Cardiac troponin T and end stage renal disease

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ABSTRACT

Objective: The aim of this study is to investigate the relationship between serum concentration of cardiac troponin T (cTnT) and other cardiac markers and ischemic heart disease (IHD) in end stage renal disease (ESRD) patients on chronic hemodialysis (HD).

Methods: This study was carried out at King Fahd Specialist Hospital, Buraidah, Kingdom of Saudi Arabia from July 2002 to September 2003. Cardiac troponin T was measured using Elecsys 2020 immunoassay system, a method that is specific for cTnT. The analytical range of cTnT assay was 0.01-25.0 µg/L. Seventy-three patients were divided into 4 groups: 20 patients with history of IHD, 17 patients with diabetes, 19 patients with diabetes and IHD and 17 patients without evidence of myocardial damage.

Results: Cardiac troponin T concentrations were ≥0.1 µg/L in 58% of HD patients. Fifty-three percent of diabetic patients had an increased cTnT, 37% of IHD patients had an increased cTnT, 59% of IHD and diabetic patients had an increased cTnT and 29% of noncardiac disease patients had an increased cTnT. Cardiac troponin T was increased more frequently in post-hemodialysis samples (13% pre-hemodialysis and 21% post-hemodialysis).

Conclusion: Dialysis may alter measured cTnT concentrations in ESRD patients undergoing chronic dialysis. Sporadic or persistently increased cTnT appear to be the most specific of the currently available biochemical markers to predict subclinical myocardial damage in ESRD patients.

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Cardiac disease is the leading cause of morbidity and mortality in patients with end stage renal disease (ESRD). Myocardial infarction accounts for 30-50 % of cardiac death. In ESRD patients, ventricular hypertrophy, interstitial myocardial fibrosis and endothelial dysformation limit the coronary flow to the myocardium during stress and may play a pathophysiological role.[1] The diagnosis of ischemic myocardial damage is difficult in the ESRD patients due to atypical symptoms and chronically elevated protein markers of cardiac damage.[2] Several studies have shown that the older cardiac markers CK and more specific CK-MB are frequently elevated or indeterminate in ESRD patients without other signs of acute ischemic heart disease.[3] Cardiac troponin T and I are specific markers of myocardial damage.[4] Cardiac troponin T (cTnT) that enables the identification of patients with latent or progressive myocardial damage can be detected in chronic renal failure patients.[5] Muller et al,[6] observed increased cTnT in serum of patients with renal failure. The possibility of cross-reactivity with skeletal troponin T was proposed by Kobayashi et al.[7] However, with the use of more specific techniques increased values of cTnT persisted in these patients.[8] Patients with end stage renal failure undergoing chronic hemodialysis have a high incidence of cardiac events.[9] These markers may be increased in these patients without evidence of ischemic myocardial damage.[10]

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Methods. Seventy-three patients on chronic hemodialysis (33 male, 40 female) without symptoms of acute myocardial ischemia were studied (median 64, range 27-78 years). At the start of the study we divided the patients into: 20 patients with history of IHD, 17 had diabetes mellitus (DM), 19 had both IHD and DM and 17 without evidence of myocardial damage. Blood was collected before and after dialysis. The samples were centrifuged for 15 minutes at 2700 gm within one hour of collection. The serum samples were stored at -70°C until analysis. Troponin T was measured using the Elecsys 2020 immunoassay system (Boehringer Mannheim, Germany), a method that is specific for cTnT.[11] The analytical range of cTnT assay was 0.02-25.0 µg/L. The recommended cut-off value for acute coronary disease is ≥0.1 µg/L. The lower detection of cTnT was 0.02 µg/L. Creatine kinase-MB mass were measured on a Stratus II analyzer (Dade Behring, Inc., Deerfield, United States of America) using the Sandwich technique, with double monoclonal antibodies. Values exceeding the upper reference limit were considered elevated; for CK male it was ≥174 U/L and for CK female it was ≥144 U/L, a CK-MB relative index was CK-MB >5% and CK-MB mass was >15 µg/L. Serum creatinine was estimated according to modified Jaffe method.[12]

Statistical analysis. Data are given as median and interquartile range. Non-parametric tests were used. Correlations between variables were tested by Spearman rank correlation test. The Mann-Whitney U-test was employed to compare unpaired data between groups. The 97.5th percentiles cTnT, and cTnI CK-MB in percentage were made by using data from pre-dialysis samples. These data had been analyzed by SPSS computer program.

Results. In all patients, cTnT concentration was ≥0.1 µg/L in 55% and no patients had CK-MB mass more than 15 µg/L. The 97.5th percentiles and range are shown in **Table 1.** Patients with IHD had a higher significant serum concentration of cTnT and CK-MB compared to patients without IHD; 0.15 (0.08-0.33) versus 0.04 (0.00-0.15) in case of cTnT and 10 (5-18) versus 4 (1.5-9) in case of CK-MB. Yet, CK showed lower values in patients with IHD versus those without IHD: 9 (3-20) versus 32 (12-61). There is no significant changes between both groups with regard to CK-MB mass (**Table 2**). There is a higher percentage of elevated cTnT concentration above the upper reference value in patients with IHD than in patients without IHD (65% versus 36%). There is no correlation between cTnT and CK-MB and %CK-MB after hemodialysis (**Table 3**). End stage renal disease patients with both diabetes and IHD had a higher percentage of increased cTnT (58%) than other groups. Cardiac troponin T values were significantly increased in post-hemodialysis patients (21%) compared to pre-hemodialysis patients (13%) ($p<0.05$). A significant positive correlation was found between serum concentration of cTnT and the following variables were remarked age, CK-MB mass and %CK-MB. Negative correlation between serum cTnT and serum creatinine was observed (**Table 4**).

Table 1 - 97.5th percentile and range in all dialyzed patients.

Parameter	97.5th percentile	Range
cTnT	0.53	0.00 - 1.5 µg /L
CK-MB mass	7.5	0.00 - 8 µg /L
%CK-MB	26	0.00 - 43

cTnT - cardiac troponin T,
CK-MB - creatine kinase-myocardial bound

Discussion. Patients with chronic renal failure on hemodialysis are at high risk for cardiovascular disease. Hypertension and diabetes are independent risk factors for cardiovascular disease. Accelerated arteriosclerosis is associated with chronic dialysis and more than one-half of the deaths in dialysis are of cardiovascular etiology.[13] The diagnosis of myocardial ischemia is difficult in ESRD patients since they often demonstrate abnormal baseline echocardiogram (ECG) and often are not able to perform adequate exercise tests due to limited exercise tolerance. Symptoms may be masked by underlying disease. Therefore, the use of reliable biochemical markers for the detection of myocardial damage is essential in these patients. Creatine kinase-MB can be elevated in ESRD without clinical signs of myocardial ischemia.[12] Therefore, one must assign reliable markers for the presence of myocardial injury and for assessment of the risk of cardiovascular events in these patients. Two proteins of troponin complex: cTnT and cTnI, have been regarded as ideal serodiagnostic markers for myocardial damage.[14] Both cTnT and cTnI can also be detected in blood of patients with chronic heart failure, which enables the identification of patients with latent or progressive myocardial damage.[15,16] Troponins are known to be better cardiac markers than CK-MB. It was demonstrated that current assay performance for cTnT is better than that for cTnI and direct comparison of cTnT and cTnI suggests a better outcome prediction for cTnT.[17] Cardiac troponin T may be an important

Table 2 - Dialyzed patients without ischemic heart disease and with ischemic heart disease.

Parameters	Without ischemic heart disease		With ischemic heart disease		*p* value
	Median	Inter-quartile range	Median	Inter-quartile range	
Cardiac troponin T (µg/L)	0.04	0.00-0.15	0.15	0.08 - 0.33	<0.05
Creatine kinase (U/L)	32	12-61	9	3 - 20	<0.05
%CK- MB	4	1.5-9	10	5 - 18	<0.05
CK-MB mass µg/L	0.6	0.0-1.7	0.9	0.2 - 1.9	>0.05

CK-MB - creatine kinase MB

Table 3 - Correlation between cTnT concentration and other parameters before and after dialysis.

Parameter	Before dialysis r	*p*	After dialysis r	*p*
cTnT versus CK-MB	0.14	>0.05	0.15	>0.05
cTnT versus %CK-MB	0.13	>0.05	0.15	>0.05

CK-MB - creatine kinase MB, cTnT - cardiac troponin T

Table 4 - Correlation between serum cTnT and other data in hemodialyses patients before and after dialysis.

Parameters	Correlation coefficient	*p*
cTnT versus age	0.41	<0.05
cTnT versus CK-MB mass	0.52	<0.05
cTnT versus %CK-MB	0.47	<0.05
cTnT versus CK	0.13	>0.05
cTnT versus creatinine	- 0.37	>0.05

CK-MB - creatine kinase MB, cTnT - cardiac troponin T

independent prognostic marker in patients on hemodialysis for chronic renal failure.[15,18,19] Furthermore, it is very sensitive for the detection of minor myocardial damage and provides prognostic information in patients with unstable coronary artery disease.[20] However, in ESRD frequent and unexplained increases of cTnT have raised questions on the cardiac specificity of this marker in patients with renal failure.[21] When we use an improved cTnT assay with a cross-reactivity <0.01% we found increased cTnT values in 58% of HD patients at cut-off of 0.1 µg/L. Similar results showed increase cTnT values in 38% of patients with ESRD and a strong association of cTnT with all cause mortality in these patients,[22,23] while others found pre-dialysis levels of cTnT >0.1 in 18.6% of patients and were associated with age, history of IHD and left ventricular hypertrophy.[24]

In this study, cTnT is increased after consistent dialysis with results described by Ooi and House.[21] On the contrary, Lowbeer et al[1] reported no difference in cTnT values before and after dialysis. We found a negative correlation between serum cTnT and serum creatinine, which can be explained by a lower muscle mass in the older severely ill patients. In HD patients without evidence of acute myocardial ischemia, those with a history of IHD showed higher serum cTnT than patients without IHD. This finding is in accordance with Haller et al[25] who reported a correlation between the plasma cTnT concentration and indicators of coronary artery disease in ESRD patients. Also, they have strengthened the argument that the increased serum cTnT found in many patients with ESRD originate in heart muscle and not regenerating skeletal muscle as suggested by McLaurin et al.[22] Furthermore, Haller et al[25] reported a high prevalence of

concentric left ventricular hypertrophy in hemodialysis population with increased cTnT levels. Thus, cTnT may be an early marker of cardiac hypertrophy. Wayand et al[26] reported that coronary artery disease (CAD) may not be the only reason for increased cTnT in ESRD patients. Not only arteriosclerotic but also non-arteriosclerotic heart disease (hypertrophy, water-overload, myocardial fibrosis, decreased arterial compliance) may lead to the release of small amounts of intracellular proteins.[27] This is in agreement with Frankel et al[2] who showed that increased myocardial lengthening and congestive cardiomyopathy lead to increased in cTnT in 18% of their patients. Some have suggested that cTnT increase in chronic renal failure patients indicated coronary disease.[28-30] Our findings of higher serum cTnT concentrations in diabetic dialysis patients (53%) than in patients without diabetes or IHD (29%) and this percentage rose to be 59% in IHD and diabetic patients. These results are consistent with Ooi and House[31] who reported a higher percentage (58%) of increased cTnT in hemodialysis patients with DM. They speculated that advanced glycosylation end products could induce cTnT expression in non-cardiac cells and affect membrane integrity. In a study on diabetic patients with chronic renal failure it showed higher serum troponin T, myoglobin and myosin light chain with those under hemodialysis having the highest values. This indicates that cTnT reflected a higher incidence of myocardial complications in diabetic nephropathy.[24] In another series of 67 patients, the single patient with increased troponin I had documented cardiovascular disease, whereas 6 of 31 patients with increased cTnT had no echocardiographic changes.[29] Diabetic patients are at high risk of developing IHD, which may be present but not diagnosed in these patients. Measurement of cTnT in patients with renal impairment is a significant predictor of subsequent mortality. Also, they suggested that the cause of raised cTnT in patients is related to their deranged renal function per se but to concomitant cardiovascular disease already present.[32,33] DeFilippi et al[34] demonstrated that among stable patients with ESRD, increasing levels of cTnT may identify patients with severe angiographic coronary disease.

In conclusion, it seems that elevated serum levels of cTnT can be expected in ESRD patients without evidence of acute myocardial infarction, which may enable the identification of patients with subclinical myocardial damage and whether these patients require some modification of their treatment. Further study of cTnT as a prognostic test in a larger number of patients over a longer period of time is needed which might add for more accuracy of cTnT in different groups.

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References

1. Lowbeer C, Ottosson S, Gustafsson A, Norman R, Hulting J, Gutierrez L. Increased cardiac troponin T and endothellin-1 concentrations in dialysis patients may indicate heart disease. ***Transplantation*** 1999; 14: 1943-1957.
2. Frankel W, Herold A, Ziegler W, Fitzgerald L. Cardiac troponin T is elevated in a symptomatic patients with chronic renal failure. ***Am J Clin Pathol*** 1996; 106: 118-123.
3. Martin S, Becker N, Schulman G. Cardiac troponin-I accurately predicts myocardial injury in renal failure. ***Nephrol Dial Transplant*** 1998; 13: 1709- 1712.
4. Bodor GS, Porter S, Landt Y, Ladenson JH. Development of monoclonal antibodies for an assay of cardiac troponin-I and preliminary results in suspected cases of myocardial infarction. ***Clin Chem*** 1992; 38): 2203-2214.
5. La Vecchia L, Mezzena G, Zanolla L, Paccanaro M, Varotto L, Bonanno C, et al. Cardiac troponin I as diagnostic and prognostic marker in severe heart failure. ***J Heart Lung Transplant*** 2000; 19: 644-652.
6. Muller M, Rallennayer K, Schroder A, Ebert C, Borgya A, Gerhardt W. National institute of health. ***National Institute of Diabetes and Digestive and Kidney Diseases*** 1998; 14: 79-99.
7. Kobayasahi S, Tanaka M, Tamura N, Rashimoto R, Rirose S. Serum cardiac troponin T in polymyositis/dermatomyositis. ***Lancet*** 1992; 340: 726.
8. Copeland K, Hollen M, Kirvan K, Sedor A. Troponin I and Troponin T in dialysis treated chronic renal failure patients. ***Clin Chem*** 1997; 43: S160.
9. Foley R, Parfrey S, Harnett D, Kent M, Martin J, Murray C et al. Clinical and echocardiographic disease in patients starting end stage renal disease therapy. ***Kidney*** 1995; 47: 186-192.
10. Li D, Keffer J, Corry K, Vazquez M, Jialal I. Non-specific elevations of troponin T levels in patients with chronic renal failure. ***Clin Biochem*** 1995; 28: 474-447.
11. Baum H, Braum S, Gerhardt W, Gilson G, Hafner G, Muller M. Multicenter evaluation of a second generation assay for cardiac troponin T. ***Clin Chem*** 1997; 43: 1877-1884.
12. Jaffe A, Ritter C, Meltzer V, Harter H, Roberts R. Unmasking artifactual increases in creatine kinase isoenzymes ill patients with renal failure. ***J Lab Clin Med*** 1984; 104: 193-202.
13. Keoman J, Leunissen K. Cardiovascular aspects in renal disease. ***Nephrol Hypertes*** 1993; 2: 791-797.
14. Larue C, Calzolai C, Bertinchant J, Leclercq F, Grolleau R. Cardiac specific immuno-enzymatic assay of troponin I in the early phase of acute myocardial infarction. ***Clin Chem*** 1993; 39: 973-979.
15. Missove E, Mair J. A novel biochemical approach to congestive heart failure: Cardiac troponin T. ***Am Heart J*** 1999; 138: 95-99.
16. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. ***J Am Coll Cardiol*** 2002; 40: 2065-2071.
17. Collinson P. Troponin T or troponin I, or CK-MB (or none). ***Eur Heart J*** 1998; 19 (Suppl N): N16-N24.

18. Choy JB, Armstrong PW, Ulan RA, Campbell PM, Gourishankar S, Prosser CI et al. Do cardiac troponins provide prognostic insight in hemodialysis patients? ***Can J Cardiol*** 2003; 19: 907-911.
19. Peetz D, Schutt S, Sucke B, Faldum A, Wandel E, Hafner G et al. Prognostic value of troponin T, troponin I, and CK-MBmass in patients with chronic renal failure. ***Med Klin (Munich)*** 2003; 98:188-192.
20. Lindahal B, Venge P, Wallentill L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. ***Circulation*** 1996; 93: 1651-1657.
21. Bahayana V, Gougoulias T, Cohoe S, Henderson R. Discordance between results for serum troponin T and troponin I ill renal disease. ***Clin Chem*** 1995; 41: 312- 317.
22. McLaurin M, Apple F, Voss M, Herzog C, Sharkey S. Cardiac troponin I and cardiac troponin T and CK-MB in dialysis patients without ischaemic heart disease. ***Clin Chem*** 1997; 43: 976-982.
23. Dierkes J, Domrose U, Westphal S, Ambrosch A, Luley C. Cardiac troponin T predicts mortality in patients with end stage renal disease. ***Circulation*** 2000; 17: 1964.
24. Ilious M, Fumeron C, Benoit M, Tuppin P, Jacquot K. Factors associated with increase serum levels of cardiac troponin T and I in chronic haemodialysis patients. ***Nephrol Dial Transplantation*** 2001; 16: 1452.
25. Haller C, Zehelein J, Remppis A, Muller M, Katus HA. Cardiac troponin T in patients with end stage renal disease: absence of expression in truncal skeletal muscle. ***Clin Chem*** 1998; 44: 930-938.
26. Wayand D, Baum H, Schatzle G, Neumeier S. Cardiac troponin T and I in end stage renal failure. ***Clin Chem*** 2000; 1345: 46-58.
27. London G, Parfrey P. Cardiac disease in chronic uremia. ***Adv Ren Replace Ther*** 1997; 4: 194-211.
28. Apple F, Sharkey S, Roeft P, Skeat R, Voss E, Dahlmeier B et al. Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: a 1-year outcome analysis. ***Am J Kidney Dis*** 1997; 29: 399-403.
29. Akagi M, Nagake Y, Ichikawa H, Makino H, Ota Z. Myocardial troponin T levels in patients with diabetic nephropathy. ***J Nephrol*** 1996; 38: 136-140.
30. Alan R, McNeil V, Mark M, Chris J, Ellis M, Robert C, et al. Why is the troponin T increased in the serum of patients with end-stage Renal Disease? ***Clin Chem*** 1998; 44: 2377-2378.
31. Ooi D, House A. Cardiac troponin T in haemodialysed patients. ***Clin Chem*** 1998; 44: 1410-1423.
32. Grahame NI, Brian K, Jaya G, Robert F, Abdalla B, Garry M, Peter A. Serum troponin measurement in patients with chronic renal impairment predicts survival and vascular disease: a 2 year prospective study. ***Neph Dial Transpl*** 2003; 18: 1610
33. Iliou MC, Fumeron C, Benoit MO, Tuppin P, Calonge VM, Moatti N et al. Prognostic value of cardiac markers in ESRD: Chronic Hemodialysis and New Cardiac Markers Evaluation (CHANCE) study. ***Am J Kidney Dis*** 2003; 42: 513-523.
34. DeFilippi C, Wasserman S, Rosanio S, Sperger H, Tocchi M, Smiley M et al. Cardiac troponin T and C-Reactive protein for predicting prognosis, coronary atherosclerosis and cardiomyopathy in patients undergoing long term hemodialysis. ***JAMA*** 2003; 290: 353.