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The frequency of irritable bowel syndrome in predialysis patients with chronic kidney disease and its associated factors

Kronik böbrek hastalığı olan diyaliz öncesi hastalarda irritabl bağırsak sendromu sıklığı ve ilişkili faktörler

Edip Erkuş[1] İbrahim Güney[2] Şeyma Kahyaoğlu[3] Mikail Dağ[2] Yasin Taşdelen[4] Fatih Ergül[2]

[1]University of Health Sciences, Erzurum Region Health Research Center, Nephrology Unit Erzurum/Türkiye

[2]University of Health Sciences Konya City Hospital, Nephrology Unit Konya/Türkiye

[3]University of Health Sciences Konya City Hospital, İnternal Medicine Unit Konya/Türkiye

[4]Aydin State Hospital, Psychiatry Unit Aydİn/Türkiye

ABSTRACT

Aim: This study aimed to determine the frequency of irritable bowel syndrome (IBS) and associated factors, as well as the levels of depression and anxiety, in patients with chronic kidney disease (CKD) not receiving dialysis. It also aimed to explore potential measures to improve quality of life.

Materials and Methods: Patients with stage III–V predialysis CKD were assessed for IBS based on the Rome IV criteria. Anxiety and depression levels were evaluated using the Hamilton Anxiety and Depression Rating Scales. Patients were divided into two groups based on the presence of IBS.

Results: Among 154 patients, 33 (21.4%) had IBS and 121 (78.6%) did not. In the IBS group, 5 patients had no anxiety, 14 had mild, and 14 had major anxiety. In the non-IBS group, 44 had no anxiety, 52 had mild, and 25 had major anxiety. A significant difference in anxiety levels was observed between the two groups, but no significant difference was found in depression levels. Subgroup analysis also revealed a significant difference in anxiety. While no significant differences were found regarding the use of phosphate binders, calcium channel blockers, or beta-blockers, ACE inhibitor/ARB use was significantly higher in the IBS group.

Conclusion: IBS was more frequent in predialysis CKD patients compared to the general population. Anxiety was more common in IBS patients, and ACEI/ARB use was associated with increased IBS frequency. IBS can begin before dialysis, so it should be considered when managing treatment in predialysis CKD patients.

Keywords: ACEI, ARB, anxiety, depression, Irritable bowel syndrome

ÖZ

***Amaç**: Bu çalışmanın amacı, diyaliz almayan kronik böbrek hastalığı (KBH) olan hastalarda irritabl bağırsak sendromu (IBS) sıklığını ve ilişkili faktörleri, ayrıca depresyon ve anksiyete düzeylerini belirlemektir. Ayrıca yaşam kalitesini iyileştirmek için olası önlemleri araştırmak amaçlanmıştır.*

***Gereç ve Yöntem:** Evre III-V prediyaliz KBH'li hastalar, Roma IV kriterlerine göre IBS açısından değerlendirildi. Anksiyete ve depresyon düzeyleri Hamilton Anksiyete ve Depresyon Derecelendirme Ölçekleri kullanılarak değerlendirildi. Hastalar IBS varlığına göre iki gruba ayrıldı.*

***Bulgular:** 154 hastanın 33'ünde (%21,4) IBS varken, 121'inde (%78,6) IBS yoktu. IBS grubunda 5 hastada hiç anksiyete yoktu, 14 hastada hafif ve 14 hastada majör anksiyete vardı. IBS olmayan grupta ise 44 hastada hiç anksiyete yoktu, 52 hastada hafif ve 25 hastada majör anksiyete vardı. İki grup*

Corresponding author: Edip Erkuş
University of Health Sciences, Erzurum Region Health Research Center, Nephrology Unit Erzurum/Türkiye
E-mail: *dr.ediperkus@gmail.com*
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arasında anksiyete düzeylerinde anlamlı bir fark gözlenirken, depresyon düzeylerinde anlamlı bir fark bulunmamıştır. Alt grup analizi de anksiyetede anlamlı bir fark olduğunu ortaya koymuştur. Fosfor bağlayıcılar, kalsiyum kanal blokerleri veya beta blokerlerin kullanımı açısından anlamlı bir fark bulunmazken, ACEI/ARB kullanımı IBS grubunda anlamlı derecede daha yüksekti.

Sonuç: *IBS, diyaliz öncesi kronik böbrek hastalığı (KBH) hastalarında genel popülasyona kıyasla daha sık görülmüştür. Anksiyete, IBS hastalarında daha yaygındı ve ACEI/ARB kullanımı, IBS sıklığının artmasıyla ilişkiliydi. IBS, diyalizden önce başlayabileceğinden, diyaliz öncesi kronik böbrek hastalığı (KBH) hastalarının tedavisini yönetirken göz önünde bulundurulmalıdır.*

Anahtar Sözcükler: *ACEI, ARB, anksiyete, depresyon, İrritabl bağırsak sendromu*

INTRODUCTION

CKD is identified as kidney deterioration or reduced kidney function lasting for three months or longer, regardless of origin (1). Uremia is a syndrome with clinical and laboratory features that develops due to kidney failure and causes malfunctioning of all organs and systems, along with the digestive system (2). Irritable bowel syndrome (IBS) is a frequent functional gastrointestinal disease, although it does not cause vital consequences, it worsens the life quality and can lead to very serious financial costs. In addition, IBS is a gastrointestinal disease described by chronic and recurring abdominal pain, constipation and/or diarrhea, and abdominal bloating (3, 4). Its prevalence has been stated as 70-80% and it has been related with psychiatric problems (5). Gastrointestinal system (GIS) symptoms and findings are very frequent in CKD patients. Studies have shown that the frequency of symptoms is nearly 77-79% (6). However, anomalies in GIS vary depending on the stage of CKD and also the kind of renal replacement therapy (RRT) administered. Moreover, it is not obvious if the reasons of GIS involvement in CKD are related to uremia or the treatment type given. Studies have also shown that psychiatric disorders are more frequent in patients with IBS. Studies about patients with IBS have shown that the frequency of anxiety is doubled and the frequency of depression is tripled. Anxiety was found in 23% and depression was found in 23.3% of these patients (7). While certain studies have shown that anxiety and depression levels are higher in individuals with IBS compared to healthy controls (8, 9), others have not found a significant association between them (10). In this study, our goal was determining the frequency of IBS in patients followed up in outpatient clinic for CKD who have not yet received dialysis treatment, to reveal the factors associated with IBS in these patients, to identify the frequency of depression and anxiety, and to investigate measures that can be taken to increase life quality of the patients depending on the data we found.

MATERIALS and METHODS

A total of 154 patients older the age of 18 having a diagnosis of predialysis stage III-V CKD who applied to the nephrology outpatient clinic were included in this study. Stage 3 CKD is classified as stage 3a if the eGFR is between 45–59 ml/min, and as stage 3b if it is between 30–44 ml/min. Stage 4 CKD is defined by an eGFR of 15–29 ml/min, and stage 5 CKD is defined by an eGFR of less than 15 ml/min (1). Patients with active IBS diagnosis, active depression and anxiety diagnosis, receiving dialysis treatment, having history of malignancy, unwilling to take part in the study and diagnosed with stage I-II CKD were not included in the study.

Patients were included in the study through face-to-face interviews after obtaining written consent. Patients' age, gender, marital status, occupation, presence of diabetes mellitus (DM), primary disease causing CKD, and smoking habits were documented after questioning them. Among the drugs used by the patients; calcium channel blockers, phosphate binders, ACEI/ARBs (Angiotensin-converting enzyme/Angiotensin receptor blocker) and beta-blockers were particularly questioned and they were recorded. The systolic and diastolic blood pressures of the patients at rest were measured and documented. Among the most recent laboratory values during routine outpatient follow-ups; calcium, phosphorus, potassium, albumin, PTH (parathormone), hemoglobin and CRP (C-Reactive Protein) values were recorded. eGFR was calculated using the CKD-EPI method.

IBS and Evaluation of Hamilton Anxiety and Depression Scales

The diagnosis of irritable bowel syndrome was made depending on the Rome IV criteria (11). Rome IV diagnostic criteria is having abdominal

pain that started at least 6 months ago and recurring at least 1 day a week in the last 3 months, associated with at least 2 of the following 3 criteria, which are being associated with defecation but being relieved after defecation, being accompanied by an alteration in the frequency of defecation, with an alteration in the appearance of the stool (12). Additionally, the Hamilton depression rating scale and the Hamilton anxiety rating scale were applied to the patients and their depression and anxiety levels were inquired. Hamilton depression scale is a scale containing verbal questions used to assess the severity of depression symptoms. It includes 17 questions totally and the highest score is 53. Scoring is made depending on the severity of the symptoms seen and total depression score is calculated. While scoring, 0-7 points shows no depression, 8-15 implies mild depression, 16-28 shows moderate depression, and 29 and above suggests severe depression. The validity and reliability of this scoring system in Turkish language are shown by Akdemir et al. (1996) (13). Hamilton Anxiety Scale is a scale developed by Hamilton to assess the severity of anxiety. It includes 14 questions in total and highest score is 56. By scoring depending on the severity of the symptoms, 0-5 points are classified as no anxiety, 6-14 points as minor anxiety, and 15 points and above as major anxiety. The validity and reliability of this scale in Turkish language were shown by Yazıcı et al. (1998) (14).

Statistical Analysis

Statistical calculations were done by using SPSS 22.0 package program. Data were assessed and shown as mean ± standard deviation and frequencies. Kolmogorov-Smirnov test was applied to evaluate the normal distribution of variables. Chi-square test and Fisher's exact test were applied to compare categorical variables. While comparing groups, normally distributed parameters were evaluated with T-test and non-normally distributed parameters were evaluated with Mann Whitney U test. If the P value is less than 0.05 in the analyzes; it was regarded to be statistically significant.

RESULTS

Of the 154 patients with stage III-V predialysis chronic kidney failure included in the study, the number of patients with IBS was 33 (21.4%). Of the 154 patients involved in the study, 78 (50.6%) were male and 76 (49.4%) were female. The average age of patients with IBS was 60.6 ± 11.9 years, while the average age of those without IBS was 59.1 ± 13.1 years. When the two groups were compared according to the age distribution, no statistically significant difference was found (P=0.583). Of the patients with a diagnosis of IBS, 13 (39.3%) were female and 20 (60.7%) were male. Although IBS incidence was higher in male patients, there was no statistically significant difference. No statistically significant difference was found between the groups in terms of gender, employment status, marital status, smoking history, presence of DM, eGFR, calcium, phosphorus, PTH, sodium, potassium, uric acid, hemoglobin, HCO3, CRP, and albumin (Table 1-2). When examined in terms of drug use between the two groups; while there was no statistically significant difference in the use of phosphate-binding drugs, calcium channel blockers, and beta-blockers, a statistically significant difference was detected in terms of ACEI/ARB use (P:0.045). 24 of 33 patients with IBS were using ACEI/ARB and 9 of them were not using them.

When compared according to the Hamilton depression and Hamilton anxiety scales, a significant difference was detected between the groups in terms of anxiety (Table-3) (P: 0.001), but no statistically significant difference was found in terms of depression. If the group with IBS and the group without IBS were examined according to Hamilton's anxiety status; it was seen that anxiety was not detected in 5 of 33 patients in the group with IBS, minor anxiety was detected in 14 and major anxiety in 14. Anxiety was not detected in 44 of the patients in the group without IBS, minor anxiety was detected in 52 and major anxiety in 25.

When patients were examined according to their anxiety, a statistically significant difference was detected between the two groups (P:0.024) (Table-3). No statistically significant difference among the two groups was found in the examination performed by Hamilton depression scale (P: 0.583).

Table-1. Statistical analysis of demographic data

Parameter	IBS (yes) n:33	IBS (no) n:121	P
Age (year)	60.6 ± 11.9	59.1 ± 13.1	0.583
Gender			
Male	20 (60.6%)	58 (47.9%)	0.137
Female	13 (39.4%)	63 (52.1%)	
Profession			
No (housewife or uneducated	26 (78.8%)	89 (73.6%)	
Yes (working or educated)			0.357
	7 (21.2%)	32 (26.4%)	
Smoking			
No	30 (90.9%)	108 (89.3%)	0.538
Yes	3 (9.1%)	13 (10.7%)	
Diabetes Mellitus			
No	18 (54.5%)	83 (68.6%)	0.098
Yes	15 (45.5%)	38 (31.4%)	
Calcium channel blocker			
No			
Yes	12 (36.4%)	55 (45.5%)	0.232
	21 (63.6%)	66 (54.5%)	
Phosphate binding drug			
No			
Yes	31 (93.9%)	105 (86.8%)	0.208
	2 (6.1%)	16 (13.2%)	
ACEI/ARBs			
No	**9 (27.3%)**	**55 (45.5%)**	
Yes	**24 (72.7%)**	**66 (54.5%)**	**0.045**
Beta blocker			
No	21 (63.6%)	76 (62.8%)	0.550
Yes	12 (36.4%)	45 (37.2%)	
Marital status			
Married	26 (78.8%)	99 (81.8%)	
Single	0 (0%)	6 (5%)	0.250
Widowed	7 (21.2%)	16 (13.2%)	

ACE inhibitor/ARBs: (Angiotensin-converting enzyme/Angiotensin receptor blocker)

Table-2. Biochemical laboratory statistical analysis

Parameter	IBS (yes) n:33	IBS (no) n:121	P
SBP (mmHg)	145 (110-200)	150 (110-200)	0.740
DBP (mmHg)	80 (60-105)	80 (50-110)	0.911
PP (mmHg)	60 (34-110)	63 (30-113)	0.801
Urea (mg/dL)	29 (11-84)	31 (11-94)	0.979
e-GFR (ml/min)	37.4 (12-59.3)	34.4 (10-59.9)	0.617
Creatinine (mg/dL)	1.53 (1.03-4.98)	1.9 (1.1-5.8)	0.208
Sodium (mmol/L)	139 (126-144)	140 (128-152)	0.180
CRP (mg/L)	3.65 (0.60-149.8)	3.41 (0.60-150)	0.968
Albumin (g/L)	4.3 (3-5.1)	4.3 (2.6-5)	0.887
Triglyceride (mg/dL)	147.5 (50-500)	159 (41-1255)	0.581
Parathormone (ng/L)	113 (25-358)	102 (18-690)	0.360
Ferritin (µg/L)	121 (30-1460)	115.5 (8-909)	0.330
Uric acid (mg/dL)	6.5 ± 1.5	6.6 ± 1.5	0.815
Calcium (mg/dL)	9.3 ± 0.5	9.2 ± 0.6	0.248
Phosphorus (mg/dL)	3.7 ± 0.6	3.6 ± 0.8	0.937
Potassium (mmol/L)	4.6 ± 0.6	4.7 ± 0.7	0.273
LDLCholesterol(mg/dL)	135.6 ± 39.3	123.8 ± 36.7	0.111
Hemoglobin (g/dL)	12.8 ± 1.9	13.3 ± 2.2	0.437
HCO3 (mmol/L)	21.0 ± 1.9	22.6 ± 3.1	0.095

IBS: Irritable Bowel Syndrome **SBP**: Systolic Blood Pression **DBP:** Diastolic Blood Pression **CRP:** C-Reactive Protein **LDL**: Low-density cholesterol **HCO3**: Bicarbonate **PP**:Pulse pressure

Table-3. Anxiety and Depression Subgroup

	IBS (yes) n:33	**IBS (no) n:121**	**P**
Hamilton depression	10 (0-25)	9 (0-35)	0.333
Hamilton anxiety	**12 (0-32)**	**7 (0-29)**	**0.001**
DEPRESSİON			
No depression	12 (36.4%)	49 (40.5%)	
Mild depression	14 (42.4%)	52 (43%)	
Moderate depression	7 (21.2%)	19 (15.7%)	0.583
Severe depression	0 (0%)	1 (0.8%)	
ANXİETY			**P**
No anxiety	**5 (15.2%)**	**44 (36.3%)**	
Minor anxiety	**14 (42.4%)**	**52 (43%)**	**0.024**
Major anxiety	**14 (42.4%)**	**25 (20.7%)**	

DISCUSSION

Two prominent findings are that while anxiety levels are statistically significant in patients with IBS, depression levels are not statistically significant and ACEI/ARB drug use in patients with IBS is statistically significant compared to patients without IBS.

Mokhtar et al. found sub-threshold depression in 32.1% of the patients in their study with 240 patients with IBS in which constipation was predominant, and they found possible major depression findings in only two patients (15). In a study on the detection of psychiatric problems in patients with IBS, major depression was detected in 33% of the patients and generalized anxiety disorder was found in 40% (16). In a study, it was shown that anxiety was more common in the early stages in patients with IBS, while depression was more frequent in the long-term (17). In their study using the Hamilton Depression and Hamilton Anxiety Scale in hemodialysis patients, Özkul et al. showed that both depression and anxiety scores were higher in patients with IBS compared to those without IBS (18). In our study, the absence of depression in the presence of anxiety in patients with IBS can be explained by the fact that 26 of our patients with IBS did not have an occupation and 7 of them had an occupation. A study by Tetyana et al. showed that depression was more frequent among employed women, which supports the results of our study (19). Furthermore, economic and cultural conditions and social life conditions may cause different results among these studies.

The relationship between the use of calcium channel blockers, phosphate binders, ACEI/ARBs and beta blockers as drugs used and the frequency of IBS was investigated in our study. While there was no statistically significant relationship between the use of calcium channel blockers, beta blockers and phosphate binders and the frequency of IBS, a significant relationship was found between the use of ACEI/ARB drugs and the frequency of IBS. The finding that ARB use increases gastrointestinal symptoms in a study by Basson et al. supports the results in our study (20). There are two other studies with similar results (21, 22). The study conducted by Daniel et al., there was no relationship found between the frequency of IBS and the use of ACEI drugs (23).

The fact that we did not specifically record which ACEI or ARB drugs were used by the patients was one of the limitations of our study.

In this study, we found the prevalence of IBS to be 21.4 % in predialysis stage III-V patients. In the study done by Karahan et al. in 2022 in predialysis stage III-V CKD patients, hemodialysis patients and patients receiving peritoneal dialysis treatment, they found the prevalence of IBS to be 16%, 11% and 12%, respectively (24). In a study directed by Özkul et al. using Rome-IV diagnostic criteria for IBS in 404 patients who received hemodialysis treatment in 2020, they found the prevalence of IBS to be 17.08% (18). In the study directed by Gökalp et al. in 80 patients receiving hemodialysis treatment, they found the frequency of IBS to be 7.5% (25). In the study of Fiderkiewicz et al. in 196 hemodialysis patients, the frequency of IBS and the factors associated with it were examined, and the prevalence of IBS in these patients was found to be 13.8% (26). Likewise, in a study involving 236 dialysis patients, evaluation was made using the Rome-II diagnostic criteria and a diagnosis of IBS was reported in 29.2% of the patient population (27). In a review study

conducted by Saito et al. in the USA, the prevalence of IBS was found to be 10-15% (28). In studies on the prevalence of IBS in Europe and America, the prevalence of IBS was found in the range of 3-25%. In studies done in the Asian continent, the prevalence of IBS was found to be in the range of 0.8-14%, and it was found to be lower than in studies conducted in the European continent (28). In studies, the prevalence of IBS was found to be higher in both predialysis CKD patients and chronic renal failure patients receiving dialysis treatment compared to the healthy population. The prevalence of IBS was found to be higher in predialysis CKD patients than in the patient population receiving dialysis treatment in most of the studies. The reason for this difference may be due to the fact that predialysis patients with chronic renal failure have more anxiety about the course of treatment compared to dialysis patients and the normal population, the fear of starting dialysis or other renal replacement treatments abruptly, and the less frequent follow-ups than dialysis patients. In addition, it may be due to the diagnostic method used for the diagnosis of IBS, the fact that the studies were conducted in different regions, the different dietary habits between the regions, the different patient groups included in the study, and the different inclusion and exclusion criteria from the study.

In our study, the male/female ratio among IBS-diagnosed patients was 3:2. Although the number was higher in males, this difference was not statistically significant. Similar findings have been reported in studies from China, Korea, and India (29, 30). Conversely, studies from Europe and America reported a higher prevalence in females, with a female/male ratio of 2:1 (31–34). In a recent study of 404 hemodialysis patients, 56.5% of those with IBS were female and 43.5% were male (18). These differences may be due to variations in patient populations and geographical factors.

Regarding age, no significant relationship was found between IBS and age in two local studies (25, 35), while another study showed a significantly higher mean age in the IBS group (61.8 vs. 58.2 years) (18). However, our study did not find a significant age-related difference.

Similarly, no association was found between marital status and IBS in previous studies (25, 27), nor in our study, where prevalence was nearly the same across married, single, and widowed individuals.

Although Özden et al. found the highest IBS prevalence among housewives (36), our study showed no significant occupational difference, though IBS was slightly more common in those without employment.

Contrary to expectations, IBS was less common in diabetic patients in our study, which aligns with a few previous findings (25, 27), although Özkul et al. reported a higher IBS prevalence in diabetic patients (18). These discrepancies may result from comorbidities, medications affecting motility, or electrolyte imbalances.

Lastly, similar to other studies (25, 27), we found no significant relationship between IBS and laboratory parameters, including calcium, phosphorus, potassium, albumin, parathormone, hemoglobin, and CRP levels.

CONCLUSION

In conclusion, our study shows that IBS is more common among predialysis stage III-V CKD patients compared to the healthy population. We found that the use of ACEI/ARB drugs is more frequent in patients diagnosed with IBS, and this drug use may increase the frequency of IBS. We also showed that anxiety is very frequent in IBS patients with predialysis CKD. This study shows that IBS is not a problem only in patients with chronic kidney failure under renal replacement therapy, that the disease starts from pre-dialysis periods and that IBS should be considered in predialysis CKD patients when drugs are prescribed. We think that our study will contribute to the literature because there are few or even lack of studies on IBS in predialysis CKD patients.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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