Importance of Troponin I in Early Diagnosis of Cardiovascular Disease in Chronic Kidney Disease

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Background: In this study, we aimed to demonstrate the significance of troponin I that has a high cardiac specificity, as a biomarker definition of risk for the cardiovascular disease in the chronic kidney patients. Methods: In this study, one hundred and ninety five patients presented to the emergency department with chest pain who had previously known chronic kidney disease and regularly followed-up and five hundred and sixty patients as a control group with normal renal functions were included. The patients were followed-up to exclude emergency pathology for the cardiovascular disease. Cardiac enzyme levels and troponin I were measured in the patients. Evaluation was made in terms of electrocardiography alterations and/or reduction and/or elevation in cardiac enzymes. Results: Troponin I measurements of the case-patients were found to be significantly higher than control group. According to the groups, the best cut-off value was determined to be for troponin I values and its cut-off value of levels demonstrated the sensitivity and specificity. Conclusion: Correlation was found between the reduced of glomerul filtration rate and increasement of troponin I levels. This condition can also show that troponin I might significantly be a marker, predictive of the cardiovascular disease.

Keywords: Cardiovascular disease risk, chronic kidney disease, troponin.

INTRODUCTION

Risk of cardiovascular disease is known to increase with decreasing glomerular filtration rate. Numerous factors contribute to the development of cardiovascular disease such as age, gender, etiology of chronic kidney disease (CKD), diabetes mellitus, hypertension and smoking.

Today, although impaired renal functions (1) are recognized as a strong predictor of cardiovascular disease, it is known that renal functions may impair also following cardiovascular diseases. Many factors like; inflammation (2), vascular calcification (3), anemia, etiology of chronic kidney disease and neurohumoral mechanisms etc., contributes to the development of cardiovascular diseases (4) in every stage of chronic kidney disease. It is known that existence of microalbuminuria and proteinuria (5) are the important risk factors. However, some of citokines such as neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) are secreted to the results of tubüler damage (6) cause inflammation and increase of risk for cardiovascular diseases. It is known; levels of NGAL, KIM-1, troponin I increase of acute kidney injury and chronic kidney diseases.

Some studies have demonstrated—the existence of association between cardiac function disorders, subclinical pathological changes of cardiac muscle and increase of morbidity with some of citokines (NGAL, KIM-1 etc. and especially troponin) (7,8) in chronic kidney disease. Currently; many studies have used this citokines prediction of the cardiovascular disease in the chronic kidney disease and results of the study have suggested its use as a biomarker. The troponins have higher cardiac specificity and have play an important role in the definition of cardiovascular disease in the
healthy population and chronic kidney patients. But; levels of troponin (9) are influenced by many factors such as renal dysfunction, age and gender, ethnical features, measurement technique etc. It is suggested to clinics should define cut-off values of troponins for more correct evaluation.

We aimed to determine cut-off the values of troponin I in the our clinics. However, the values of troponin I when compared had no emergency pathology for cardiovascular disease in the healthy patients and chronic kidney disease. In our study; diagnostic importance of troponin I and ratio of increased of troponin I were aimed to demonstrate estimation of the cardiovascular disease in chronic kidney patients who were compared with the healthy population.

MATERIAL AND METHODS

This study was approved by the Ethics Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital and conducted in accordance with the principles of the Declaration of Helsinki. All participants gave their written informed consent prior to participation in the study. In this study, 195 patients presented to the emergency department between 2012 and 2013 with chest pain who have previously known CKD (chronic kidney disease) and regularly followed-up and, 560 patients (control group) with normal renal functions were included. The condition of mean age and gender distribution have to be similar were provided in both groups.

In order to rule out diagnosis of emergency pathology of cardiovascular disease (myocard infarctus, pericarditis etc.); patients' medical histories were obtained, physical examination for symptoms was carried out, electrocardiography (ECG) was ordered and monitoring and cardiac markers were assessed. The patients whose chest pains continued in the first 24 hours during follow-up, the patients determined to have ST elevation in ECG and high troponin levels and/or the patients with ST, T changes in ECG were not included in the study since they could be at lower risk or high-risk for cardiovascular diseases.

In the patient groups, diseases and conditions like prosthetic valve, cirrhosis, malignancy, chest trauma, rhabdomyolysis, viral infections, rheumatoid arthritis, systemical lupus erythematosus (SLE) and cocaine use that could be at lower risk or high risk for cardiovascular disease were excluded from the study.

Urea and creatinine levels were measured from the venous blood samples of patients in order to evaluate renal functions. Volume of urine was calculated by collecting 24-hour urines of the patients and measurements of microalbuminuria and proteinuria were performed. In evaluation of renal functions; Modification of Diet in Renal Disease (MDRD) formula (10) was used for verification (to ensure it would be standard).

MDRD formula: MDRD =Glomerular Filtration Rate = 186 * SerumCreat^1.154 + 0.018 * Age^-0.203 + 0.154 * Gender * Race

ECGs including additional leads (V3R, V4R, V7-V9) were obtained and were evaluated ECG ST elevation, ST depression, Q wave and the presence of emerging ECG findings. In case of the findings, the patients were excluded from the study. Same device (EDAN/SE-1201 LCD interpretive 12-lead) was used for ECG orders, and the evaluation was carried out by the same physician.

Venous blood samples were collected from the patients in order to study the levels of CK-MB and troponin I enzymes within the first 30 minutes of admission and 4th, 6th and 12th hours. Elevation and/or reduction in the levels of cardiac enzymes were evaluated together with ECG changes.

In the serum analyses, urea was analyzed with Abbott ARCHITECT device, Urease with Kinetic Method and creatinine with Abbott ARCHITECT device using Alkaline Pichrate method. First, volume of urine was calculated in 24-hour urine sample. Afterwards, in assessment of protein, albumin and creatinine levels in the urine, Beckman Coulter preanalytic and modular system (UniCel Dxc 800, USA) device was used with photometric method.

For the biochemical analyses of the cardiac enzyme levels, blood sample of 5 mL was taken into gel containing dry tubes; kept for about 30 minutes and centrifuged at 4000 rpm for 10 minutes. Serum analyses for CK-MB enzyme activities were studied with original kits using Abbott Architect C16000 autoanalyzer (Abbott Laboratories. Abbott Park, Illinois, U.S.A.). Enzyme activities were expressed as U/L. Determination of serum levels of cardiac troponin I was studied again with the original kits using Beckman Coulter Access 2 autoanalyzer (Beckman Coulter's AccuTnI troponin test, USA) and the outcomes were expressed as ng/mL.

STATISTICAL EVALUATIONS

NCSS (Number Crunched Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used for the statistical analysis. During the evaluation of the study data, Mann Whitney U test was used for the intergroup comparisons of descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum) as well as the intergroup comparisons of parameters without normal distribution. Yates Continuity Correction test (Yates Corrected Chi-Square) was used for the comparison of qualitative data. Diagnostic screening tests (sensitivity, specificity, PPV, NPV) and ROC curve analysis were used for determination of cut-off point for the parameters. Significance was evaluated at the levels of p<0.01 and p<0.05.

RESULTS

This study was performed with a total 755 cases comprising of 51,9% females (n=392) and 48,1% males (n=363) in Emergency Clinic of Bakirkoy Dr Sadi Konuk Training and Research Hospital between 2012 and 2013. Mean age of the cases were determined to be 55,64±16,67 years (Table 1). Creatinine levels of the cases ranged between 0,47 and 9,74 mg/dl and the mean levels of creatinine were found to be 1,67±1,84 mg/dl. Troponin levels of the cases ranged between 0 and 3,49 U/L and the mean levels of troponin were found to be 0,04±0,20 U/L (Table 1).

Seventy-eight of the cases have being the dialysis patients. Proteinuria levels of 677 cases with urinary discharge ranged between 80 and 650 mg/day and the mean levels of proteinuria were found to be 287,92±100,81 mg/day; microalbuminuria levels ranged between 2 and 250 mg/day and the mean levels of microalbuminuria were determined to be 55,79±36,88 mg/day (Table 1). While mean creatinine levels of the cases in the patient group were found to be 4,22±2,11 mg/dl, mean creatinine levels of the cases in the control group were determined to be 0,79±0,16 mg/dl and the creatinine levels of the cases in the patient group were found to be significantly higher than the creatinine levels of the cases in the control group (p=0,001; p<0,01) (Table 2).

While mean proteinuria levels of the cases in the patient group were determined to be 391,79±105,42 mg/day, mean proteinuria levels of the cases in the control group were found to be 266,21±85,16 mg/day.
Table 1. Demographic features and laboratory findings.

<table>
<thead>
<tr>
<th></th>
<th>Min-Max</th>
<th>Mean±SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>17-100</td>
<td>55,64±16,67</td>
<td>56,0</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0,47-9,74</td>
<td>1,67±1,84</td>
<td>0,85</td>
</tr>
<tr>
<td>Troponin (U/L)</td>
<td>0-3,49</td>
<td>0,04±0,20</td>
<td>0,01</td>
</tr>
<tr>
<td>Proteinuria (n=677) (mg/day)</td>
<td>80-650</td>
<td>287,92±100,81</td>
<td>275,0</td>
</tr>
<tr>
<td>Microalbuminuria (n=677) (mg/day)</td>
<td>2-250</td>
<td>55,79±36,88</td>
<td>45,0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>392</td>
</tr>
<tr>
<td>Male</td>
<td>363</td>
</tr>
</tbody>
</table>

Table 2. Groups according to laboratory findings assessment.

<table>
<thead>
<tr>
<th></th>
<th>Patient group (n=195)</th>
<th>Control group (n=560)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD (Median)</td>
<td>Mean±SD (Median)</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>4,22±2,11 (3,57)</td>
<td>0,79±0,16 (0,77)</td>
<td>0,001**</td>
</tr>
<tr>
<td>Troponin (U/L)</td>
<td>0,12±0,39 (0,03)</td>
<td>0,02±0,05 (0,01)</td>
<td>0,001**</td>
</tr>
<tr>
<td>Proteinuria (mg/day)</td>
<td>391,79±105,42 (400)</td>
<td>266,21±85,16 (260)</td>
<td>0,001**</td>
</tr>
<tr>
<td>Microalbuminuria (mg/day)</td>
<td>65,28±47,21 (50)</td>
<td>53,81±34,06 (45)</td>
<td>0,041*</td>
</tr>
</tbody>
</table>

Mann Whitney U Test *p<0,05 **p<0,01

Table 3. Diagnostic test for troponin and ROC Curve results.

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Area</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin ≥ 0,02</td>
<td>68,21</td>
<td>70,71</td>
<td>44,78</td>
<td>86,46</td>
<td>0,742</td>
<td>0,700-0,784</td>
<td>0,001</td>
</tr>
</tbody>
</table>

PPV: Positive Predictive Value  NPV: Negative Predictive Value  CI: Confidence Interval

Table 4. Relationship between groups according to serum troponin levels (cut-off: 0,02).

<table>
<thead>
<tr>
<th>Troponin</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0,02</td>
<td></td>
<td></td>
<td>≥ 0,02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groups</td>
<td>Control</td>
<td>396</td>
<td>86,5</td>
<td>164</td>
<td>5,2</td>
</tr>
<tr>
<td>Patient</td>
<td>62</td>
<td>13,5</td>
<td>133</td>
<td>44,8</td>
<td></td>
</tr>
</tbody>
</table>

Yates’ Continuity Correction Test **p<0,01

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Table 5. Relationship between serum creatinine levels and serum troponin levels (cut-off: 0,02).

<table>
<thead>
<tr>
<th>Troponin &lt; 0,02</th>
<th>Troponin ≥ 0,02</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD (Median)</td>
<td>Mean±SD (Median)</td>
<td>p</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1,19±1,31 (0,78)</td>
<td>2,41±2,26 (1,10)</td>
</tr>
</tbody>
</table>

Mann Whitney U Test **p<0,01

When the proteinuria levels of the cases were compared according to the groups, the proteinuria levels of the cases in the patient group were determined to be statistically significantly higher (p=0,001; p<0,01) (Table 2).

While mean microalbuminuria levels of the cases in the patient group were found to be 65,28±47,21 mg/day, the mean microalbuminuria levels of the cases in the control group were found to be 53,81±34,06 mg/day. A statistically significant difference was determined between the microalbuminuria levels of the cases according to the groups (p=0,041; p<0,05). The microalbuminuria levels of the cases in the patient group were found to be significantly higher than the microalbuminuria levels of the cases in the control group (Table 2).

When the troponin levels were compared according to the groups, a highly statistically significant difference was found between the groups and the troponin levels of the cases in the patient group were determined to be higher than the troponin levels of the cases in the control group (p=0,001; p<0,01) (Table 2).

A cut-off point was calculated for troponin by considering the significant difference between the troponin measurements of the groups (Table 2). According to the groups, the best cut-off value was determined to be 0,02 U/L for troponin values. Sensitivity, specificity, positive prediction value, negative prediction value and accuracy for cut-off value of 0,02 U/L of troponin level were found to be 68,21%, 70,71%, 44,78, 86,46 and 70,71 respectively (Table 3).

A statistically significant relationship was determined between the patient and control groups and 0,02 U/L cut-off value of troponin level (p<0,01). The risk for chronic kidney disease in the cases with troponin levels of ≥ 0,02 was found to be 5,2-fold higher (ODDS ratio 5,18 (95% CI: 6,643-7,366)) (Table 4). A highly statistically significant difference was determined between the creatinine measurements of the cases according to the troponin levels (p=0,001; p<0,01). Creatinine measurements of the cases with troponin levels of ≥ 0,02 U/L were determined to be significantly higher than the cases with troponin levels of < 0,02 U/L (Table 5).

While mean troponin levels of the cases in the control group were found to be 0,12±0,39 U/L, mean troponin levels of the cases in the control group were determined to be 0,02±0,05 U/L. When the troponin levels were compared according to the groups, the troponin levels of the cases in the patient group were determined to be significantly higher than the troponin levels of the cases in the control group (p=0,001; p<0,01) (Table 2). When the ROC Curve related to troponin measurements according to the groups were evaluated, 74,2% standard error of AUC of the ROC Curve was obtained to be 2,2% (Figure 1).
DISCUSSION

Synergic effects of the renal diseases and cardiovascular diseases on one another are known. Numerous biomarkers are known in definition of the functions and lesions in the cardiovascular diseases existence of the chronic kidney disease. Some of these included biomarkers (11) include creatinine, cystatin C, neutrophil gelatinase-associated lipocalin, urinary cystatin C, natriuretic peptides and troponin.

Troponins and CK-MB find in the myocardium which should not be detected in serum, normally. Compared the levels of troponins and CK-MB; troponins detect to 13 folds higher than CK-MB in the myocardium. Many factors lead to differences in evaluation of the troponin levels such as the systemic diseases (12), serum waiting time, the tubes used for venous blood to contain EDTA and/or heparin (13), device of measurement and the method using for evaluation.

In this study, we compared the levels of troponin I, haven being in the normal renal functions and in the chronic kidney patients who had chest pain presented to our emergency department. We aimed to demonstrate that the relationship between impairment of renal function and serum troponin I levels in the patients who were ruled out emergency cardiovascular diseases. Also; the cut-off value for serum troponin I levels were determined in the chronic kidney patients followed-up in the our clinic.

Because all over the world, it is accepted that the use of the more sensitive measurement of troponin I (14) would achieve more accurate results and using of the 99th percentile level obtained from the reference population as the cut-off value of troponin I (15) might be more proper.

Results of many studies have shown that the elevation of troponin levels were associated with mortality despite lack of the diagnosis for coronary syndrome (16) in chronic renal disease. However, it has not been clearly shown that the correlation between decrease of glomerular filtration rate and the elevation of troponin levels were associated with cardiovascular morbidity and mortality.

In recent years, the opinion has been suggested to as the more common that many factors might be attributed to the elevation of troponin levels in chronic kidney patients. Elevated troponin values in the kidney transplant patients even the renal functions return to the normal following the transplantation process, suggesting elevated troponin levels (17) should not contribute only to the decrease of renal clearance.

In our study, we found that microalbuminuria, proteinuria and serum troponin I values of the group with chronic kidney disease were significantly higher than the control group. It was shown that the presence of microalbuminuria (18) was also important as increased creatinine levels, reduced glomerular filtration rate to determine the risk for cardiovascular disease in chronic kidney disease. Additionally, it is suggested that presence of proteinuria (19) without hypertension and diabetes mellitus can cause to the increase of cardiovascular disease risk in every stage of chronic kidney diseases.

Presence of microalbuminuria, proteinuria and decrease of glomerul filtration rate have been important in the development of the cardiovascular diseases. Evaluation of the results of our study; would be considered to the high risk for cardiovascular disease in our patient group who were rule out of the existence of the emergency cardiovascular diseases. Also, determination of a positive correlation between high levels of serum troponin I values and increased serum creatinine, microalbuminuria and proteinuria in the patient group. We believed that this results show the association between existence of cardiovascular diseases or the high risk of cardiovascular diseases with serum troponin I levels. Summary; elevated troponin I level might be an early indicator of several diseases such as myocarditis, left ventricular hypertrophy and increase of the myocardial infarction risk and cardiac overload etc., it was associated with decrease of glomerular filtration rate except in the patients group of our study.

The adopted opinion; increase of troponin levels are detected due to decrease of the glomerul filtration rate in the chronic kidney disease. In recent years; it is suggested that increase of the levels of troponin I should be accepted as significant and increase of troponin levels should be evaluated together with the clinical and comorbidity factors and CK-MB in the emergency conditions, in the chronic kidney disease.

The levels of troponin I are affected by many factors and requiring precise measurement methods may cause measurement differences between the clinics. Therefore, there is not a clearly defined cut-off value for the diagnosis of the coronary syndrome in the chronic kidney disease. In our study; cut-off values of troponin I were demonstrated by our clinic. However; we showed the sensivity and specificity of troponin I. We believe that troponin I would be important as a biomarker in the chronic kidney disease.

CONCLUSION

It is not known how the cardiac biomarkers effect in nonvascular chest pain and the effects of elevated creatinine on the biomarkers in the patients with the chronic kidney disease. We believe that more knowledge obtained on the biomarkers will contribute to early period diagnosis of the cardiovascular disease therefore would be made to the faster and the approach and more efficient treatment.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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