Cardiac Enzymes, Renal Failure and Renal Transplantation

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Diagnostic accuracy of the currently available serum markers of cardiac injury, such as myoglobin, creatine kinase and its myocardial isoform, are altered in patients with renal failure. It is shown that cardiac troponins have decreased diagnostic sensitivity and specificity in patients receiving renal replacement therapy. Data regarding serum levels of these cardiac biomarkers, especially those of the cardiac troponins, in patients with a transplanted kidney are limited. Current data show that levels of cardiac troponin I are unaltered in patients who have undergone renal transplantation, while levels of cardiac troponin T may be elevated. We believe that cardiac troponin I should be the biomarker of choice for diagnosis of myocardial injury in these patients. However, further trials are required for conclusive results.

Keywords: Cardiac enzymes; Cardiac troponins; Renal failure; Renal transplantation

End-stage renal disease (ESRD) patients receiving renal replacement therapy have an excess of cardiovascular mortality.^{1,2} Although decreasing in incidence, cardiovascular diseases are still the most-common cause of death in patients who have undergone renal transplantation and have a functioning kidney graft.^{3,4} Therefore, accurate diagnosis of acute cardiac syndromes in these patients is important.

Available biochemical markers, especially those other than troponins, used to detect myocardial injury have been found to be falsely elevated in patients receiving maintenance dialysis. In this article, we review the literature regarding cardiac enzymes (particularly that of the cardiac troponins) in patients with ESRD, possible mechanisms for the false positive elevations, and present the data regarding the behavior of these markers in patients who have undergone renal transplantation.

Cardiac Enzymes

Troponins are the structural proteins of both cardiac and skeletal muscles and are responsible for regulation of actin-myosin binding. Cardiac troponins are specifically determined by monoclonal antibody assays since they are encoded by genes that are different from their skeletal counterparts.⁵ Troponin T, I, and C are three types of cardiac troponins that form the troponin

complex. Both cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are very sensitive and specific markers of myocardial damage and are used widely for this aim. However, in the absence of a major, clinically evident cardiac injury, troponins are found to be elevated in several clinical conditions like ESRD, sepsis, pulmonary embolism and acute stroke.⁶⁻⁹ Creatine kinase myocardial isoform (CK-MB) is another marker commonly used for diagnosis of myocardial infarction.

ESRD and Cardiac Enzymes

Renal failure is one of the conditions in which serum markers of myocardial damage are falsely elevated. It is well known that levels of creatine kinase, CK-MB and myoglobin are altered in patients with uremia.¹⁰⁻¹² Angina may be atypical or not observed due to silent ischemia and can be caused by factors other than coronary artery disease. In addition, nonspecific electrocardiogram findings are very common in these patients due to electrolyte imbalance, left ventricular hypertrophy and drug effects. Therefore, the value of specific biochemical markers of myocardial injury is crucial to this patient population.

In some studies it is demonstrated that elevated cardiac troponins are a sign of coronary artery disease when these patients were investigated invasively by angiography¹³ or non-invasively using stress cardiac isotopic imaging.¹⁴

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Table 1. Possible causes of cardiac troponin elevation in patients with end-stage renal disease

Uremic myopathy
Expression of fetal cardiac troponins in the skeletal muscle
Altered protein clearance
Abnormal protein metabolism
Silent myocardial injury, microinfarctions
Uremic milieu-uremic toxins, nonischemic damage to the myocardium
Left ventricular hypertrophy
Inflammatory condition

However, there are reports showing that cardiac troponins, especially cTnT, might be elevated in patients with uremia without a clinically evident coronary ischemic event.^{15,16} Elevations in cardiac troponins in patients with ESRD result from a number of potential sources (table 1). First, a potential source is skeletal muscle. Patients with uremia may have some pathologic changes in their skeletal muscles (so-called uremic myopathy). There are reports indicating that elevated cTnT levels might be the result of re-expression of fetal cTnT in myopathic skeletal muscles.^{16,17} However, with development of the third generation assays this problem seemed to be resolved.¹⁸ The second potential source is small, silent myocardial injuries or microinfarcts, which are not easily detected using conventional methods.¹⁹ Microinjury in these patients may result from conditions like silent ischemia, cardiotoxicity from changes in osmolarity/ion fluxes, increased preload and myocardial stretch, and nonischemic myocardial injury due to uremic toxins. These microinfarctions are at the center of the arguments that cardiac troponins are of the cardiac origin. One might argue that prevalence of ischemic heart disease is high in these patients, as are microinfarctions, because of ischemic episodes.

A third potential mechanism is the lack of clearance of cardiac troponins from the blood or alterations of their metabolism by nonfunctioning kidneys. There is a school of thought that the kidneys are responsible for troponin clearance, but the data show that the elimination rate of elevated troponin levels in patients with ESRD having myocardial infarction is no different than it is in patients with normal renal function.²⁰

Protein metabolism becomes abnormal in patients undergoing dialysis as does the metabolism of troponins. It is therefore possible that false-positive troponin results are the result of degradation products.²¹ Phosphorylation of troponins may be altered in renal failure.²²

Left ventricular hypertrophy seems to be another cause of elevated troponin levels in patients with ESRD.²³ Correlation between cardiac troponins and left ventricular hypertrophy

was demonstrated in the studies involving ESRD patients on hemodialysis²⁴ and continuous ambulatory peritoneal dialysis.²⁵ The relation between left ventricular hypertrophy and elevated cardiac troponins is not clearly known. However, since it contributes to ischemia because of the supply-demand problem and high prevalence of ischemic heart disease with calcified coronary arteries, it may be considered a likely explanation for positive troponin results.

Roppolo and colleagues²⁶ hypothesized that the inflammatory condition in patients on dialysis may be the cause of marker elevation. They proposed that there is an ongoing inflammatory condition once patients start receiving renal replacement therapy, and that this may lead to plaque rupture, increasing cardiac events.

As can be seen, there are many hypotheses, but the actual source of elevated cardiac troponins in the absence of a demonstrable myocardial injury in these patients is not clearly known. Myopathic skeletal muscle in patients with uremia seems to be one of the sources of falsely elevated levels of CK-MB. However, there is no clear reason for elevation of cTnI and cTnT without myocardial insult. Data derived from the trials evaluating the diagnostic power of troponins in patients with ESRD for the diagnosis of myocardial damage vary widely. In some studies, sensitivity for cTnT was reported to be as high as 100%²⁷ and in other studies, specificity for cTnI was demonstrated to be as high as 100%,²⁸ while other trials showed very low percentages of sensitivity and specificity for cardiac troponins.^{16,29} Available data, although not conclusive, suggest that cTnI has higher specificity for cardiac injury in patients with ESRD.^{27,30}

With regard to the prognostic significance of elevated cardiac troponins in ESRD, the data are conflicting. In some studies, positive results of cTnT were found to have more prognostic importance,^{13,25,31,32} in others cTnI were found to be more powerful for the prediction of future events.^{28,33,34} In some studies, combinations of them were shown to be good predictors of cardiovascular events,^{26,35,36} while some trials showed no prognostic value of positive troponin findings in the follow-up of these patients.^{37,38} But, when looking at the results of all these studies, the prevalence of elevated levels of cTnT was more frequent and seems to have more prognostic value than cTnI.

Renal Transplantation and Cardiac Enzymes

The question is whether or not these false positive results might be observed after renal transplantation. Currently, there is not enough data to conclusively state whether these false positive results are observed after permanent restoration of renal function by kidney transplantation.

Krol and colleagues³⁹ evaluated serum cTnT levels in a cross-sectional study in patients receiving different renal replacement therapies. They included 17 patients on hemodialysis, 23 patients on continuous ambulatory peritoneal dialysis (CAPD) and 23 patients with a functioning

transplanted kidney. In the absence of myocardial damage, an elevated level of cTnT was found in 29% of the patients undergoing hemodialysis, 35% of those receiving CAPD and none of those with a functioning transplanted kidney.³⁹

To our knowledge, there are only three prospective trials that have examined levels of cardiac troponins in patients who had undergone renal transplantation (table 2). In the first, Wu and coworkers⁴⁰ determined the levels of cTnT and cTnI in patients undergoing renal transplantation before and after the operation. In all the patients, cTnI levels were below the acute myocardial infarction limit before and after the operation (the cut-off value for myocardial infarction was 2.5 µg/l). When they took 0.5 µg/l as the upper reference limit, cTnI was found to be elevated in 8% of the patients preoperatively and in 4% of the patients postoperatively. Therefore, according to recommended reference values, cTnI was below the myocardial infarction limits in all patients, both preoperatively and postoperatively. On the other hand, levels of cTnT (the upper reference limit was 0.1 µg/l) was found to be above the reference level in 15% of the cases preoperatively and 4% postoperatively.⁴⁰ An important result of this study was that cTnT elevation was more common during the pre-transplantation period than it was during the post-transplantation period. The authors thought that this decrease in the rate of false positive cTnT elevations might be the result of improved clearance.

In the second study, Fredericks and colleagues⁴¹ studied cTnT in patients undergoing renal transplantation. They determined cTnT levels preoperatively at baseline and at 1, 3, 6 and 12 months after the operation. Here, they used a third-generation assay for cTnT analysis for which the upper reference limit

was 0.1 µg/l. They found that cTnT was above this limit in three (9.4%) patients preoperatively, and that five (15.6%) patients developed elevated cTnT levels during the year following the operation.⁴¹ Those patients with elevated cTnT levels had multiple cardiac risk factors or explainable pathologies. However, the authors concluded that the overall trend in circulating cTnT concentrations did not seem to be affected after kidney transplantation. They also noted that there was neither myopathy in any of the patients nor any evidence that these elevations might have resulted from the drugs they were taking. One of the major limitations of this study is that cTnI was not determined. If it had been, we could have compared cTnI and cTnT in this patient population during the postoperative year.

In the third study, Bozbas et al⁴² evaluated the levels of cardiac enzymes before and after renal transplantation. We determined the levels of CK-MB and cTnI which were analyzed by a microparticle enzyme immunoassay (Axsys System Abbott, Abbott Park, IL) with a normal range of cTnI values from 0.02 to 2.3 ng/ml. Unlike the previous studies, we correlated our results with echocardiographic and myocardial perfusion scintigraphic findings to objectively document whether myocardial ischemia/damage had occurred. There was no cTnI elevation beyond the acute myocardial infarction reference level (<2.3 ng/ml) in any of the patients before transplantation and for a month after operation, which correlates with the findings that neither new wall motion abnormality developed on echocardiography nor any ischemia/new perfusion defect on myocardial perfusion scintigraphy.⁴² In this respect, our study differs from the earlier studies^{40,41} in that we correlated our biochemical marker results with the results of noninvasive testing of

Table 2. Studies evaluating the levels of cardiac enzymes before and after renal transplantation.

Author	Wu et al ⁴⁰	Fredericks et al ⁴¹	Bozbas et al ⁴²
Year	1999	2001	2004
Number of patients	26	32	34
Preoperative elevation of cTnT (%)	First assay: 54% Second assay: 15%	9.4%	—
Postoperative elevation of cTnT(%)	First assay: 12% Second assay: 4%	15.6%	—
Preoperative elevation of cTnI (%)	None	—	None
Postoperative elevation of cTnI (%)	None	—	None
Preoperative elevation of CK-MB (%)	—	—	None
Postoperative elevation of CK-MB (%)	—	—	38.2%
Noninvasive assessment for myocardial damage	—	—	2-D echocardiography Thallium-labeled MPS

cTnT, cardiac troponin T; cTnI, cardiac troponin I; CK-MB, creatine kinase myocardial isoform; MPS, myocardial perfusion scintigraphy
—, not studied

myocardial damage. The mean levels of CK-MB increased during the early postoperative period and then decreased to normal levels on follow-up. This increase was above the myocardial infarction reference limit in 38.2% of the patients. That was an expected finding that resulted from muscle injury during the early postoperative period. Although far below the myocardial infarction cut-off value, we observed a slight increase in the levels of mean cTnI after the operation, which decreased to preoperative levels at the end of the first postoperative month. This led us to speculate that this slight increase might have resulted from muscle injury, and its decrease to preoperative levels might be a result of restored or improved protein clearance and metabolism by the functioning transplanted kidney. We, therefore, can say that restoration of renal function in these patients led to unaltered cTnI levels in the absence of acute cardiac syndromes, as is the case in the general population.

By restoring renal function through kidney transplantation, some of the possible causes of troponin elevation, such as the uremic milieu, abnormal protein clearance and abnormal protein metabolism, can be eliminated. However, other possible causes like left ventricular hypertrophy and silent ischemia must still be taken into consideration. To be conclusive, the corresponding roles of each of these factors need to be documented.

Another issue for patients with a transplanted kidney is that the drugs they take (e.g., statins, cyclosporine and tacrolimus) may cause myopathy.⁴³ This, by itself, may be a cause of elevated troponin levels. However, a study by Fredericks and colleagues,⁴¹ although having a limited number of patients, failed to demonstrate such a correlation.

Considering all three prospective studies⁴⁰⁻⁴² together, a total of 92 patients whose cardiac troponin levels were determined before and after renal transplantation were acquired (table 2). From these data, we can conclude that levels of cTnI are unchanged after restoration of renal function, and that cTnI has high sensitivity and specificity for the diagnosis of myocardial damage in patients who had undergone renal transplantation.

Cardiac Troponins and Cardiac Events in Patients with a Transplanted Kidney

It is well known that cardiac mortality is high in patients with ESRD. Studies indicate that even mild elevations in serum creatinine levels increase cardiovascular mortality.^{44,45} Compared with dialysis, renal transplantation offers a significant survival benefit, in addition to improving the quality of life.⁴⁶ Meier-Kriesche and colleagues⁴⁷ have shown that cardiac mortality decreases following renal transplantation. In that study, they showed that cardiovascular mortality decreased 3 months after transplantation. When considering duration of ESRD to post-transplantation survival, the authors noted that the longer the duration of ESRD, the lower the 10-year survival after transplantation.

With a functioning transplanted kidney, mortality rates remained low. The authors concluded that restoration of renal function, together with the other very important measures like effective blood pressure control, treatment of dyslipidemia, smoking cessation and exercise, could decrease or even reverse progression of cardiovascular disease in patients with uremia, and that this effect is long lasting.

Although cardiovascular mortality is significantly reduced following renal transplantation, it remains one of the most common causes of mortality in this population,^{3,4,48} indicating that there are multiple factors at work causing heart disease and heart failure in these patients. The frequency of elevations in cardiac troponin levels in the absence of a clinically evident myocardial injury, and if so, whether or not high cardiac troponin levels in patients with a transplanted kidney are at greater risk for cardiac mortality, is not known. Currently, no controlled trials with long-term follow-up have answered this question. Further trials with long-term follow-up are needed.

Conclusions

Studies suggest that CK-MB has relatively low sensitivity and specificity for identifying myocardial injury in patients with uremia. However, we believe it can be used in patients who have undergone renal transplantation with a normal functioning graft kidney except during the early postoperative period and after noncardiac surgical procedures.

In light of the available data, we can conclude that cTnI is more useful than cTnT and CK-MB for diagnosing myocardial injury. cTnI is a highly sensitive and specific marker of myocardial damage in patients who have undergone renal transplantation. It is exclusively of cardiac origin and does not have cross-reactivity with the skeletal muscle. Available evidence indicates that cTnI should be the biomarker of choice for diagnosing myocardial injury in patients with renal failure who have undergone renal transplantation. A better means of evaluating patients with ESRD or with a functioning kidney graft would be to combine the patient's clinical and electrocardiographic findings with a repeat measure of cardiac markers (of which cTnI should be given the highest priority), cTnT, CK-MB and CK-MB mass. Further studies with increased numbers of patients are needed to define this matter.

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