Is Loss of Residual Renal Function Related to Longitudinal Uric Acid and CRP Levels in Peritoneal Dialysis Patients?

Periton Diyalizi Hastalarında, Rezidüel Renal Fonksiyonların Kaybı Boylamsal Ürik Asit ve CRP Düzeyleri ile İlişkili midir?

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ABSTRACT

Aim: Residual renal functions have positive effects on morbidity and mortality among patients undergoing peritoneal dialysis. Our aim is to investigate the effects of baseline laboratory data and longitudinal uric acid and C-reactive protein (CRP) levels on loss of residual renal functions within the first three years of peritoneal dialysis.

Materials and Methods: This is a retrospective cohort study. Thirty-four patients who started peritoneal dialysis due to end-stage renal disease were included. The primary endpoint was loss of residual renal function and was defined as residual urine volume of less than 200 mL/24 hours. Patients were followed for three years after the onset of peritoneal dialysis or until loss of residual renal functions. Demographic and clinical data were recorded retrospectively.

Results: The follow-up period was 32.7 (12.9-36) months. Ten patients lost residual renal function 22.1±9.8 months after the initiation of peritoneal dialysis. Longitudinal uric acid level was 6.1±1.2 mg/dL and longitudinal CRP level was 0.5 (0.3-0.7) mg/dL. In patients with residual renal function loss, baseline sodium and triglyceride were lower, while parathormone were higher. There was no difference between the groups in terms of longitudinal uric acid and CRP levels. Baseline parathyroid hormone [hazard ratio (HR), 1,003; 95% confidence interval (CI) 1,001-1,006; p=0.013], body mass index (HR 0.817; 95% CI 0.684-0.975; p=0.025), and baseline sodium level (HR 0.801; 95% CI; 0.665- 0.965; p=0.019) were risk factors for residual renal function loss.

Conclusion: In peritoneal dialysis patients, residual renal function loss were associated with baseline sodium, triglyceride, and body mass index. There was no correlation between residual renal function loss and longitudinal CRP and uric acid levels. Prospective studies are needed to determine the optimal uric acid and CRP levels.

Keywords: C-reactive protein, peritoneal dialysis, residual renal functions, sodium, uric acid

ÖZ

Amaç: Periton diyalizi yapan hastalarda rezidüel renal fonksiyonların morbidite ve mortalite üzerinde olumlu etkileri vardır. Amacımız, periton diyalizi başlanmadan önceki bazal verilerin ve başlandıktan sonra ilk üç yıldaki boylamsal ürik asit ve C-reaktif protein (CRP) düzeyinin rezidüel renal fonksiyon kaybı üzerindeki etkilerinin araştırılmasıdır.

Gereç ve Yöntem: Retrospektif kohort bir çalışmadır. Son dönem böbrek yetmezliği nedeni ile periton diyalizi başlanan 34 hasta çalışmaya dahil edildi. Primer sonlanım noktası rezidüel renal fonksiyon kaybıydı ve rezidüel idrar miktarının 200 mL/24 saatten az olması olarak tanımlandı. Hastalar, periton diyalizi başlandıktan sonra üç yıl boyunca veya RRF kaybı olana kadar takip edildi. Hastaların klinik ve laboratuvar verileri hasta dosyalarından kaydedildi.

Bulgular: Takip süresi 32,7 (12,9-36) aydı. Periton diyalizi başlandıktan 22,1±9,8 ay sonra 10 hastada rezidüel renal fonksiyon kaybı oldu. Boylamsal ürik asit düzeyi 6,1±1,2 mg/dL ve boylamsal CRP düzeyi 0,5 (0,3-0,7) mg/dL idi. Rezidüel renal fonksiyon kaybı olan hastalarda, bazal sodyum,

trigliserid düzeyleri daha düşük iken parathormon düzeyi daha yüksekti. Her iki grup arasında boylamsal ürik asit ve CRP düzeyi açısından fark yoktu. Periton diyalizi başlanmadan önceki parathormon [tehlike oranı (HR), 1.003; %95 güven aralığı (GA) 1.001-1.006; p=0,013], sodyum (HR 0,801; %95 GA 0,665-0,965; p=0,019) ve vücut kitle indeksi (HR 0,817; %95 GA 0,684-0,975; p=0,025) rezidüel renal fonksiyon kaybı için risk faktörüydü.

Sonuç: Periton diyalizi hastalarında, bazal sodyum, trigliserid ve vücut kitle indeksi rezidüel renal fonksiyon kaybı için risk faktörü olarak bulunmuştur. Rezidüel renal fonksiyon kaybı ile boylamsal CRP ve ürik asit düzeyi arasında ilişki gösterilememiştir. İdeal ürik asit ve CRP düzeyinin belirlenmesi için prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: C-reaktif protein, periton diyalizi, rezidüel renal fonksiyon, sodyum, ürik asit

INTRODUCTION

Peritoneal dialysis (PD) is one of the renal replacement therapies in end-stage renal disease (ESRD). In patients undergoing PD, residual renal function (RRF) has positive effects on anemia, blood pressure and volume control, bone metabolism, and patient survival[1-3]. Therefore, it is important to maintain RRF in PD patients. Loss of RRF occurs earlier in patients with a history of diabetes mellitus (DM), heart failure, and peritonitis[4]. In addition, inflammation has also been found to be associated with loss of RRF[5].

Uric acid is the end product of purine metabolism. It has been shown that uric acid causes endothelial dysfunction, vascular smooth muscle cell damage and inflammation[6-8]. Hyperuricemia is a risk factor for chronic kidney disease, diabetes and hypertension[9-11]. It has been reported that mortality is higher in hemodialysis and PD patients with high uric acid levels[12,13]. In epidemiological studies, it has been shown that the risk of chronic kidney disease increases in people with high uric acid levels[11,14]. In patients with chronic kidney disease, inconsistent results have been reported regarding the effect of uric acid on disease progression[14-17]. In two different studies examining the relationship between the basal uric acid level at the onset of PD and RRF, it was reported that high serum uric acid levels were associated with loss of RRF[18,19]. The number of studies examining the relationship between RRF loss and the longitudinal uric acid level measured until the loss of RRF and the loss of RRF is quite limited. In this study, it was aimed to investigate the effects of clinical and laboratory data before the initiation of PD and longitudinal uric acid and C-reactive protein (CRP) levels in the first three years after the initiation of PD on RRF.

MATERIALS AND METHODS

In this retrospective cohort study, patients older than 18 years of age, who started PD due to ESRD between January 01, 2010 and October 31, 2018, were evaluated retrospectively. Exclusion criteria were: 1. Follow-up of less than three months after the initiation of PD (n=6), 2. Having a kidney transplant (n=12), and 3. Residual urine less than 200 mL/24 hours at the time of the initiation of PD and within three months (n=6). After excluding a total of 24 patients, 34 patients were included in our study. Ege University of Local Ethics Committee (protocol number: 21-11T/21, date: 04.11.2021) was obtained for our study. Patients underwent continuous ambulatory PD or automated PD.

In general, continuous ambulatory PD consisting of 4-5 exchanges/24 hours was applied to the patients. Patients who were treated with automated PD underwent six or more exchanges/24 hours. Dialysis type, dialysate and number of exchanges were determined according to the peritoneal equalization test, Kt/Vurea and ultrafiltration need of the patients. Dialysate glucose concentration and icodextrin requirement were adjusted according to the patient's ultrafiltration need.

In our study, the primary endpoint was loss of RRF. RRF loss was defined as a residual urine volume of less than 200 mL/24 hours. Patients were followed for three years after the initiation of PD or until residual urine volume was <200 mL/24 hours. Patients who switched to another renal replacement therapy, died or were lost to follow-up were followed up to their last registered visit.

Demographic and clinical data (age, gender, height, weight, cause of ESRD, office blood pressure, DM, cardiovascular disease) and medications before the initiation of PD were recorded from patient files. Laboratory data (urea, creatinine, sodium, potassium, calcium, phosphorus, uric acid, albumin, CRP, triglyceride, low-density lipoprotein, parathormone (PTH), ferritin, hemoglobin) belonging to one month before starting PD were obtained from patient files and electronic hospital information management system. The type of PD at the initiation of PD and the weekly total Kt/Vurea measured between the third and sixth months after the initiation of PD were recorded. Body mass index (BMI) was obtained by dividing the patient's body weight (kg) by the square of the height (m). Peritonitis attacks were also recorded. During the follow-up period, serum uric acid and CRP levels which were obtained during approximately quarterly visits were recorded from the patient files. If the patients had active infection during the visit, the CRP and uric acid levels at that visit were not included in the study. If the patient did not attend the visit, the CRP and uric acid levels evaluated within a month before or after that visit were recorded.

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Statistical Analysis

Data analysis was performed with the statistical package program of IBM Statistical Package for the Social Sciences Statistics 25.0 (IBM Corp., Armonk, New York, USA). The distribution of normality for continuous variables was evaluated with the Shapiro-Wilk test. Descriptive statistics were given as frequency (n), percentage (%), mean, standard deviation, median (M), 25th percentile (C_1), 75th percentile (C_3). Longitudinal uric acid and CRP levels were calculated as the mean of uric acid and CRP levels measured during the follow-up period. Independent sample t-test, Mann-Whitney U test and Fisher's exact chi-square test were used for comparisons between the groups. Risk factors for RRF loss were evaluated by cox regression analysis. A p value of <0.05 was considered statistically significant.

RESULTS

The study included 34 patients. Baseline demographic, clinical and laboratory data of the patients are shown in Table 1. The mean age of the patients was 49.1±13.1 years and 58.8% were female. The cause of ESRD was unknown in 38.2% of the patients. The most common causes of ESRD were diabetic nephropathy, hypertensive nephrosclerosis and chronic glomerulonephritis. Three patients had autosomal dominant polycystic kidney disease. At the time of initiation of PD, six patients had DM and two had cardiovascular disease. In tour study, 88.2% of the patients were undergoing continuous ambulatory PD. At the time of the initiation of PD, five patients were receiving allopurinol and 25 patients were receiving diuretics. Before the initiation of PD, baseline creatinine level was 7.5 (6.6-8.7) mg/dL, sodium level was 139.4±3.3 mEq/L, uric acid level was 7.3±1.9 mg/dL, and CRP level was 0.3 (0.2-0.7) mg/dL.

The mean follow-up period was 32.7 (12.9-36) months (Table 2). Longitudinal uric acid level was 6.1±1.2 mg/dL and longitudinal CRP level was 0.5 (0.3-0.7) mg/dL. The rate of patients who had peritonitis attack was 52.9%. RRF loss was observed in 10 patients 22.1±9.8 months after the initiation of PD.

The baseline within data of patients with and without loss of RRF during the follow-up are shown in Table 3. There was no significant difference between the two groups in terms of age, gender, BMI and history of cardiovascular disease. Urea, creatinine, and hemoglobin levels were similar before the initiation of PD. Compared to patients without RRF loss, baseline sodium level was lower in those with RRF loss. Triglyceride was lower in those with RRF loss, while PTH was higher. BMI was lower in those with RRF loss, although it was not statistically significant. There was no difference between the two groups in

terms of longitudinal uric acid and CRP levels.

Baseline uric acid, baseline CRP, longitudinal uric acid and longitudinal CRP levels before the initiation of PD were not risk factors for loss of RRF (Table 4). The presence of DM, history of peritonitis and use of diuretics were also not

Table 1. Demographic and clinical data of the patients before starting peritoneal dialysis	
Age (years)	49.1±13.1
Gender	
Female (n, %)	20 (58.8%)
Cause of end-stage renal disease	
Diabetic nephropathy (n, %)	5 (14.7%)
Hypertensive nephropathy (n, %)	5 (14.7%)
Chronic glomerulonephritis (n, %)	5 (14.7%)
Autosomal dominant polycystic kidney disease	3 (8.8%)
Unknown (n, %)	13 (38.2%)
Other (n, %)	3 (8.8%)
Diabetes mellitus	6 (17.6%)
Cardiovascular disease	2 (5.9%)
PD type	
Continuous ambulatory PD (n, %)	30 (88.2%)
Automated PD (n, %)	4 (11.8%)
Drugs	
Allopurinol (n, %)	5 (14.7%)
Antihypertensive drug (n, %)	27 (79.4%)
Diuretic (n, %)	25 (73.5%)
Phosphorus binding agent (n, %)	29 (85.3%)
Vitamin D analogue (n, %)	17 (50%)
Kt/Vurea	2.5±0.4
Systolic blood pressure (mmHg)	141.2±17.9
Diastolic blood pressure (mmHg)	85 (80–90)
Body mass index (kg/m²)	24.9±4.9
Urea (mg/dL)	170.6±64.3
Creatinine (mg/dL)	7.5 (6.6–8.7)
Sodium (mEq/L)	139.4±3.3
Potassium (mEq/L)	4.7±0.8
Calcium (mg/dL)	9.1 (8.6–9.6)
Phosphorus (mg/dL)	6 (4.9–6.8)
Uric acid (mg/dL)	7.3±1.9
Albumin (g/dL)	4.3 (3.9–4.5)
CRP (mg/dL)	0.3 (0.2–0.7)
Triglyceride (mg/dL)	150±54
LDL (mg/dL)	120 (99–144)
PTH (pg/mL)	337.5 (192.1–477)
Ferritin (ng/mL)	244 (114–430)
Hemoglobin (g/dL)	10.4±1.6

CRP,: C-reactive protein, LDL: Low density lipoprotein, PD: Peritoneal dialysis, PTH: Parathormone

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associated with RRF loss. Before the initiation of PD, baseline sodium (HR 0.801; 95% CI 0.665-0.965, p=0.019), baseline PTH (HR, 1.003, 95% CI 1.001-1.006, p=0.013), and BMI (HR 0.817; 95%CI 0.684-0.975, p=0.025) were the risk factors for RRF loss. In the multivariate cox regression analysis including age at the initiation of PD, gender, DM, history of peritonitis, baseline PTH, baseline sodium, and baseline BMI, none of these parameters were risk factors for RRF loss.

DISCUSSION

In this study, 29.4% of the patients had loss of RRF 22.1±9.8 months after the initiation of PD. Compared to patients without RRF loss, patients with RRF loss had lower baseline sodium, lower triglyceride levels and higher PTH levels. Longitudinal uric acid and CRP levels were similar between the two groups. Baseline uric acid and CRP and longitudinal uric acid and CRP levels were not risk factors for RRF loss. Low sodium level, high PTH level, and low BMI at the initiation of PD were risk factors for RRF loss.

Table 2. Follow-up data in the first three years of peritoneal dialysis

Follow-up time (months)	32.7 (12.9-36)
Those with RRF loss (n, %)	10 (29.4%)
Time of RRF loss (month)	22.1±9.8
Longitudinal uric acid (mg/dL)	6.1±1.2
Longitudinal CRP (mg/dL)	0.5 (0.3-0.7)
History of peritonitis (n, %)	18 (52.9%)

CRP: C-reactive protein, RRF: Residual renal function

Table 3. Baseline clinical and laboratory data of patients with and without residual renal function loss at follow-up

	Without RRF loss (n=24)	With RRF loss (n=10)	p
Age (years)	46.7 (42.1-60)	54.5 (29-63.3)	0.926
Male (n, %)	8 (33.3%)	6 (60%)	0.252
Diabetes mellitus (n, %)	5 (20.8%)	1 (10%)	0.644
Cardiovascular disease (n, %)	2 (8.3%)	0 (0%)	1
History of peritonitis (n, %)	11 (45.9%)	7 (70%)	0.270
Peritoneal dialysis type			
Continuous ambulatory PD (n, %)	21 (87.5%)	9 (90%)	1.000
Automated PD (n, %)	3 (12.5%)	1 (10%)	
Antihypertensive drug use (n, %)	5 (20.8%)	2 (20%)	1.000
Allopurinol use (n, %)	3 (12.5%)	2 (20%)	0.618
Diuretic use (n, %)	7 (29.2%)	2 (20%)	0.692
Duration of follow-up (months)	36 (9.2-36)	22 (15.1-31.9)	0.079
Kt/Vurea	2.5±0.5	2.4±0.3	0.370
Systolic blood pressure (mmHg)	139.4±17.9	146.1±18.3	0.349
Diastolic blood pressure (mmHg)	82.5 (80-90)	90 (80-100)	0.437
Body mass index (kg/m²)	25.9±5.1	22.4±3.8	0.052
Urea (mg/dL)	168.3±45	176.1±99.8	0.754
Creatinine (mg/dL)	7.8 (7-8.7)	6.7 (5.4-7.3)	0.101
Sodium (mEq/L)	140.3±3.2	137.7±3.2	**0.042**
Potassium (mEq/L)	4.8±0.9	4.7±0.8	0.682
Calcium (mg/dL)	9±0.9	9±1.4	0.871
Phosphorus (mg/dL)	6 (5.4-6.7)	5 (4.7-7.1)	0.592
Uric acid (mg/dL)	7.3±1.8	7.3±2.2	0.997
Albumin (g/dL)	4.4 (4-4.6)	4 (3.8-4.3)	0.142
CRP (mg/dL)	0.3 (0.2-0.4)	0.7 (0.3-0.9)	0.068
Triglyceride (mg/dL)	161.6±50.5	115.3±52.6	0.048
LDL (mg/dL)	121 (108-144)	99.5 (82-130)	0.175
PTH (pg/mL)	288.7±153.8	605±253.7	0.016
Hemoglobin (g/dL)	10.6±1.4	10.1±2.2	0.461
Ferritin (ng/mL)	224 (119-413)	222 (95-714)	0.964
Longitudinal uric acid (mg/dL)	6.4±1.2	5.6±1.2	0.099
Longitudinal CRP (mg/dL)	0.6 (0.3-0.7)	0.5 (0.3-0.8)	0.669

CRP: C-reactive protein, LDL: Low density lipoprotein, PD: Peritoneal dialysis, PTH: Parathormone

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Table 4. Risk factors associated with loss of residual renal function

	HR (95% CI)	p	Model p
Age (years)	0.997 (0.949-1.047)	0.905	0.905
Female gender	1.556 (0.438-5.528)	0.494	0.491
Diabetes mellitus	0.439 (0.055-3.470)	0.435	0.422
Body mass index (kg/m^2)	0.817 (0.684-0.975)	0.025	0.023
Automated PD	0.792 (0.100-6.262)	0.825	0.825
Allopurinol use	1.426 (0.302-6.745)	0.654	0.653
Diuretic use	1.086 (0.230-5.122)	0.917	0.917
Kt/Vurea	0.638 (0.133-3.065)	0.574	0.573
Sodium (mEq/L)	0.801 (0.665-0.965)	0.019	0.018
Uric acid (mg/dL)	1.054 (0.675-1.646)	0.816	0.816
CRP (mg/dL)	1.673 (0.415-6.754)	0.469	0.464
Triglyceride (mg/dL)	0.981 (0.962-1.001)	0.068	0.075
PTH (pg/mL)	1.003 (1.001-1.006)	0.013	0.006
Longitudinal uric acid (mg/dL)	0.685 (0.412-1.137)	0.143	0.141
Longitudinal CRP (mg/dL)	1.064 (0.401-2.822)	0.901	0.901
CRP: C-reactive protein, LDL: Low density lipoprotein, PD: Peritoneal dialysis, PTH: Parathormone			

Loss of RRF develops in PD patients over time due to risk factors such as peritonitis, DM, and heart failure. In PD patients, RRF was found to be associated with better volume and blood pressure control, improvement of anemia, phosphorus control, and better survival[1-3]. Therefore, long-term preservation of RRF is sought in PD patients.

In our study, patients with RRF loss had lower sodium and triglyceride levels. The BMI and albumin levels of these patients were also lower, although not statistically significant. These laboratory findings are parameters related to nutrition. In addition, low triglyceride and sodium levels were found to be risk factors for RRF loss. Our findings support that RRF loss may be associated with malnutrition. In one study, malnutrition-inflammation complex syndrome was found to be associated with loss of RRF[20]. Palomo-Piñón et al.[21] showed that baseline CRP level is high and albumin level is low in patients with RRF loss, and baseline CRP and albumin levels are risk factors for RRF loss. However, in our study, no correlation was found between baseline and longitudinal CRP levels and RRF.

Hyperuricemia causes inflammation, endothelial dysfunction and oxidative stress[22]. As hyperuricemia is associated with inflammatory markers such as interleukin-6, CRP, and tumor necrosis factor-alpha, it has been suggested that uric acid has a role in inflammatory processes[8]. In the general population, it has been shown that hyperuricemia is associated with hypertension, cardiovascular diseases and mortality[23,24]. In the CKD process, the results of studies on its relationship with disease progression and patient survival are contradictory[14-17].

The number of studies examining the relationship between uric acid level and clinical outcomes in PD patients is very few. Park et al.[18] Showed that there was a correlation between baseline uric acid level and loss of RRF at the end of 24-month follow-up. In a more recent study, a U-shaped relationship was found between baseline uric acid level and loss of RRF[19]. Most of the studies in the literature have evaluated the relationship between uric acid level at the initiation of PD and loss of RRF. In the only study examining the relationship between longitudinal uric acid levels and RRF after the initiation of PD, it was reported that longitudinal uric acid levels of <6.77 mg/dL and ≥7.64 mg/dL were associated with loss of RRF[25]. In our study, however, no relationship could be demonstrated between longitudinal uric acid level and loss of RRF. In our study, a relationship between RRF loss and longitudinal uric acid level may not have been determined due to the lower mean uric acid level and the small number of patients.

Study Limitations

The limitations of our study are its retrospective nature and the small number of patients. On the other hand, the longitudinal evaluation of uric acid and CRP levels can be considered as the strengths of our study.

CONCLUSION

In conclusion, while loss of RRF was associated with low baseline sodium, triglyceride and BMI in PD patients, no relationship could be shown between longitudinal CRP and uric acid levels and RRF loss. Larger, prospective studies are

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needed to determine the effects of hyperuricemia on RRF loss and, in this respect, to determine the target uric acid level.

Ethics

Ethics Committee Approval: The study were approved by the Ege University of Local Ethics Committee (protocol number: 21-11T/21, date: 04.11.2021).

Informed Consent: It is a retrospective cohort study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ç., M.S.D., M.Ö., Design: A.Ç., M.Y., M.S.D., G.A., H.T., M.Ö., Data Collection or Processing: A.Ç., Z.A., M.Y., M.S.D., G.A., H.T., M.Ö., Analysis or Interpretation: A.Ç., Z.A., M.Y., G.A., H.T., M.Ö., Literature Search: A.Ç., Z.A., M.Y., Writing: A.Ç., M.Y., M.S.D., H.T., M.Ö.

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