The impact of dialysis type on biomarkers for cardiovascular diseases

Diyaliz tipinin kardiyovasküler biyobelirteçler üzerine etkisi

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ABSTRACT

Objectives: The impact of dialysis type on the biomarkers that reflect the severity of cardiovascular diseases is not clearly known. We aimed to investigate the effect of dialysis type on biomarkers of cardiovascular diseases in patients with end-stage renal disease (ESRD).

Study design: The study included 108 patients who had been on dialysis treatment (57 patients receiving hemodialysis, 51 patients receiving peritoneal dialysis) for ESRD for at least three months. Blood samples were collected just after the dialysis. Serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), cardiac troponin I (TnI), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and plasma fibrinogen levels were measured and compared between the two dialysis groups.

Results: The two dialysis groups were similar with respect to age and gender. The frequency of hypertension was significantly higher in patients receiving peritoneal dialysis. This group also had higher total cholesterol, HDL cholesterol, LDL cholesterol, and hemoglobin levels. Serum levels of NT-proBNP, hs-CRP, IL-6, and TNF-α, and plasma fibrinogen levels were similar in the two dialysis groups ($p>0.05$), but TnI was significantly higher in patients receiving peritoneal dialysis ($p=0.04$). Comparison of the patient subgroups based on the duration of dialysis (<12 months, 12-36 months, and >36 months) showed that longer dialysis duration was associated with significantly lower values of NT-proBNP, TNF-α, and hs-CRP ($p<0.05$).

Conclusion: The dialysis type does not affect serum NT-proBNP, hs-CRP, IL-6, TNF-α, and plasma fibrinogen levels, but TnI level is higher in patients treated with peritoneal dialysis.

ÖZET

Amaç: Diyaliz tipinin kardiyovasküler hastalık ciddiyetini yansıtan biyobelirteçler üzerindeki etkisi tam olarak bilinmemektedir. Bu çalışmada, son dönem böbrek hastalarında diyaliz tipinin kardiyovasküler hastalık belirteçleri üzerindeki etkisi araştırıldı.

Çalışma planı: Çalışmaya, son dönem böbrek hastalığı nedeniyle en az üç aydır kronik diyaliz tedavisi görmekte olan 108 hasta alındı. Elli yedi hasta hemodiyaliz tedavisi görürken, 51 hastaya periton diyalizi uygulanıyordu. Kan örnekleri diyalizin hemen sonrasında toplandı. Serumda beyin natriüretik peptidi N-terminal prohormonu (NT-proBNP), yüksek duyarlıklı C-reaktif protein (hs-CRP), kardiyak tropinin I (TnI), interlökin-6 (IL-6), tümör nekroz faktörü-alfa (TNF-α) düzeyleri ve plazma fibrinojen düzeyleri ölçüldü ve iki diyaliz grubu arasında karşılaştırıldı.

Bulgular: İki diyaliz grubu yaş ve cinsiyet açısından benzerdi. Periton diyalizi uygulanan hastalarda hipertansiyon sıklığı ve total kolesterol, HDL-kolesterol, LDL-kolesterol ve hemoglobin düzeyleri anlamlı derecede daha yüksek idi. Serum NT-proBNP, hs-CRP, IL-6, TNF-α düzeyleri ve plazma fibrinojen düzeyi iki diyaliz grubu arasında anlamlı farklılık göstermedi; serum TnI düzeyi ise periton diyalizi grubunda anlamlı derecede daha yüksek bulundu ($p=0.04$). Tüm hastalar diyaliz süresine (<12 ay, 12-36 ay ve >36 ay) göre gruplandırılarak karşılaştırıldığında, daha uzun diyaliz süresinde NT-proBNP, TNF-α ve hs-CRP düzeyleri anlamlı derecede daha düşük bulundu ($p<0.05$).

Sonuç: Uygulanan diyaliz tipi serum NT-proBNP, hs-CRP, IL-6 ve TNF-α ve plazma fibrinojen düzeylerini etkilememekte, ancak TnI düzeyi periton diyalizi uygulanan hastalarda daha yüksek seyretmektedir.

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Patients with end-stage renal disease have significantly higher mortality and morbidity rates compared to normal population. Despite the advances in diagnosis and treatment, cardiovascular diseases are still the leading cause of death in this patient group.[1,2] The effect of dialysis type on cardiovascular mortality and morbidity in ESRD patients is also controversial.[3,4]

Brain natriuretic peptide (BNP) is a hormone secreted by ventricular myocytes in pathological overload conditions. Serum BNP level has been shown to increase in heart failure and significant ischemia. Increased BNP levels have been demonstrated in several studies, suggesting a prognostic value of BNP in ESRD.[5,6]

There are abundant data showing a close relationship between inflammation and cardiovascular mortality and morbidity. High-sensitivity C-reactive protein (hs-CRP) is a diagnostic indicator of systemic inflammation. Interleukin-6 and tumor necrosis factor-alpha are proinflammatory cytokines that induce synthesis of CRP in the liver.[7,8] All these biomarkers have been shown to predict cardiovascular complications and mortality in patients with ESRD.[5,6]

Cardiac troponin I is a strong diagnostic and prognostic marker of the severity of myocardial injury in patients with normal renal function.[9,10] Although the power of TnI to diagnose myocardial infarction is lower in ESRD patients, it has been shown to have a prognostic value even in this patient group.[11]

Fibrinogen, the precursor of fibrin which is the major protein in the coagulation system, plays a great role in blood viscosity and platelet aggregation.[12] Large epidemiological studies have demonstrated a significant association between plasma fibrinogen levels and coronary artery disease.[13,14]

In this study, we aimed to compare serum and plasma levels of biomarkers which have been shown to have a prognostic value in cardiovascular diseases in patients under different dialysis treatment methods.

PATIENTS AND METHODS

The study included 108 patients with ESRD who had been on chronic dialysis treatment for at least three months. All the patients were receiving dialysis using a low-flux synthetic membrane dialyzer and bicarbonate dialysate bath. The local ethics review board approved the study.

Abbreviations:

EF	*Ejection fraction*
ESRD	*End-stage renal disease*
hs-CRP	*High-sensitivity C-reactive protein*
IL-6	*Interleukin-6*
TNF-α	*Tumor necrosis factor-alpha*
TnI	*Troponin I*

The patients were divided into two groups based on the type of dialysis treatment: 57 patients received hemodialysis, and 51 patients received peritoneal dialysis. Patients with a known cardiovascular disease (coronary artery disease, history of coronary revascularization, stroke, and heart failure), malignancy, active infection or inflammatory disease were excluded from the study. Data on baseline characteristics and medical history were obtained from patient interviews and hospital charts. Hypertension was defined as active use of antihypertensive drugs or documentation of blood pressure higher than 140/90 mmHg. Diabetes mellitus was defined as a fasting glucose level over 126 mg/dl or glucose level over 200 mg/dl at any measurement or active use of antidiabetic drugs or insulin. Smoking was defined as current smoking. Family history for coronary artery disease was defined as the presence of coronary artery disease or sudden death in a first-degree relative before the age of 55 years for men and 65 years for women.

Blood samples for measurement of serum NT-proBNP, hs-CRP, TnI, IL-6, TNF-α, and plasma fibrinogen levels were collected just after the dialysis. Whole blood samples were centrifuged and the aliquots were stored at -80 °C. Serum NT-proBNP levels were measured via the ELISA method using Biomedica kits. Serum levels of hs-CRP and TnI were evaluated with ELISA kits (DRG International, Inc., USA) using the high-sensitivity enzyme immunoassay method. Serum levels of TNF-α and IL-6 were measured using the Biosource ELISA kits. Plasma fibrinogen levels were determined by using the Tokra reagent of M.T.I. F-2610 fibrinogen on a M.T.I. 1C coagulometer.

Statistical analysis

Categorical variables were presented as numbers and percentages and compared using the chi-square test. The Kolmogorov-Smirnov test was performed for checking the distribution of numeric parameters. Continuous variables were presented as mean ± standard deviation if normally distributed and as median with 25th and 75th percentiles otherwise. Independent continuous variables were compared using the t test, ANOVA, Mann-Whitney U-test, or Kruskal-Wallis test where appropriate, and a *post-hoc* comparison was also performed. Potential factors for elevations in the biomarkers were evaluated with multivariate linear regression analyses. A P value of <0.05 was con-

Table 1. Baseline characteristics of the dialysis patients

	Hemodialysis (n=57)			Peritoneal dialysis (n=51)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			43.8±13.7			46.6±13.7	0.29
Gender							0.14
Male	37	64.9		26	51.0		
Female	20	35.1		25	49.0		
Weight (kg)			64.9±13.7			69.5±15.2	0.10
Smoking	13	22.8		5	9.8		0.07
Hypertension	35	61.4		45	88.2		**0.001**
Diabetes mellitus	8	14.0		6	11.8		0.73
Duration of dialysis (months)†			51 (3-190)			38 (3-130)	0.14
Total cholesterol (mg/dl)			168.0±45.5			198.3±48.8	**0.001**
HDL cholesterol (mg/dl)			34.1±10.3			38.9±9.8	**0.015**
LDL cholesterol (mg/dl)			98.5±33.3			123.8±39.4	**<0.001**
Triglycerides (mg/dl)†			156 (106-212)			152 (106-207)	**0.98**
Hemoglobin (g/dl)			10.4±2.1			11.2±1.9	**0.04**
Creatinine (mg/dl)			8.6±2.6			9.1±3.0	0.29
Fasting blood glucose (mg/dl)			103.8±46.4			95.0±24.9	0.23
Uric acid (mg/dl)			5.7±1.1			5.7±1.2	0.92
Parathyroid hormone (pg/ml)†			264 (139-504)			380 (142-616)	0.40
Calcium (mg/dl)			8.9±0.9			9.1±0.7	0.33
Phosphorus (mg/dl)			4.8±1.3			4.9±1.1	0.63
Alkaline phosphatase (U/l)			128.4±54.2			113.3±49.0	0.13
Left ventricular ejection fraction (%)			62.3±4.5			61.0±5.9	0.18
Medications							
Erythropoetin	34	59.7		29	56.9		0.77
Salicylate	11	19.3		7	13.7		0.44
Beta-blocker	14	24.6		20	39.2		0.089
Angiotensin-converting enzyme inhibitor/ Angiotensin receptor blocker	9	15.8		15	29.4		0.23
Calcium channel blocker	24	42.1		32	62.8		**0.032**
Hypolipidemic‡	10	17.5		14	27.5		0.22
Vitamin D	24	42.1		30	58.8		0.083
Phosphate binders#	37	64.9		33	64.7		0.98

†Median with 25th and 75th percentiles; ‡Statins and/or fibrates; #Including Ca-acetate, Ca-carbonate, Sevelamer, and combined drugs.

sidered statistically significant. All statistical calculations were made using the SPSS (for Windows ver. 13.0) statistical software.

RESULTS

Baseline clinical characteristics of the patients are shown in Table 1. The frequency of hypertension was significantly higher in patients receiving peritoneal dialysis. This group also had higher total cholesterol, HDL cholesterol, LDL cholesterol, and hemoglobin levels. The two groups were similar in use of medications except for calcium channel blockers ($p<0.05$).

Comparison of the two dialysis groups with respect to ESRD etiologies is shown in Table 2. There were no etiological differences between the two groups ($p>0.05$).

Table 2. Etiologies of end-stage renal disease in the two dialysis groups

	Hemodialysis (n=57)		Peritoneal dialysis (n=51)	
	n	%	n	%
Hypertensive nephropathy	6	10.5	13	25.5
Diabetic nephropathy	8	14.0	6	11.8
Glomerulonephritis	17	29.8	10	19.6
Chronic pyelonephritis	5	8.8	1	2.0
Nephrolithiasis	1	1.8	4	7.8
Polycystic kidney disease	2	3.5	1	2.0
Amyloidosis	10	17.5	12	23.5
Multiple myeloma	5	8.8	–	
Unknown	3	5.3	4	7.8

Serum levels of NT-proBNP, hs-CRP, IL-6, and TNF-α, and plasma fibrinogen levels were similar in the two groups (p>0.05, Table 3). However, TnI level was significantly higher in patients receiving peritoneal dialysis (p=0.04).

The patients were also divided in subgroups based on the duration of dialysis, that is <12 months (n=20), 12-36 months (n=37), and >36 months (n=51). In this comparison, IL-6, fibrinogen, and TnI levels did not differ between the three groups. However, NT-proBNP, TNF-α, and hs-CRP levels showed significant differences. In *post-hoc* tests, longer dialysis duration was associated with lower values of NT-proBNP, TNF-α, and hs-CRP (Table 4).

In multivariate linear regression analysis, there was not any independent predictor of TnI and TNF-α. The only independent predictor of NT-proBNP was left ventricular ejection fraction (t=-2.871, p=0.005), and the independent predictors of hs-CRP were EF (t=-2.107, p=0.038) and serum creatinine (t=2.520, p=0.013).

DISCUSSION

To date, many studies have tried to determine the ideal type of dialysis with better survival rates. However, these studies have yielded conflicting data regarding the survival benefit of one type over the other.[3,4,15,16] The main reason of increased mortality and morbidity rates in patients with ESRD is cardiovascular diseases.[1,2] Cardiovascular diseases are progressive diseases related with many pathophysiologic mechanisms such as inflammation, increased wall stress, volume and pressure overload, and myocardial injury. Biomarkers reflecting the extent and severity of these pathophysiologic mechanisms may help determine the ideal dialysis type. For this aim, we compared serum levels of NT-proBNP, hs-CRP, IL-6, TNF-α, TnI, and plasma levels of fibrinogen in patients receiving hemodialysis or peritoneal dialysis. We found higher serum TnI levels in patients who had been under peritoneal dialysis. The other biomarkers exhibited similar levels in the two dialysis groups.

It is well known that inflammation significantly contributes to arterial damage in ESRD patients. Increased incidence of traditional risk factors such as diabetes mellitus, hypertension, and dyslipidemia among ESRD patients, low-grade infection, adrenergic overactivity, and repeated exposure to dialysis filters induce inflammation in these patients.[17] We evaluated three inflammatory markers to compare the impact of dialysis types on the degree of inflammation: hs-CRP, IL-6, and TNF-α. These markers did not show significant differences between the two dialysis groups. The results of the studies investigating the degree of inflammation with different dialysis types are

Table 3. Comparison of the two dialysis groups with respect to the levels of biomarkers

	Hemodialysis (n=57)	Peritoneal dialysis (n=51)	
	Mean±SD/ Median (Q_1-Q_3)	Mean±SD/ Median (Q_1-Q_3)	*p*
N-terminal proBNP (fmol/ml)	190 (138-250)	169 (84-310)	0.32
Interleukin-6 (pg/ml)	5.9 (1.8-11.1)	7.4 (3.1-23.5)	0.21
Fibrinogen (mg/dl)	329.7±122.0	344.5±120.1	0.53
Tumor necrosis factor-alpha (pg/ml)	30.8±12.2	33.3±6.2	0.18
High-sensitivity C-reactive protein (mg/l)	5.1 (2.8-12.9)	8.1 (4.6-11.5)	0.35
Troponin I (ng/ml)	0.7 (0.6-0.8)	0.9 (0.7-0.9)	**0.04**

Table 4. Comparison of the levels of biomarkers in relation to the duration of dialysis

	Duration of dialysis			
	Group 1 <12 months (n=20)	Group 2 12-36 months (n=37)	Group 1 >36 months (n=51)	
	Mean±SD/ Median (Q_1-Q_3)	Mean±SD/ Median (Q_1-Q_3)	Mean±SD/ Median (Q_1-Q_3)	*p*
N-terminal proBNP (fmol/ml)	196 (91-403)	143 (65-202)	191 (150-299)	**0.024****
Interleukin-6 (pg/ml)	7.9 (3.6-26.2)	7.2 (2.5-13.2)	5.9 (1.5-12.3)	0.60
Fibrinogen (mg/dl)	312±121	349±107	337±130	0.56
Tumor necrosis factor-alpha (pg/ml)	36.2±10.2	32.7±11.2	29.7±7.8	**0.036***
High-sensitivity C-reactive protein (mg/l)	11.2 (4.9-15.3)	7.9 (3.9-12.7)	6.0 (2.1-10.0)	**0.018*****
Troponin I (ng/ml)	0.7 (0.6-1.0)	0.8 (0.76-0.9)	0.7 (0.7-0.8)	0.57

*p=0.032 between group 1 and 3 by *post-hoc* Tukey Test; **p=0.006 between group 2 and 3, and ***p=0.01 between group 1 and 3 by Mann-Whitney U-test with Bonferroni correction.

not clear. Higher levels of inflammatory parameters have been reported with hemodialysis[18] or peritoneal dialysis.[19] Tonbul et al.[20] found similar CRP and fibrinogen levels and erythrocyte sedimentation rates in their study comparing peritoneal dialysis and hemodialysis. Hence, large scale studies are required to draw a definite conclusion regarding this issue.

End-stage renal disease increases ventricular wall stress due to volume and pressure overload on the heart. The treatment method which effectively decreases this volume overload also decreases wall stress. Acute changes in blood pressure during dialysis also affect this wall stress. The severity of wall stress can be determined by NT-proBNP levels. The prognostic value of NT-proBNP has been shown clearly in patients with ESRD.[21,22] In this study, NT-proBNP levels were similar in the two dialysis groups. This finding proves once more that both dialysis methods are equally effective in removing extra volume in patients with ESRD.

Myocardial cells do not have regenerative capacity and permanently degenerate after an injury. Troponin I is a unique molecule for myocardial cells, which is released into the circulation only in case of definite myocardial injury. The chronic myocardial injury during dialysis treatment causes continuous release of small amounts of TnI into the circulation. Several studies have documented the prognostic value of TnI in patients with ESRD.[11,23] In our study, we found higher TnI levels in patients receiving peritoneal dialysis. Left ventricular hypertrophy which is very common in ESRD patients was found to be associated with higher levels of cardiac troponins.[24] We did not assess left ventricular hypertrophy in our study, but the incidence of hypertension was higher in the peritoneal dialysis group. This difference may account for higher TnI levels in patients receiving peritoneal dialysis.

Increased plasma fibrinogen levels have been found to be related with increased cardiovascular mortality and morbidity rates.[13,14] The active role of fibrinogen in blood viscosity and coagulation may lead to adverse cardiovascular events. Both ESRD and dialysis treatment lead to hematological changes and increases in fibrinogen levels. The extent of this increase in fibrinogen level induced by dialysis treatment may differ between hemodialysis and peritoneal dialysis. Malyszko et al.[25] found significantly higher fibrinogen levels in patients receiving peritoneal dialysis compared to those receiving hemodialysis. In contrast, Tonbul et al.[20] found similar fibrinogen levels in these two dialysis groups. Similarly, we did not find a significant difference in fibrinogen levels between the two dialysis groups. On the other hand, hemoglobin level was lower in the hemodialysis group. This may be explained by increased red blood cell deformation during hemodialysis and by the cumulative effect of small amounts of blood loss during each procedure.

In multivariate linear regression analysis, we found that EF was the only independent predictor of NT-proBNP. This finding is not surprising, since NT-proBNP is directly correlated with the systolic performance of the left ventricle. We also found that EF and serum creatinine level were the independent predictors of hs-CRP. Higher hs-CRP level may be a reflection of higher coronary atherosclerotic burden in patients with lower EF and higher creatinine level.

The relatively small number of the study population may be a limitation for the interpretation of the results. The other limitation of the study is its cross-sectional nature. We did not repeat the measurements for the biomarkers. Nonetheless, we included patients who had been under dialysis treatment for at least three months, so there was sufficient time for both dialysis types to show dialysis-induced effects on the biomarker levels. When we compared the biomarker levels based on the duration of dialysis, we found that NT-proBNP, TNF-α, and hs-CRP levels were significantly different between the subgroups. Patients who had been under dialysis treatment for >36 months had significantly lower levels of NT-proBNP, TNF-α, and hs-CRP compared to those with a dialysis duration of <12 months. This finding shows a decline in the responses such as inflammation, apoptosis, and wall stress as the dialysis time increases. This may be a reflection of adaptation process to dialysis treatment. Despite its limitations, we think that this study may provide more insight into the effects of dialysis type on biomarkers used for cardiovascular diseases.

In conclusion, the dialysis type does not affect serum NT-proBNP, hs-CRP, IL-6, TNF-α, and plasma fibrinogen levels, but TnI level is higher in patients treated with peritoneal dialysis. Based on this finding, hemodialysis may be preferred in patients with extensive myocardial injury. Further studies with larger patient groups are required to draw definite conclusions.

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Key words: Biological markers; cardiovascular diseases; dialysis/adverse effects; kidney failure, chronic/complications.

Anahtar sözcükler: Biyolojik belirteç; kardiyovasküler hastalık; diyaliz/yan etki; böbrek yetersizliği, kronik/komplikasyon.