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Serum Troponin I in Patients Suffering from Chronic Renal Disease with Acute Coronary Syndrome

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Introduction:

Chronic Kidney Disease (CKD) is a fairly new term that has become popular after End-Stage Renal Disease (ESRD) was discovered. ESRD is the final stage of CKD and constitutes a clinical state associated with a uremic syndrome that has a very poor prognosis for the patient. CKD is the most important risk factor for ESRD (Levey & Coresh, 2012). After its various aspects were identified, CKD became recognized as an actual disorder that entails significant complications besides ESRD. This disease is now known as a risk factor for conditions such as cardiovascular diseases, anemia, electrolyte disorders, bone diseases, cognitive and psychiatric disorders and many other diseases (Alan, 2015). Increased blood pressure, hyperlipidemia, hyperthyroidism, calcium and phosphorus metabolism disorder, aging, diabetes and other systemic diseases that affect cardiac function are profuse in CKD patients. Mortality occurs in these patients as a result of an increased frequency of atherosclerosis, myocardial infarction, left ventricular hypertrophy, congestive heart failure, hypertension, pericardial effusion and high tamponed (Lopez-Gomez *et al.*, 1998). A large number of CKD patients are hospitalized

Abstract

Myocardial infarction is one of the common causes of death in patients with Chronic Kidney Disease (CKD). Cardiac troponins are myofibril proteins. The present study aims to assess the serum troponin I level in CKD patients with acute coronary syndrome through a cross-sectional study conducted on stage-3 to stage-5 CKD patients. The patients' serum troponin I and biochemical factors were measured. Angiography was also performed and the results were compared with the serum levels of troponin I and biochemical factors. Out of 98 patients who took part in the present study, 19.4% had no venous obstruction, 30.6% with single-vein obstruction, 28.6% with double-vein obstruction and 21.4% with triple-vein obstruction. The angiography results were not significantly differed from BMI, the Glomerular Filtration Rate (GFR), serum creatinine and serum troponin I. No significant relationships were observed between age, creatinine, GFR, and troponin I in patients with no venous obstruction. A significant and positive relationship was observed between creatinine and troponin I in patients with single-vein obstruction. GFR was found to have a significant and negative relationship with creatinine and troponin I in patients with double- and triple-vein obstructions.

every year for the acute coronary syndrome (ACS), and a percentage of them have Acute Myocardial Infarction (AMI) and the rest suffer from unstable angina. AMI is known as a clinical disease caused by atherosclerosis of the arteries feeding the heart. The most common complaint in AMI patients is chest pain, which usually lasts for more than 15 minutes. AMI can also present with symptoms other than chest pain, which are known as angina equivalents and include sudden dyspnea, weakness and lethargy (Wright *et al.*, 2002). For several years, especially in recent decades, new up-to-date diagnostic tools have become available to physicians for the diagnosis of AMI, and these early diagnoses have reduced the mortality rate associated with this condition and its potential complications. The World Health Organization criteria for the diagnosis of AMI include at least two of the three clinical symptoms indicating ischemic heart disease, including ECG variations and an increase and decrease in serum cardiac markers (Salehi Omran *et al.*, 2005). Cardiac biomarkers are a useful tool for the diagnosis of AMI. Cardiac troponins are myofibril proteins that include troponin T, I and C. The troponin complex regulates the process of skeletal muscle

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contraction that occurs through calcium. Troponin C binds to calcium, troponin I binds to actin and the interaction of actin and myosin is thus inhibited, and troponin T binds to tropomyosin and makes the troponin complex connect to the thin filament (Farah & Reinach, 1995). Troponin T and I are found in both the cardiac and skeletal muscles but are encoded with different genes and amino acid sequences, and antibodies specific to cardiac troponin T and I are thus synthesized (Antman *et al.*, 1996). The cardiac troponin I test is specific to the myocardial tissue, and its values above the reference are regarded as an indicator of AMI in people with normal kidney function (Adams *et al.*, 1993). Troponin I values may be higher in CKD patients than in others due to minor myocardial damage, which is not detectable by regular cardiac imaging (Martin *et al.*, 1998). A number of studies have demonstrated the value of troponin I in the diagnosis of acute coronary syndrome in CKD patients, but others have emphasized the inability of this test in diagnosing acute coronary syndrome (Jafari Fesharaki *et al.*, 2016). The present study was conducted to investigate serum troponin I levels in CKD patients with acute coronary syndrome.

Methodology:

This study was conducted following to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (von Elm *et al.*, 2014). The descriptive epidemiologic study was conducted on patients presenting to the emergency departments of Imam Khomeini and Golestan hospitals in Ahwaz in 2017-18.

Participants were then Stage-3 to stage-5 CKD patients with chest pain referred for angiography were included in the study after submitting their written consent. The exclusion criteria consisted of being a critical patient, the loss of consciousness, having no kidney problems, having kidney problems but no chest pain and unwillingness to undergo angiography despite being its candidate.

Data collection: stages 3 to 5 of CKD were defined by a GFR < 60 mL/min/1.73 m² of the body surface for over three months. A retrosternal pain initiated acutely and abated by sublingual nitroglycerine and often lasting over 20 minutes was also taken as chest pain. The results of the physical examination and cardiovascular nuclear scan (if performed) and the demographic details, including age, gender, weight, height and smoking status, were recorded. On the day of the visit, the patients' weight was carefully measured with minimal clothing without shoes using a scale, and their height was measured in a standing position with no shoes using a wall-mounted stadiometer with a 1-cm precision and with the buttocks, shoulders and heels touching the wall and the head looking forward. BMI was calculated as the weight to height ratio (kg/m²). Serum lipids, creatinine, and troponin I levels were measured using standard kits and relevant laboratory techniques in the

central laboratory. The patients underwent angiography by a specialist. Cardiac biomarkers and other variables were ultimately assessed in the patients and compared to the angiography results.

Statistical analysis: the collected data were analyzed in SPSS-22. The quantitative variables were reported as mean with standard deviation and the qualitative variables as frequency (percentage). The normality of the quantitative variables was assessed using the Shapiro-Wilks test. The relationships were assessed using the Pearson or Spearman correlation tests for the quantitative variables and using the Chi-square test for the qualitative variables. The quantitative variables were compared between the two groups using the independent t-test or its non-parametric equivalent (Mann-Whitney's test). The quantitative variables were compared between more than two groups using the ANOVA or its equivalent (the Kruskal-Wallis test). The tests were two-tailed and the level of statistical significance was set at $p < 0.05$.

Results:

A total of 98 patients participated in this study. Their mean age was 59.82 ± 11.4 , and 48 (49%) were male and 50 (51%) were female. According to the angiographic results, 19 patients (19.4%) did not have venous obstruction and 79 (80.6%) did have venous obstruction, including 30 (30.6%) with single-vein obstruction, 28 (28.6%) with double-vein obstruction and 21 (21.4%) with triple-vein obstruction (Table-1). No significant difference was observed in the frequency of angiographic results in the study population ($p > 0.997$). No significant differences were observed in the angiographic results by gender, smoking status, blood pressure or serum lipids. Serum creatinine and serum troponin I were significantly higher in the patients with venous obstruction compared to those without. The mean BMI and GFR were significantly lower in patients with obstruction compared to those without ($p < 0.05$). The results showed no significant relationship between the noted factors in the patients without venous obstruction (Table-1).

In patients without venous obstruction, no significant relationships were observed between creatinine and troponin I ($p > 0.095$, $r = 0.200$) or between GFR and creatinine ($p > 0.768$, $r = -0.209$) and GFR and troponin I ($p > 0.101$, $r = -0.374$); (Fig.-1).

A positive and significant relationship was observed between creatinine and troponin I in the patients with single-vein obstruction ($p < 0.015$, $r = 0.254$). There was no significant negative relationship between GFR and creatinine ($p > 0.335$, $r = -0.015$) or between GFR and troponin I ($p > 0.066$, $r = -0.015$); (Fig.-2).

In addition, a positive and significant relationship was observed between troponin I and creatinine ($p < 0.00$, $r = 0.254$) and significant negative relationships were

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observed between GFR and creatinine ($p < 0.003$, $r = -0.416$) and between GFR and troponin I ($p < 0.00$, $r = -0.588$) in the patients with double-vein obstruction (Fig.-3). In the patients with triple-vein obstruction, significant negative relationships were observed between GFR and creatinine ($p < 0.006$, $r = -0.466$) and between GFR and troponin I ($p < 0.016$, $r = -0.581$). A positive and significant relationship was also observed between troponin I and creatinine ($p < 0.001$, $r = 0.509$); (Fig.-4).

Table-1: Baseline information of patients as per vessel obstruction

Demographics						
Total (n = 98)	Lack of obs.(n=19)	1 vessel obs.(n=30)	2 vessel obs.(n=28)	3 vessels obs. (n=21)	'P'- value	
Age (Years)						
59.82±11.4	56.26±13.1	59± 10.85	62.89±9.22	60.10± 12.81	>0.085	
Male (%)						
48 (49)	11 (22.9)	10 (20.8)	18 (37.5)	9 (18.8)	>0.997	
BMI (Kg/m²)						
30.77±4.53	34.12 ± 3.16	33.15± 2.18	29.39± 4.80	26.20± 3.22	<0.000	
Clinical Characteristics						
Current smoker (%)						
43 (44.9)	7 (16.3)	8 (18.6)	16 (37.2)	12 (27.9)	>0.058	
Hypertension (%)						
68 (69.4)	9 (13.2)	24 (35.3)	20 (29.4)	15 (22.1)	>0.11	
Laboratory						
High blood lipids(%)						
54 (55.1)	13 (24.1)	20 (37)	12 (22.2)	9 (16.7)	>0.114	
Serum creatinine (mg/dl)						
2.15±0.60	1.79 ± 0.32	1.91 ± 0.36	2.31 ± 0.65	2.61 ± 0.85	<0.000	
Serum Glomerular Filtration Rate (GFR) (mL/min/1.73 m²)						
46.71±10.55	53.09±6.37	50.59±7.72	44.52±11.02	38.30±10.52	<0.000	
Troponin I (ng/dl)						
1.47±2.55	0.094±0.41	0.30±1.07	1.72±2.70	4.52±3.00	<0.000	

Discussion:

According to the results obtained, the mean troponin I level was 0.094 ± 0.41 ng/dL in those with no vein obstruction, 0.03 ± 1.07 ng/dL in single-vein obstruction, 1.72 ± 2.70 ng/dL in double-vein obstruction and 4.52 ± 3.00 ng/dL in triple-vein obstruction, comprising a significant difference. In line with the present findings, Flores *et al.* (2006) reported significantly higher troponin I level in patients with CKD compared to those without. In a study conducted by Giocoechea *et al.* (2005), CKD patients with cardiovascular diseases had high troponin I levels compared to others. In a study by Chen *et al.* (2013), higher levels of troponin I was observed in 43.34% of the CKD patients with acute coronary syndrome and 26.03% of the CKD patients without the acute coronary syndrome, which suggests higher troponin I levels in patients with the non-acute coronary syndrome. Apple *et al.*, (1997) reported on the 16 CKD patients undergoing hemodialysis had a history of ischemic heart disease (unstable angina), and their troponin I level was higher than the reference (0.8 ng/ml). In a study conducted by Fesharaki *et al.* (2016), the mean troponin I level was 0.95 ± 1.44 ng/dL in the patients with normal angiography

Figure-1: Plot between creatinine & troponin I (A). Correlation between GFR & creatinine (B). Correlation between GFR & troponin I (C).

Figure-2: Plot between creatinine & troponin I in the patients with single-vein (A). Correlation between GFR & creatinine (B). Correlation between GFR & troponin I (C).

Figure-3: Plot between creatinine & troponin I in the patients with double-vein obstruction (A). Correlation between GFR & creatinine (B). Correlation between GFR & troponin I (C).

Figure-4: Plot correlation between GFR & creatinine and troponin I in the patients with triple-vein (A). Correlation between GFR & troponin I (B). Correlation between creatinine & troponin I (C).

and 1.82 ± 2.96 ng/dL in those with abnormal angiography. However, we didn't get any significant differences in terms of gender, smoking status, blood pressure or serum lipids in the angiographic results. Moreover, the mean BMI, GFR, and serum creatinine was higher in patients with venous obstruction. A number of studies have reported BMI, blood pressure, hyperlipidemia and smoking as risk factors for acute coronary syndrome in CKD patients, although some other studies did not report a significant difference. Ohtake *et al.* (2005), reported that the coronary artery stenosis in stage-5 renal failure or ESRD patients was related significantly to the total triglyceride, total cholesterol, and LDL. Further, as per Hase *et al.* (1993), the risk factors of acute coronary syndrome in 101 CKD patients, including some who were undergoing hemodialysis existed. And the

step-wise logistic regression analysis of the risk factors showed that the prevalence of acute coronary syndrome had a significant relationship with diabetes and smoking. In another study of Jungers *et al.* (1977), atherosclerotic coronary artery disease was found to have a significant relationship with smoking and high systolic blood pressure. Moreover, CKD patients with atherosclerotic coronary artery disease had lower levels of HDL and higher levels of triglyceride, LDL, and homocysteine. Muntner *et al.* (2005) reported that smoking, high blood pressure, high blood fat, diabetes, high BMI and high waist circumference were risk factors related to the prevalence of coronary heart disease in CKD patients. The researchers argued that the risk factors of coronary heart disease in CKD patients are the same as those in the general public, but given the higher prevalence of heart disease in CKD patients, these risk factors have to be controlled. In the present study, venous obstruction was statistically higher in those with a higher BMI and also higher in those with hyperlipidemia and high BP and also in the smokers, although not supported by Statistics.

Smoking disrupts the function of the coronary capillaries and causes myocardial damage by inducing oxidative stress. High blood pressure is also associated with an increased risk of coronary artery disease and left ventricular hypertrophy in patients with CKD. The increase in blood pressure is caused by an increased volume of fluids, the activation of the renin-angiotensin system and increased nitric oxide inhibitors in the blood circulation, such as ADMA. Left ventricular hypertrophy causes an increase in left ventricular end-diastolic pressure and a reduction in subendocardial coronary blood flow, which then leads to the necrosis of small myocardial cells, apoptosis, the leakage of intracellular content due to the enhanced permeability of myocytes, increased levels of troponin T and I and ultimately an increased risk of ischemic heart disease (Foley *et al.*, 1995). Hyperlipidemia is one of the known risk factors for coronary artery disease and atherosclerosis progress, and the increase in certain types of plasma lipids has been shown to exacerbate the atherosclerotic engagement of the coronary arteries. Recent evidence suggests that a slight increase in triglycerides leads to an increased risk of coronary incidents and hastens coronary artery disease and also leads to the formation of new lesions and further extends coronary artery engagement. The relationship between serum blood lipids and obstructive coronary artery disease is well known, although only a few studies have been conducted on the role of lipoproteins as indices of the severity of coronary artery engagement (Korhonen *et al.*, 1996).

Our study showed that the troponin I level has no significant relationships with creatinine or GFR in patients with no venous obstruction in the angiographic results, but in patients with venous obstruction, it has a positive and significant relationship with creatinine and a negative and

significant relationship with GFR. In line with the present findings, Fesharaki *et al.* (2016) showed that serum creatinine was significantly higher in patients with troponin I >0.1ng/ml than in those with troponin I <0.1ng/ml. In addition, GFR was significantly lower in patients with troponin I >0.1ng/ml (Fesharaki *et al.*, 2016). In a study of Zand Parsa *et al.* (2012), troponin I had no significant relationships with GFR or serum creatinine in CKD patients with no heart problems, which agrees with the present findings since no relationships were observed between troponin I and GFR and creatinine in the patients with no venous obstruction. Otsuka *et al.* (2010) reported that troponin T had a significant relationship with the risk factors of heart disease, including age, blood flux, GFR, smoking and left ventricular hypertrophy. Troponin T had an inverse relationship with GFR. In fact, troponin I and T showed an increase in CKD patients with no cardiac disease, which is probably due to the reduced troponin I clearance.

Conclusion:

The present findings showed no significant differences in the severity of acute coronary syndrome by gender, smoking status, blood pressure, and serum lipids, but significant differences were observed in this severity by the mean BMI, GFR, serum creatinine and serum troponin I. Moreover, in patients with no venous obstruction, no significant relationships were found between age, serum creatinine, GFR or troponin I. A positive and significant relationship was observed between creatinine and troponin I in the patients with single-vein obstruction and a negative and significant relationship between GFR and creatinine and between GFR and troponin I and a positive and significant relationship between troponin I and creatinine in the patients with double-vein and triple-vein obstruction.

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