Prognostic value of troponin T and homocysteine in patients with end-stage renal disease

Son dönem böbrek hastalarında troponin T ve homosistin düzeylerinin prognostik değeri

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Objectives: The most important cause of increased mortality in end-stage renal disease (ESRD) is cardiovascular diseases. We investigated the prognostic value of cardiac troponin T (cTnT) and homocysteine in the long-term follow-up of ESRD patients.

Study design: The study included 78 patients (54 males, 24 females; mean age 53.2±16.6 years) with ESRD, who had been on hemodialysis treatment for at least three months. Baseline troponin T and homocysteine levels were measured and the patients were followed-up from March 2002 to May 2007 for major adverse cardiovascular events (MACE).

Results: Major adverse cardiovascular events occurred in 26 patients (33.3%), including cerebrovascular events (n=3, 3.9%), congestive heart failure (CHF) (n=18, 23.1%), coronary artery disease (CAD) (n=19, 24.4%), and death (n=19, 24.4%). Two-thirds of diabetic patients developed MACE and the mean age in the MACE group was significantly greater (p<0.001). Troponin T levels were significantly higher in patients who developed MACE (0.21±0.43 ng/ml *vs* 0.06±0.28 ng/ml, p=0.002), whereas homocysteine levels did not differ significantly between the two groups (p=0.82). For a cutoff value of 0.10 ng/ml, cTnT was ≥0.1 ng/ml in 17 patients (21.8%), and <0.10 ng/ml in 61 patients (78.8%). Patients having a cTnT level of ≥0.10 ng/ml showed significantly higher rates of MACE (64.7% vs 24.6%; p=0.003), CHF (47.1% vs 16.4%; p=0.02), and death (52.9% vs 16.4%; p=0.004). There was also a greater tendency to CAD in this group (41.2% vs 19.7%, p=0.10). In multivariate logistic regression analysis, age and diabetes mellitus were the independent predictors of MACE development.

Conclusion: Homocysteine levels cannot predict MACE in ESRD patients in the long-term follow-up. Despite a significantly higher incidence of MACE in patients with high cTnT levels, cTnT was not an independent predictor of cardiovascular outcome.

Key words: Biological markers/blood; cardiovascular diseases; homocysteine/blood; kidney failure, chronic/complications; renal dialysis; troponin T/blood.

Amaç: Son dönem böbrek hastalığında (SDBH) artmış mortalitenin en önemli nedeni kardiyovasküler hastalıklardır. Bu çalışmada. SDBH hastalarının uzun dönem takibinde kardiyak troponin T (cTnT) ve homosistin düzeylerinin prognostik değeri araştırıldı.

Çalışma planı: Çalışmaya, en az üç aydır hemodiyaliz tedavisi görmekte olan, SDBH'li 78 hasta (54 erkek, 24 kadın; ort. yaş 53.2±16.6) alındı. Çalışmanın başında tüm hastalarda cTnT ve homosistin düzeyleri ölçüldü ve hastalar Mart 2002'den Mayıs 2007'ye kadar olumsuz kardiyovasküler olay (OKVO) gelişimi açısından takip edildi.

Bulgular: Yirmi altı hastada (%33.3) OKVO gelişti (3 serebrovasküler olay, %3.9; 18 konjestif kalp yetersizliği, %23.1; 19 koroner arter hastalığı, %24.4; 19 ölüm, %24.4). Diyabetli hastaların 2/3'ünde OKVO görüldü (p<0.001); ayrıca, OKVO gelişen grupta ortalama yaş anlamlı derecede yüksekti (p<0.001). Troponin T düzeyi OKVO gelişen grupta gelişmeyenlere göre anlamlı derecede yüksek bulunurken (0.21±0.43 ng/ml ve 0.06±0.28 ng/ml, p=0.002), homosistin düzeyi bu açıdan anlamlı farklılık göstermedi (p=0.82). Troponin T için kesim değeri 0.10 ng/ml olarak alındığında, cTnT 17 hastada (%21.8) ≥0.10 ng/ml, 61 hastada (%78.8) <0.10 ng/ml bulundu. Troponin T düzeyi ≥0.10 ng/ml olan hastalarda OKVO gelişimi (%64.7 ve %24.6; p=0.003), konjestif kalp yetersizliği (%47.1 ve %16.4; p=0.02) ve ölüm (%52.9 ve %16.4; p=0.004) anlamlı derecede fazlaydı. Bu hastalarda koroner arter hastalığı açısından da artmış bir eğilim vardı (%41.2 ve %19.7, p=0.10). Çokdeğişkenli lojistik regresyon analizinde ise, sadece yaş ve diyabetes mellitus OKVO'nun bağımsız öngördürücüsü bulundu.

Sonuç: Homosistin düzeyi SDBH'li hastaların uzun dönem takibinde OKVO gelişimini öngörmede yardımcı değildir. Yüksek cTnT düzeyi olan hastalarda OKVO gelişimi anlamlı derecede daha fazla olsa da, cTnT de OKVO'nun bağımsız bir göstergesi değildir.

Anahtar sözcükler: Biyolojik belirteç/kan; kardiyovasküler hastalık; homosistin/kan; böbrek yetersizliği, kronik/komplikasyon; renal diyaliz; troponin T/kan.

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Mortality rate is significantly high in end-stage renal disease (ESRD). The most common cause of death in these patients is cardiovascular events.[1] Since silent myocardial ischemia and abnormal perception of chest pain are very common in ESRD patients, diagnosis of coronary artery disease (CAD) usually becomes difficult.[2] Diagnosis of heart failure is also difficult due to frequent volume alterations in patients on hemodialysis therapy. Recognition of high-risk markers for early diagnosis of cardiovascular disease is important to understand the magnitude of the risk and decide the treatment strategy.

Cardiac troponin T (cTnT) represents myocardial injury and is an important diagnostic and prognostic marker in the population with normal renal function.[3-5] The diagnostic power of cTnT in ESRD patients is thought to be low due to very common pathological values in the absence of acute coronary syndrome.[6] However, the prognostic power of cTnT in ESRD patients has been shown in many studies.[7-12] But none of these studies documented the exact mechanism between high cTnT and worse outcome and there was a significant heterogeneity among the studies.

Homocysteine is an amino acid which occurs in the metabolism of methionine. It is known that renal dysfunction causes an increase in plasma homocysteine. In the presence of normal renal function, increased homocysteine levels are associated with an increased risk for atherosclerosis.[13] The results of studies on the effect of increased homocysteine level on cardiovascular events in ESRD patients are conflicting. Some studies showed an increased cardiovascular event rate with increased homocysteine level,[10,14-16] whereas some did not find an independent relationship.[17] Even, a reverse relationship between homocysteine level and mortality has been reported.[18]

In this study, we aimed to evaluate the long-term prognostic value of cTnT and homocysteine level for cardiovascular diseases in patients with ESRD.

PATIENTS AND METHODS

The study included 78 patients (54 males, 24 females; mean age 53.2±16.6 years; range 22-84 years) who had been on chronic hemodialysis treatment for at least three months. Data for baseline characteristics and medical history were obtained from patient interviews and hospital charts. Patients with a known cardiovascular disease (CAD, history of revascularization, heart failure, and stroke), malignancy, or any systemic disease other than renal failure were excluded. Cardiac troponin T measurements and other biochemical tests were performed in March 2002.

Cardiac troponin T was determined immediately before the hemodialysis session. The standard diagnostic cutoff value for myocardial injury (0.10 ng/ml) was considered to be a high or positive cTnT test. Homocysteine level and other biochemical tests were also measured from predialysis blood samples.

To determine any occurrence of major adverse cardiovascular events (MACE) including congestive heart failure (CHF), CAD, stroke, or cardiac death, patient charts were reviewed and patients were interviewed in May 2007.

Statistical analysis. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as numbers and percentages. For comparison of the continuous variables, independent samples t-test or Mann-Whitney U-test were used, where appropriate. Categorical variables were compared using the chi-square test. A multivariate logistic regression model was created to find out the independent determinants of MACE. A *P* value of less than 0.05 was considered statistically significant.

Table 1. Characteristics of patients with end-stage renal disease

	Baseline (n=78)			MACE present (n=26)			MACE absent (n=52)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			53.2±16.6			66.6±11.2			46.3±14.7	<0.001
Gender										N.S
Male	54	69.2		16	61.5		38	73.1		
Female	24	30.8		10	38.5		14	26.9		
Diabetes mellitus	21	26.9		14	53.8		7	13.5		<0.001
Hypertension	27	34.6		9	34.6		18	34.6		N.S
Creatinine (mg/dl)			9.5±3.4			8.5±2.5			10.0±3.7	N.S
Hemoglobin (g/dl)			10.4±1.6			10.4±1.7			10.5±1.6	N.S
Albumin (g/dl)			3.9±0.4			3.8±0.4			4.0±0.4	N.S

NS: Not significant.

Table 2. Troponin T levels in the presence and absence of major adverse cardiovascular events (MACE)

	MACE present		MACE absent		
	n	Troponin T (ng/ml)	n	Troponin T (ng/ml)	*p*
Total MACE	26	0.21±0.43	52	0.06±0.28	0.002
Congestive heart failure	18	0.24±0.49	60	0.07±0.28	0.007
Death	19	0.25±0.49	59	0.06±0.27	0.002
Coronary artery disease	19	0.12±0.22	59	0.10±0.38	0.075
Cerebrovascular event	3	0.03±0.07	75	0.11±0.35	0.88

Statistical data were analyzed using the SPSS software (version 10.0).

RESULTS

Characteristics of the study group are shown in Table 1. We observed MACE in 26 patients (33.3%), including cerebrovascular events in three patients (3.9%), CHF in 18 patients (23.1%), CAD in 19 patients (24.4%), and death in 19 patients (24.4%).

There were no significant differences between patients who developed MACE and who did not with respect to gender, hypertension, baseline hemoglobin, creatinine, and albumin levels. However, two-thirds of diabetic patients developed MACE and the mean age in the MACE group was significantly greater ($p<0.001$; Table 1).

Cardiac troponin T levels were significantly higher in patients who developed MACE (0.21±0.43 ng/ml *vs* 0.06±0.28 ng/ml, p=0.002; Table 2), whereas homocysteine levels did not differ significantly between the two groups (p=0.82; Table 3)

When the cTnT levels were grouped according to the cutoff value of 0.10 ng/ml, cTnT was ≥0.10 ng/ml in 17 patients (21.8%), and <0.10 ng/ml in 61 patients (78.8%). Patients having a cTnT level of ≥0.1 ng/ml showed significantly higher rates of MACE (64.7% *vs* 24.6%; p=0.003), CHF (47.1% *vs* 16.4%; p=0.02), and death (52.9% *vs* 16.4%; p=0.004). Albeit not significant, there was also a greater tendency to CAD in this group (41.2% *vs* 19.7%, p=0.10).

In multivariate logistic regression analysis including age, gender, hypertension, diabetes mellitus, and baseline creatinine, hemoglobin, albumin, and cTnT levels, we found that age and diabetes mellitus were the independent predictors of MACE development (Table 4).

DISCUSSION

Biomarkers that have a high predictive value for cardiovascular events may be helpful in deciding treatment strategy and determining prognosis in ESRD patients. In this study, we investigated the long-term prognostic value of cTnT and homocysteine in hemodialysis patients. We observed a significantly higher incidence of MACE in ESRD patients with a high baseline cTnT. However, in regression analysis, this finding was not independent from other confounding factors such as age, gender, diabetes mellitus, and hypertension, hemoglobin, creatinine, and albumin levels. The independent predictors of MACE were age and diabetes mellitus.

Since cTnT increases in the serum even with a very small amount of myocardial injury, it is a very useful tool for the diagnosis of acute myocardial infarction.[4] Increased cTnT concentrations are frequently seen in ESRD patients without an acute myocardial injury. The mechanisms responsible for cTnT elevation in ESRD patients are not known. It may be due to small amounts of myocardial injury that occur chronically during dialysis process or inadequate oxygenization of the myocardium resulting from increased consumption because of left ventricular hypertrophy, which is very common in ESRD patients. Mallamaci et al.[19] found an association between increased cTnT concentrations and left ventricular hypertrophy. This hypoth-

Table 3. Homocysteine levels in the presence and absence of major adverse cardiovascular events (MACE)

	MACE present		MACE absent		
	n	Troponin T (ng/ml)	n	Troponin T (ng/ml)	*p*
Total MACE	26	24.77±8.76	52	25.32±10.45	0.82
Congestive heart failure	18	25.00±9.29	60	25.13±10.10	0.99
Death	19	23.03±7.86	59	25.87±10.41	0.29
Coronary artery disease	19	25.50±9.22	59	24.98±10.12	0.85
Cerebrovascular event	3	26.89±5.57	75	25.04±9.99	0.75

Table 4. Multivariate logistic regression analysis for major adverse cardiovascular events

	Wald χ^2	*p*	OR	95% confidence interval
Age	8.321	0.004	1.122	1.038-1.213
Gender (male)	0.226	0.635	1.566	0.247-9.940
Hypertension	0.192	0.661	1.508	0.240-9.471
Diabetes mellitus	10.758	0.001	28.931	3.874-206.071
Hemoglobin	0.638	0.424	1.242	0.730-2.114
Creatinine	0.055	0.815	1.041	0.742-1.460
Albumin	0.225	0.635	0.555	0.049-6.340
Homocysteine	0.025	0.874	0.992	0.897-1.097
Troponin T	1.220	0.269	3.215	0.405-25.530

esis also formed the basis for the studies concerning the prognostic value of troponins in ESRD patients. Another mechanism may be decreased excretion of cTnT by kidneys in ESRD patients. Although cTnT is known to be cleared by the reticuloendothelial system, a recent study showed contribution of the kidneys to clear cTnT from the circulation.[20] In ESRD patients, accumulation of cTnT fragments may cause increased cTnT concentrations. Uremic myopathy may be another reason for increased cTnT, since cTnT is also found in skeletal muscle in small amounts.[21]

Initially, increased cTnT levels in ESRD patients were accepted as meaningless, but recent studies have provided findings in favor of its prognostic value. DeFilippi et al.[22] showed a relationship between higher cTnT concentrations and angiographically defined CAD. Several studies found a relationship between cTnT levels and mortality in ESRD patients.[7-12] In contrast, Möckel et al.[23] reported that there was no association between cTnT and mortality. A recent meta-analysis included 17 studies concerned with the long-term prognostic value of cTnT in ESRD patients.[24] Although a strong association was found between mortality and cTnT levels, the authors emphasized that a significant heterogeneity existed among the studies and that there was evidence for publication bias. When they excluded the largest study, the heterogeneity disappeared and they found that the relation was only modest.

On the other hand, research on the prognostic value of troponin I has yielded conflicting results.[25-27] Some of the studies failed to show an independent association between troponin I and mortality.[6] Conflicting results were attributed to the standardization problems of troponin I assays.[28] Since the prognostic value of troponin I in acute coronary syndromes is very well documented without conflicting results due to standardization problems,[29,30] similar results may be expected from studies using troponin I, showing increased troponin I levels as a result of chronic myocardial damage and a potential relationship with the prognosis in ESRD patients. However, several studies failed to show such a relationship.[24,27] In our study, although the incidence of MACE was significantly higher in patients with increased cTnT levels, cTnT was not an independent predictor of MACE including death. This finding may be due to relatively small number of patients in our study group. As there is not yet sufficient data to explain the mechanism that provides prognostic value for cTnT at the expense of troponin I, we think that prognostic use of cTnT in ESRD patients should await further studies.

Hyperhomocysteinemia is a risk factor for CAD in subjects with normal renal functions.[31] Increased homocysteine levels are remarkable in ESRD patients compared to general population.[32] Decreased clearance from kidneys and decreased vitamin levels due to malnutrition may be responsible for high levels of homocysteine in ESRD patients. Conflicting results have been reported on the relationship between homocysteine and mortality.[14-18] Because of potential adverse effects of homocysteine on the endothelium and coagulation system, hyperhomocysteinemia may be expected to be associated with an adverse prognosis. On the other hand, hypohomocysteinemia associated with malnutrition may have a role in the absence of a relationship between homocysteine level and mortality. In our study, there was no relationship between the homocysteine level and MACE and the homocysteine levels in our study group were relatively low compared to those reported in the studies showing a significant relationship between hyperhomocysteinemia and mortality.[14-16]

In conclusion, despite a significantly higher incidence of MACE in patients with high cTnT levels, cTnT was not an independent predictor of cardiovascular outcome. Further studies are needed to clarify the mechanisms of cTnT increase and its prognostic value in ESRD patients.

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