

Cardiac Troponins in Patients With Chronic Kidney Disease and Kidney Transplant Recipients Without Acute Cardiac Symptoms

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Introduction. Cardiovascular diseases are the most common causes of death in chronic kidney disease (CKD) and kidney transplant patients. This study aimed to evaluate cardiac troponins in transplant recipients and CKD patients without cardiac symptoms.

Materials and Methods. Two groups of patients (CKD and kidney transplant recipients) were evaluated for troponins T and I levels. These values were associated with renal replacement therapy and demographic and clinical characteristics of the patients.

Results. Eighty CKD patients and 80 kidney transplant recipients were studied. There was a significant difference in Troponins T and I levels were significantly higher in the CKD group than in the transplant recipients. In the CKD group, 14 patients (17.5%) had an elevated troponin T level and 8 (10.0%) had an elevated troponin I, all of whom were in stage 4 of CKD. None of the kidney transplant patients had a positive troponin. Among CKD patients, decreased glomerular filtration rate was associated with elevated troponin I level. Elevated troponin T level was significantly associated with age and decreased glomerular filtration rate. In multivariable analysis, significant associations were found between troponin T level and age, serum creatinine, and glomerular filtration rate. A significant relationship was also found between troponin I and cholesterol and glomerular filtration rate.

Conclusions. The assessment of troponin T and I in CKD and kidney transplant patients shows that in patients with CKD and without any symptoms of acute coronary syndrome, serum level of cardiac troponins increase and it is linked to serum creatinine and GFR.

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INTRODUCTION

Patients with chronic kidney disease (CKD) are at a high risk of cardiovascular diseases such as acute myocardial infarction and cardiovascular mortality.¹ Cardiovascular diseases are common among patients with end-stage renal disease (ESRD)

and kidney transplantation,² and constitute their main cause of mortality.^{3,4} Cardiac troponins I and T are sensitive and specific indicators of myocardial damage. Also, a high level of troponin T has been associated with poor prognosis.^{5,6} However, they are sometimes found to be increased in patients

with kidney failure even in the absence of acute myocardial infarction. In kidney failure, serum cardiac troponins are falsely elevated, which can be caused probably by included uremic myopathy, expression of fetal cardiac troponin in the skeletal muscles, altered protein clearance, abnormal protein metabolism, silent myocardial injury, uremic toxins, left ventricular hypertrophy, and inflammation.²

Data on false positive results of cardiac troponin levels after kidney transplantation are insufficient. We know that restoring kidney function in kidney transplant patients may eliminate some possible causes of troponin elevation, such as uremic toxins, abnormal protein clearance, and abnormal protein metabolism; however, other causes like left ventricular hypertrophy and silent ischemia should also be considered. In such patients, other factors such as administration of statins, cyclosporine, and tacrolimus may lead to myopathy, although this correlation was poor in Fredericks and colleagues' study.^{7,8}

On the other hand, the level of cardiac troponins in CKD patients and kidney transplant recipients, especially those who are asymptomatic for acute cardiac diseases, have a determinant role in diagnosis and risk assessment of cardiovascular diseases. In addition, the level of cardiac troponins may indicate ischemia without myocardial symptoms. Therefore, by evaluating cardiac troponins in transplant recipients and CKD patients, we aimed to identify those with a higher risk of cardiovascular diseases and mortality, especially patients without cardiac symptoms. Accordingly, more attention can be paid to high-risk patients and unnecessary preparations can be avoided for patients with lower risks.

MATERIALS AND METHODS

This cross-sectional study was performed in the Transplant Unit and Nephrology Special Clinic of Imam Khomeini University Hospital, Tehran, Iran, in 2010 and 2011. The study was approved by the Committee of Research Ethics of Tehran University of Medical Sciences. Patients voluntarily participated in this study and informed consent was obtained from all participants. Patients with CKD (serum creatinine level, ≥ 1.5 mg/dL) and patients who had received a kidney transplant at least 3 months prior to the study with stable kidney function (serum creatinine level ≤ 1.3 mg/

dL) were included in the study. Kidney transplant recipients were receiving mycophenolate mofetil, cyclosporine, and prednisolone. Only patients who were completely asymptomatic for acute cardiac symptoms were included; patients who had acute cardiac symptoms within the past month were excluded from the study.

Data on sex, age, history of diabetes mellitus and hypertension, cigarette smoking, disease duration, and cardiac disease were extracted from the medical records. Body weight, height, body mass index, hemoglobin, and serum levels of albumin, phosphorus, calcium, and creatinine were measured for each patient. Glomerular filtration rate (GFR) was calculated according to the Cockcroft-Gault equation. Serum intact parathyroid hormone was measured by immunochemilumetric assay (upper limit of normal, 65 pg/mL). C-reactive protein was measured by the quantitative method of high-sensitivity enzyme-linked immunosorbent assay. Troponins I and T were measured in all CKD and transplant recipient participants. Troponin T was regarded positive for levels higher than 0.1 ng/dL) and troponin I for levels higher than 0.1 ng/dL. All of the tests were performed on a single sample of blood taken from each patient.

Statistical analysis was performed with the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). Frequencies were calculated for qualitative variables and 95% confidence intervals were reported. Univariable analysis was done using the *t* test and Pearson correlation test. Linear regression models were used for multivariable analyses. *P* values less than .05 were considered significant.

RESULTS

One hundred and sixty patients participated in this study. Eighty (50%) of them were transplant recipients and 80 were CKD patients. Characteristics of the patients in each group are shown in Table 1. Among CKD patients, 82.5% were in stage 3 or 4 of the disease. Table 2 shows the frequency of CKD patients in each stage of CKD and also the mean Cr level for each group.

There was a significant difference in the mean value of troponins T and I between the two groups of CKD and transplant recipients (troponin T, 0.04 ± 0.003 ng/dL versus 0.010 ± 0.006 ng/dL, *P* = .001 and 0.020 ± 0.003 ng/dL versus $0.010 \pm$

Table 1. Basic Characteristics in Each Group of Patients

Parameter	Chronic Kidney Disease	Kidney Transplant	P
Age	62.1 ± 14.5	59.7 ± 14.6	.30
Sex			
Male	43 (53.8)	40 (50.0)	
Female	37 (46.3)	40 (50.0)	.60
Hypertension	63 (78.8)	36 (45.0)	.001
Diabetes mellitus	22 (27.5)	15 (18.8)	.10
Smoking	8 (10.0)	6 (7.5)	.50
Ischemic heart disease history	11 (13.8)	5 (6.3)	.30
Duration of kidney disease, y	4.5 ± 3.3	5.1 ± 3.2	.20
Glomerular filtration rate, mL/min	35.9 ± 17.6	96.4 ± 12.5	.001
Body mass index, kg/m ²	25.8 ± 4.0	25.1 ± 9.9	.50

Table 2. Stage and Serum Creatinine Values of Patients With Chronic Kidney Disease (CKD)

CKD Stage*	Number of Patients	Serum Creatinine, mg/dL
1	1	1.05
2	6	1.16 ± 0.26
3	39	1.78 ± 0.40
4	30	3.16 ± 0.86
5	4	6.23 ± 3.00

*Stages of the disease were according to the glomerular filtration rate (mL/min): Stage 1, ≥ 90; stage 2, 60 to 89; stage 3, 30 to 59; stage 4, 15 to 29; and stage 5, < 15.

0.007 ng/dL, $P = .001$; Table 3). In the CKD group, the number of patients with a positive troponin T (higher than 0.1 ng/dL) was 14 (17.5%) and the number of patients with a positive troponin I (higher than 0.1 ng/dL) was 8 (10.0%), all of whom were in stage 4 of CKD. None of the participants in the transplant group had a positive troponin T or I.

In CKD patients, there was a significant association between cholesterol elevation and increase in troponin I level ($r = 0.27$, $P = .03$). Decreasing GFR was also associated with elevated

troponin I level ($r = -0.30$, $P = .004$). No significant association was seen between elevated level of troponin I and other laboratory parameters (Table 4). Elevated troponin T level was significantly associated with increasing age ($r = 0.27$, $P = .01$) and decreasing GFR ($r = -.34$, $P = .006$; Tables 5 and 6).

In multivariable analysis, significant associations were found between troponin T level and age, serum creatinine, and GFR, among the CKD patients. A significant relationship was also found between troponin I level and cholesterol and GFR.

DISCUSSION

Cardiovascular diseases are the most common causes of death in CKD patients. They are considered as the most important and common cause of mortality in kidney transplant recipients, too. In our study, among the patients of CKD, 14 (17.5%) were positive for troponin T elevation and 8 (10%) for troponin I, whereas no cases with positive troponin T or I were seen in transplant recipients group.

Table 3. Mean Values of Laboratory Data in Each Group of Patients

Parameter	Chronic Kidney Disease	Kidney Transplant	P
Fasting blood glucose, mg/dL	108.5 ± 45.9	97.16 ± 49.4	.10
Serum creatinine, mg/dL	2.4 ± 1.4	1.1 ± 0.4	.001
Serum triglyceride, mg/dL	156.4 ± 82.1	136.9 ± 60.3	.09
Serum cholesterol, mg/dL	171.4 ± 46.1	168.9 ± 33.1	.60
Serum calcium, mg/dL	9.5 ± 0.9	9.6 ± 0.9	.60
Serum phosphorus, mg/dL	4.1 ± 0.9	3.9 ± 0.5	.70
Troponin T, ng/dL	0.040 ± 0.003	0.010 ± 0.006	.001
Troponin I, ng/dL	0.020 ± 0.003	0.010 ± 0.007	.001
Serum albumin, g/dL	4.3 ± 0.7	4.3 ± 0.3	.20
C-reactive protein, ng/mL	9.6 ± 19.3	7.2 ± 12.9	.90
Serum parathyroid hormone, pg/mL	110.6 ± 101.7	93.1 ± 79.6	.20
Hemoglobin, g/dL	13.0 ± 1.8	13.4 ± 1.6	.10

Table 4. Mean Values of Variables in Chronic Kidney Disease Patients With and Without Elevated Troponin I

Parameter	Normal Troponin I	Elevated Troponin I	P
Age, y	61.4 ± 14.5	67.9 ± 14.9	.20
Fasting blood glucose, mg/dL	108.1 ± 42.1	119.1 ± 81.7	.50
Serum creatinine, mg/dL	2.5 ± 1.8	3.1 ± 0.9	.30
Serum triglyceride, mg/dL	153.3 ± 76.9	183.8 ± 122.9	.30
Serum cholesterol, mg/dL	167.8 ± 42.2	203.6 ± 67.7	.03
Serum calcium, mg/dL	9.5 ± 0.9	9.6 ± 0.7	.90
Serum phosphorus, mg/dL	4.2 ± 0.9	3.9 ± 0.6	.30
Serum albumin, g/dL	4.3 ± 0.7	4.0 ± 0.3	.10
C-reactive protein, ng/mL	9.2 ± 17.8	13.5 ± 31.0	.50
Serum parathyroid hormone, pg/mL	104.0 ± 89.0	169.5 ± 178.8	.08
Hemoglobin, g/dL	13.0 ± 1.8	12.7 ± 1.5	.50
Glomerular filtration rate, mL/min	37.2 ± 17.8	24.1 ± 9.5	.04
Body mass index, kg/m ²	25.7 ± 3.9	26.9 ± 5.1	.40

Table 5. Mean Values of Variables in Chronic Kidney Disease Patients With and Without Elevated Troponin T

Parameter	Normal Troponin T	Elevated Troponin T	P
Age, y	60.2 ± 14.3	70.7 ± 12.9	.01
Fasting blood glucose, mg/dL	108.9 ± 43.8	110.8 ± 61.3	.80
Serum creatinine, mg/dL	2.5 ± 1.6	3.2 ± 2.2	.04
Serum triglyceride, mg/dL	154.0 ± 79.7	167.2 ± 95.1	.80
Serum cholesterol, mg/dL	168.7 ± 43.0	184.1 ± 58.9	.10
Serum calcium, mg/dL	9.5 ± 0.9	9.5 ± 0.6	.20
Serum phosphorus, mg/dL	4.1 ± 0.9	3.8 ± 0.6	.10
Serum albumin, g/dL	4.3 ± 0.7	4.2 ± 0.4	.10
C-reactive protein, ng/mL	17.8 ± 8.9	25.5 ± 13.0	.30
Serum parathyroid hormone, pg/mL	104.9 ± 92.3	137.4 ± 138.8	.40
Hemoglobin, g/dL	13.1 ± 1.7	12.4 ± 2.0	.20
Glomerular filtration rate, mL/min	38.3 ± 18.0	24.3 ± 9.5	.006
Body mass index, kg/m ²	26.0 ± 3.9	25.0 ± 4.5	.30

Table 6. Correlation Between Troponins T and I and Quantitative Variables in Chronic Kidney Disease Patients

Parameter	Troponin T		Troponin I	
	Pearson Coefficient	P	Pearson Coefficient	P
Age, y	0.269	.02	0.078	.49
Duration of disease, y	-0.055	.63	-0.126	.27
Fasting blood glucose, mg/dL	0.050	.66	0.136	.23
Serum creatinine, mg/dL	0.291	.009	0.131	.25
Serum triglyceride, mg/dL	0.064	.57	0.161	.16
Serum cholesterol, mg/dL	0.129	.25	0.276	.01
Serum calcium, mg/dL	-0.032	.78	0.083	.47
Serum phosphorus, mg/dL	-0.167	.14	-0.127	.26
Serum albumin, g/dL	-0.119	.29	-0.190	.09
C-reactive protein, ng/mL	0.101	.37	-0.032	.78
Serum parathyroid hormone, pg/mL	0.009	.93	0.080	.48
Hemoglobin, g/dL	-0.101	.37	-0.163	.15
Glomerular filtration rate, mL/min	-0.340	.002	-0.290	.009
Body mass index, kg/m ²	-0.110	.33	0.020	.86

In the study of Krol and colleagues, 17 hemodialysis patients on hemodialysis for about 66 months, 23 patients on peritoneal dialysis for

47 months, and 23 kidney transplant recipient patients (27 months after transplantation) were evaluated and levels of troponin T.⁹ Results of

this investigation showed that troponin T was increased in 29% of the hemodialysis patients and 35% of the patients on peritoneal dialysis, whereas no increase was observed in kidney transplant patients.⁹ Few studies have compared cardiac troponin levels in patients before and after kidney transplantation. Results of these studies indicate different contradicting findings. Wu and coworkers found that troponin T elevation was more common in the pretransplant period than posttransplant period. They concluded that this decline was due to improved creatinine clearance.¹⁰ Another study by Hickson and colleagues showed pretransplant troponin T levels were associated with patients' survival rate.¹¹

In 2001, another study was conducted on ESRD patients before and after transplantation.¹² This study was performed on 32 ESRD patients, and troponin T amounts were measured before transplantation and within 1, 3, 6, and 12 months after transplantation. The researchers found that troponin T was high in the preoperative period in 9.4% of patients and 15.6% had elevated troponin T during postoperative period,⁹ which can be related to drugs taken in this period. Comparison of the levels of troponin I before and after transplantation showed that serum troponin I level was increased postoperatively in 47% of the patients, decreased in 17.9% of them, and did not have any change in 35% of the patients, and there was no difference in the troponin I levels in patients with ESRD without cardiac events before and after transplantation.¹² In our study, none of the transplanted patients had a positive troponin T or I. Because we selected patients with serum creatinine levels less than 1.3 mg/dL, in kidney transplant patients with stable kidney function, the serum level of cardiac troponins was not increased. However, abundant studies show an increase in cardiac troponins in ESRD patients without cardiac symptoms.¹³⁻¹⁵

In another investigation carried out on 103 CKD patients with CKD stages of 3 to 4, 28% of the patients had a troponin T level greater than 0.01 µg/L and 2% had a troponin T level greater than 0.1 µg/L.¹⁶ Troponin T concentration was commonly increased in patients with more severe CKD in stage 3 and patients in stage 4. In addition, troponin T increased more at the higher stages. An obvious association was found between increasing troponin T and cigarette smoking, hypertension,

diabetes mellitus, and increasing age.¹⁶ In our study, the frequency of patients with a positive troponin T was 14 (17.5%), and the frequency of patients with a positive troponin I was 8 (10%). Most of the patients were in stage 4 CKD group and there was a significant negative correlation with alterations in troponin T and I levels. In the study of Zand-Parsa and associates on 150 CKD patients, serum troponin T was significantly higher in patients with higher levels of creatinine, but this relationship was not significant between troponin I and serum creatinine.¹⁷ In the study of Sezar and colleagues, troponin T correlated with GFR, uric acid, blood pressure, triglyceride, and C-reactive protein.¹⁸ The authors concluded that increased troponin T was not only associated with inflammation but also a sensitive marker for kidney function.¹⁸

In another study performed in 2005 in United Kingdom, 227 CKD patients were followed up for 1 year.⁶ Of 222 patients, 95 (43%) had a troponin T level of 0.01 µg/L and higher, which was associated with progression of the disease (decreasing GFR). In this study, an obvious association was observed between increasing troponin T and increasing age and diabetes mellitus. In addition, a significant association was seen between troponin T and calcium-phosphorus precipitation, while a reverse association was detected between the amounts of hemoglobin and troponin T.⁶

In our study, a direct association was detected between troponin T and age, as was shown previously by many studies.^{5,6,16,19,20} The direct association between troponin T elevation and age has even been shown in healthy subjects.²¹ We also found an association between troponin T and creatinine level, which is consistent with the findings of Arroyo and coworkers.¹⁹ We also observed a relationship between troponin T and blood glucose. Although some studies have shown an association between elevated troponin T and diabetes mellitus, they have not evaluated the relation between blood glucose and troponin T.^{5,16} A significant association was seen between the level of troponin I and cholesterol in our study. This is in contrast with the findings of Hussein and colleagues.²² In their study of 150 hemodialysis and peritoneal dialysis patients, they did not find any significant difference between the levels of total cholesterol among patients with and without

positive troponin I. Moreover, in our study GFR showed an inverse association with levels of troponins T and I.

CONCLUSIONS

Our findings indicate that in patient with CKD and without any symptoms of acute coronary syndrome, serum level of cardiac troponins will increase and it is associated with serum creatinine and GFR. It is well recognized that cardiovascular diseases mortality increase significantly with the reduction of GFR. Therefore, compared with kidney transplant patients, patients with CKD are at higher priority for measuring cardiac troponins. Further prospective studies are recommended for monitoring the patients with cardiovascular and kidney diseases and introducing the most effective preventive strategies to these patients.

CONFLICT OF INTEREST

None declared.

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