogorov Smirnov test, while Levene test was used to analyze the homogeneity of the variances. Descriptive statistics were expressed as mean±standard deviation or median (range) for continuous and ordinal numerical variables, while number of cases and percentage (%) were used for the presentation of categorical variables. The variances between three groups were assessed by using one-way ANOVA test, since Kruskal-Wallis test was used for the values with abnormal distribution or unequal variances. When a significance was identified with Kruskal Wallis test, Conover's non-parametric pairwise comparison test was used to determine the group responsible for the significant difference. Categorical variables were assessed using Pearson's chi-square test, Fisher's Exact test or likelihood ratio.

Multiple logistic regression analysis was used to identify the independent determinants for differentiating between con-

Table 1. Demographical characteristics of the study groups

	Group I, normal (n=107)		Group II, possible fibromyalgia (n=7)		Group III, fibromyalgia syndrome (n=13)		p
	n	%	n	%	n	%	
Age, y (mean±SD)	37.9±11.3		31.4±9.8		37.7±11.0		0.334[a]
Female gender	41	8.3	4	57.1	13	100.0	<0.001*[b]
Marital status							
Single	39	36.4	4	57.1	3	23.1	
Married	65	60.7	3	42.9	9	69.2	0.545[b]
Widow/divorced	3	2.8	0	0.0	1	7.7	
Smoking	6	5.6	1	14.3	1	7.7	0.705[c]

SD: Standard deviation; [a]Kruskal-Wallis test; [b]Chi-square test; [c]Fisher's exact test; *p<0.05.

Table 2. Comparison of the groups with regard to clinical characteristics

	Group I, normal (n=107)		Group II, possible fibromyalgia (n=7)		Group III, fibromyalgia syndrome (n=13)		p
	n	%	n	%	n	%	
Findings and symptoms							
Joint swelling	7	6.5	0	0.0	3	23.1	0.118[b]
Paresthesia	22	20.6	1	14.3	5	38.5	0.334[b]
Restless leg syndrome	21	19.6	3	42.9	1	7.7	0.182[b]
Sleep disturbance	33	30.8	3	42.9	13	100.0	<0.001*[b]
Fatigue	47	43.9	3	42.9	12	92.3	0.002*[b]
Irritable colon syndrome	10	9.3	1	14.3	5	38.5	0.035*[b]
History of depression	16	15.0	1	14.3	6	46.2	0.045*[b]
Family history of depression	13	12.1	0	0.0	4	30.8	0.091[c]
Medications							
Tacrolimus	57	53.3	1	14.3	7	53.8	0.109[b]
Sirolimus	28	26.2	3	42.9	6	46.2	0.255[c]
Cyclosporine	21	19.6	3	42.9	0	0.0	0.022*[b]
Antidepressant	3	2.8	3	42.9	4	30.8	<0.001*[c]
FIQ Score, (mean±SD)	12.4	1.5–63.0	34.4	23.4–46.6	58.4	20.4–65.2	<0.001*[a]

SD: Standard deviation; [a]One-way ANOVA test; [b]Chi-square test; [c]Fisher's exact test; *p<0.05.

trols and "possible fibromyalgia" and "fibromyalgia syndrome" groups. All candidate factors that were found to have an impact on univariate statistical analyses were included in the regression model. Odds ratio and 95% confidence intervals were calculated for each variable. Analyses were performed by Statistical Package for Social Sciences version 11.5 program (SPSS Inc., Chicago, IL). A p value <0.05 was considered as statistically significant.

Results

A total of 128 patients were included in this study. Table 1 shows demographical characteristics of the patients. There was no difference found between age, marital status and smoking history of the groups (p=0.334, p=0.545, p=0.705, respectively). The frequency of FMS in females was significantly higher compared to males with possible fibromyalgia and controls (100%, 57.1%, p=0.007; 100%, 38.3%, p<0.001; respectively). There was no significance found between groups among each of the following etiological factors: Alport syndrome, crush syndrome, diabetes, focal segmental glomerulosclerosis, glomerulonephritis, gut, hypertension, IgA nephropathy, nephritic syndrome, nephrotic syndrome, oxalosis, polycystic kidney disease, pyelonephritis, urolithiasis, vesicoureteral reflux, congenital renal disease, and unknown etiology (p>0.05 for all). Groups also did not show any difference in terms of serum Alanine transaminase (ALT), Aspartate-Aminotransferase (ALP), creatinine, Calcium, Phosphorus, CRPESR, albumin, thyroid stimulating hormone (TSH), parathyroid hormone, or lactate dehydrogenase (LDH) levels (p>0.05 for all).

Table 2 compares the groups with regard to symptoms and findings, medications and FIQ score. Fatigue was higher in Group

III compared to Group I and Group II (92.3%, 43.9%, p<0.001; 92.3%, 42.9%, p=0.031, respectively). Sleep disturbance was found higher in Group III than in Group I and Group II (100.0%, 30.8%, p<0.001; 100.0%, 42.9%, p=0.007, respectively). The frequency of irritable colon syndrome and depression history in Group III were significantly higher compared to Group I (38.5%, 9.3%, p=0.001; 46.2%, 15.0%, p=0.014, respectively). Cyclosporine use was found higher in Group II than in Group III (42.9%, 0%, p=0.031, respectively). Antidepressant use was significantly higher in Group II and Group III compared to Group I (42.9%, 2.8%, p=0.003; 30.8%, 2.8%, p=0.003, respectively).

The FIQ score was higher in Group II and Group III, than in Group I (34.4 vs. 12.4, p<0.001; 58.4, 12.4, p<0.001, respectively). A multivariate logistic regression analysis showed that FIQ score (OR 1.2 [95% CI 1.1–1.3], p<0.001) and antidepressant use (OR 21.0 [95% CI 1.2–357.2], p=0.035) was significant independent predictors of fibromyalgia syndrome, where they were also significant independent predictors of possible fibromyalgia (OR 1.1 [95% CI 1.1–1.2, p=0.002; OR 13.3 [95% CI 1.4–127.4], p=0.025, respectively).

Discussion

The present study found a remarkably high frequency of fibromyalgia in renal transplant patients and findings indicate that FIQ scores and antidepressant use represent independent predictors of fibromyalgia syndrome and possible fibromyalgia in this group of patients.

The ACR 1990 criteria are commonly used to establish a diagnosis of fibromyalgia, which requires the presence of widespread pain for more than three months as well as tender points (in at least 11 of the 18 test points) on physical examination.[11] Comorbidities does not rule out the diagnosis of fibromyalgia. In a study by Middleton et al. a group of patients failing to meet the ACR diagnostic criteria in spite of the presence of fibromyalgia symptoms had been isolated and identified as patients with "possible fibromyalgia".[14] These individuals experience pain in at least four quadrants in addition to positive exam result in six to 10 tenderness points. Based on this categorization, we also opted to define a group of patients with "possible fibromyalgia".

The frequency of fibromyalgia syndrome was found in 10.15% of our 128 renal transplant patients which is two-fold of reported values for the general population as ranged from 0.5% to 5.8%.[3] Furthermore, inclusion of patients with positive physical examination findings, in spite of failing to meet the diagnostic criteria, would further increase the number of subjects with fibromyalgia and fibromyalgia associated status (15.6%). A possible explanation for that is the sample population which included the patients with multi-drug use, frequent visits to hospital due to infections or rejection, fear of graft loss, psychosomatic disorders, and a low threshold for pain due to chronic and serious health conditions.

Patients with a diagnosis of FMS or possible FMS were found to have significantly higher FIQ scores. In addition, the FIQ score is an independent predictor of FMS or possible FMS. The evidence that FIQ score is helpful for establishing the diagnosis of FMS in renal transplant patients those generally exhibit different characteristics compared to general population may have clinical implications. The presence of higher FIQ scores in patients with FMS and possible FMS, which evaluate the effect of pain or other health conditions on daily activities, suggested that FIQ may have a useful role in the assessment and treatment of renal transplant patients for FMS.

In contrast to the association between fibromyalgia syndrome and psychiatric disorders, several studies have reported an increased frequency of depression in renal transplant patients.[15,16] Disorders associated with chronic pain may lead to depression, and nearly 20% of FMS patients have depressive symptoms and experience difficulty in coping with stress that has a negative impact on daily activities.[16] Although conflicting data have been published, it has been proposed that fibromyalgia may be associated with personal or family history of depression in individuals diagnosed with FMS.[17]

In the current study, history of depression was observed higher in patients with FMS than others since no difference in family history was detected. Previous studies have generally focused on populations without chronic conditions, and in a study sample like ours, higher rates of depression than in the general population may be noted even in the absence of family history of depression. In general, our findings support the association between FMS and depression. Therefore, it can be speculated that FMS and depression share some common diagnostic criteria, even if the clinicians decide to use routine anti-depressant therapy without the presence of fibromyalgia in renal transplant patients. Furthermore, the content and dosage of anti-depressants in renal transplant patients diagnosed with FMS requires close monitorization for the potential drug toxicity which might be elucidated by further studies.

Fibromyalgia Syndrome is four to nine times more common in females than males.[4] The lower incidence in males could be associated with the few numbers of tender points leading to incorrect or missed diagnosis.[18] In the study by Buskila et al., females were found to have a lower threshold for pain than males, thus explains the more frequent occurrence of FMS among females.[19] In our study, all patients in Group III were female. Although FMS is known to be more common among females than males in general population, it is interesting to note that all renal transplant patients in our study diagnosed with FMS were female. This is probably due to the small sample size of our study. Nevertheless, this observation is consistent with the reported female predominance in FMS.

The link between fibromyalgia syndrome, fatigue, and sleep disturbances has been well established. Sixty to 90% of FMS patients report sleep disturbance when clinically assessed.[20] The effect of sleep disturbance on the quality of life was examined in previous studies that showed the presence of poor sleep quality was demonstrated in 96% of the participants.[21]

Generally, FMS patients experience fatigue and weakness

more frequently, which may be associated with the increased occurrence of depression and sleep disturbance. Dailey et al. reported significantly increased frequency of both physical and cognitive fatigue in fibromyalgia patients.[22] Although these parameters were not significant predictors in our study, patients diagnosed with FMS had significantly higher frequency of fatigue.

Soft tissue swelling, dysmenorrhea, Raynaud's phenomenon, and restless leg syndrome have been reported to occur in approximately 61%, 41%, 18.2%, and 31% of FMS patients, respectively.[23–26] In our study, there were no significant differences between FMS and control group with regard to these conditions, which is most likely due to low sample size.

Fibromyalgia Syndrome with irritable bowel syndrome (IBS) have been reported to occur together in a significant proportion as 40% of FMS patients.[27] Similarly, our patient groups exhibited significant differences in terms of IBS frequency in which was significantly higher among FMS patients (38.5%).

No specific diagnostic laboratory tests exist for FMS, and laboratory parameters are generally within the normal range and are mostly used for differential diagnosis. Extensive diagnostic testing is rarely required and may lead to clinical confusion.[28] In our study, the evaluation of the mean values of CRP, ESR, creatinine, ALT, calcium, albumin, LDH, TSH, and parathormone in the past 6-month period did not reveal any significant associations with the diagnosis of FMS. In addition, no associations between FMS and the etiology of renal failure were observed.

Currently there is a lack of data on the relationship between fibromyalgia and the use of immunosuppressive treatment in renal transplant patients. Our patients with FMS (Group III) had no use of cyclosporine. This may be due to a switch to other medications such as tacrolimus and sirolimus from cyclosporine due to complications such as calcineurin toxicity or acute rejection.

Conclusions

Fibromyalgia syndrome occurs more commonly in renal transplant patients,particularly in female transplant patients, compared to general population. Depression may co-exist with both of these conditions. The treatment strategy could be established on the relief of sleep disturbance, fatigue and irritable colon syndrome those are observed higher in patients with Fibromyalgia syndrome. We believe that further studies with larger sample size are warranted to confirm these observations.

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