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## Correlation of Serum Creatine Kinase, Creatine Kinase-MB, and Troponin I with Cardiac Pathology in End-Stage Renal Disease Patients

### Corelarea Nivelelor Serice ale Creatin Kinazei, Izoenzimei MB a Creatin Kinazei și ale Troponinei I cu Afectarea Cardiacă la Pacienți cu Boală Renală Terminală

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#### Abstract

*Background:* The increase of serum troponins, especially troponin I, have been reported in patients with and without coronary artery diseases. *Methods:* We studied 51 end stage renal disease (ESRD) patients with or without clinical myocardial infarction (MI) and correlated cardiac findings with serum creatine kinase (CK), its MB isoenzyme (CK-MB), and cardiac troponin I (cTnI). *Results:* There was no myocardial pathology in 11 patients. Cardiac pathologies were in five groups: scarring from previous MI or patchy ventricular fibrosis (n = 5), recent MI (n = 8), recent microinfarct (n = 8), healing MI (n = 5), degenerative myocyte changes consistent with congestive heart failure CHF; (n = 8), and other cardiac pathologies (n = 6). The median concentrations in the five groups were not significantly different for either CK or CK-MB. Compared with the no-pathology group, only the MI group was significantly different for cTnI. For patients with recent MI, 37.5%, 25% and 75%, had increased CK, CK-MB and cTnI, respectively; for CHF the percentages were 62.5%, 25% and 25% respectively. Only one patient without myocardial pathology had an increase of CK-MB, cTnI. *Conclusions:* All patients with increased serum CK-MB, and cTnI, had significant cardiac changes. cTnI assay appears to be a more sensitive indicator of MI and other myocardial pathologies than the CK-MB assay used in this study.

"cTnI" in Source

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## Rezumat

Creșterea în ser a troponinelor, în special a troponinei I, a fost raportată la pacienți cu și fără boli arteriale coronariene. **Metode.** Am studiat 51 de pacienți cu boală renală în stadiu terminal, cu și fără infarct miocardic (IM) și am corelat investigațiile cardiace cu nivelele serice de creatin kinază (CK), izoenzima MB a acesteia (CK-MB) și cu troponina I cardiacă (cTnI). **Rezultate.** Un număr de 11 pacienți nu au avut afectare miocardică. Afectarea cardiacă găsită la ceilalți pacienți a fost împărțită în 5 categorii: cicatrici post-infarct miocardic sau fibroză ventriculară (n = 5), IM recent (n = 8), microinfarct recent (n = 8), IM în curs de vindecare (n = 5), modificări degenerative miocitare asociate cu insuficiență cardiacă congestivă, ICC (n = 8) și alte afecțiuni cardiace (n = 6). Medianele concentrațiilor nu au fost semnificativ diferite la cele 5 grupuri pentru CK și CK-MB. În comparație cu grupul fără patologie cardiacă, numai grupul cu IM a fost diferit în ceea ce privește cTnI. Dintre pacienții cu IM recent, 37,5%, 25% și, respectiv 75% au avut nivele crescute de CK, CK-MB și cTnI; dintre pacienții cu ICC, valori crescute ale acestor parametri au fost găsite la 62,5%, 25% și, respectiv 25%. Un singur pacient fără patologie miocardică a avut CK-MB și cTnI crescute. **Concluzii.** Toți pacienții cu nivele serice crescute de CK-MB și cTnI au prezentat afectare cardiacă. Determinarea cTnI pare a fi un indicator mai sensibil pentru IM și alte afecțiuni miocardice decât testul pentru CK-MB utilizat în acest studiu.

Over the last 10 years, increases in cardiac troponin I (cTnI) have been studied in end-stage renal disease (ESRD) patients,<sup>1,3,5,8,11,14,19,23,27</sup> and the prevalence of increased troponins is correlated with increased risk of coronary artery disease.<sup>14</sup> Serum cTnI appears to be a valuable predictive marker of cardiovascular events in asymptomatic dialysis patients. For those patients who might benefit from thorough cardiac investigation and treatment, information on cTnI could be useful in preventing cardiac events<sup>7</sup>. A high percentage of end-stage renal failure patients show increased cardiac troponin I (cTnI) in the absence of acute cardiac ischemia<sup>12,28</sup>. Minimal quantities of cTnI released into the blood stream of a healthy subject are easily extracted and eliminated by the kidney, while in uraemic patients they tend to accumulate, reaching significant plasma levels. That could be one of the reasons that cTnI levels are so significant in nephropathic patients<sup>7</sup>.

In the present study, we investigated 51 hemodialysis patients with increased cTnI with or without clinical myocardial infarction and the results were correlated with serum creatine kinase (CK), its MB isoenzyme (CK-MB).

## Materials and Methods

We studied 51 patients. Patients were selected from the Clinical County Emergency Hospital of Timisoara, Nephrology Dialysis and Transplantation Department. Patients in whom no suitable plasma samples were available were excluded from the study.

Samples were routine clinical samples and they were processed in the routine manner using (PST<sup>®</sup> or SST<sup>®</sup>; Becton Dickinson) tubes. 51% of the samples (from 26 patients) were obtained within 8 days before death. The rest of the samples were obtained more than 6 months before death. All samples were frozen at -70 °C within 72 h. Serum markers were analyzed for clinical reasons. Creatine kinase CK and CK-MB was measured on the Vitros 950, using manufacturer's reagents; and cardiac troponin I (cTnI) was measured on the Dimension RxL (Dade Behring). The cutoff values used in our laboratory are as follows: CK, 215 U/L for males and 160 U/L for females; CK-MB, 10 U/L; cTnI, 2.0 mg/L. The interassay imprecision (CV) for each assay is as follows: for CK, 3% at 245 U/L; for CK-MB, 5.5% at 10 U/L and 4.5% at 12.4 U/L; for cTnI, 6.1% at 3.3 mg/L and 7.0% at 34.2 mg/L.

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**Table 1. Description of the studied lot of patients with respect to myocardial status and serum levels of cardiac markers**

	n	Males	No. of patients with increased serum levels		
			CK	cTni	CKMB
No myocardial pathologies	11	4	5	1	1
Old MI or fibrosis	5	2	3	1	3
Recent MI	8	7	3	6	2
Recent microinfarct	8	6	3	5	2
Healing MI	5	4	3	1	1
CHF	8	4	5	2	2
Other myocardial pathologies	6	3	1	3	1

### Statistical analysis

Means were compared using the Analysis ToolPak of Microsoft Excel, Ver. 7.  $\chi^2$  analysis and the Fisher's exact two-tailed test were performed. Odds ratios were calculated to determine the relationship between increased serum markers and the presence of cardiac pathology, using OpenEpi, Version 2. (P) indicates an one-tail P-value for Protective or negative association; otherwise one-tailed exact P-values are for a positive association<sup>13</sup>. Statistical significance was defined as  $P < 0.05$  unless otherwise stated. We calculated clinical sensitivities and specificities for acute MI (recent and healing) and for all cardiac pathologies.

### Results

A summary of 51 patients for whom all cardiac markers were measured is shown in *Table 1*. There was no myocardial pathology in 11 patients; there was old MI or ventricular fibrosis in 5, recent MI in 16 (8 microinfarcts), healing MI in 5, chronic heart failure in 8, and other myocardial pathology in 6 patients.

In the patients with no myocardial pathology, CK was increased in 5 of 11, and

cTnI was just below the cutoff concentration in 1 patient. In patients with myocardial pathology, cTnI was most frequently increased. Increased CK-MB was not associated with increased cTnI in all patients.

The median concentrations and the percentages of patients with increased CK-MB and cTnI, but not CK, were higher in patients with myocardial pathology than for those with no myocardial pathology (*Table 2*). However, the odds ratio for the presence of acute MI was significant for cTnI. There was no significant difference between the groups with recent MI and micro infarcts, nor did the size of the infarct appear to have any effect; hence, they were studied together. When all cardiac pathologies were considered, the clinical sensitivities (95% confidence intervals) for CK, CK-MB, cTnI, were 45%, 28%, 45%, respectively.

For acute MI, the specificities for CK, CK-MB, and cTnI, were 51%, 77%, and 77%, respectively. The clinical sensitivities for acute MI were 38%, 25% and 69%, respectively. For acute MI, the sensitivity of cTnI was significantly different from both CK-MB and CK.

The presence of acute myocardial ischemia was the most common cause of increased serum concentrations of CK-MB and cTnI. Interestingly, patients with microinfarcts were just as likely to have increased values as patients with larger infarcts.

**Table 2. Comparison among the serum levels of CK, cTnI and CK-MB of patients in the studied lot, according to their myocardial status**

	No myocardial pathology	Old MI or fibrosis	Recent/healing MI	CHF	Other myocardial pathologies
<b>CK</b>					
n	11	5	21	8	6
Median, U/L	57	70	47	78	45
Range, U/L	7-255	19-922	7-430	8-300	20-400
Odds ratio	1.0	1.7	0.9	1.9	0.2
95%CI		0.13-28.99	0.16-5.07	0.22-19.39	0.004-3.631
<b>cTnI</b>					
n	11	5	21	8	6
Median, µg/L	0.1	0.4	2.7	3.2	2.1
Range, µg/L	0.0-2.7	0.1-2.8	0.0-140	0.0-5	0.0-10
Odds ratio	1.0	2.3	12.3*	3.1	1.9
95%CI		0.02-215.50	1.32-625.60	0.13-215.90	0.02-172.40
<b>CKMB</b>					
n	11	5	21	8	6
Median, U/L	2	4	12	10	8
Range, U/L	1-6	1-6	2-25	2-28	1-20
Odds ratio	1.0	11.8	3.0	3.1	1.4
95%CI		0.62-863.00	0.27-162.30	0.13-215.90	0.02-123.20

\* Significance based on Fisher exact;  $p=0.02$  for two-tailed test

## Discussion

It is well known that dialyzed patients show more important alterations of coronary arteries than do control subjects of the same age with identical risk factors. Myocytic injury causes the release of minimal quantities of cTnI into the blood stream, and as a result, its blood levels can fluctuate if only the myocyte membrane has been damaged<sup>7</sup>

CK-MB, a serological marker of myocardial injury, is not of significance in this population. In fact, it appears increased in 5–50% of chronic dialysis patients in the absence of cardiac symptoms or evidence of myocardial injury. Abnormal protein metabolism and muscle wasting are possible causes of this increase<sup>6</sup>. The findings of this study confirm the increased clinical sensitivity of serum troponins over CK and CK-MB in acute coronary syndromes. In this study, we used a single plasma sample with serum troponins following an acute ischemic

event. We found a difference between patients with acute ischemia and those with other myocardial disorders. The percentage of patients with increased cTnI was 69%. In patients with other myocardial pathologies increasing of cTnI was 50% and for CK-MB was 17%. This may explain the discordance seen between the cTnI values in end-stage renal failure patients but not seen in acute coronary syndromes.

This discrepancy could lead to hypothesize that cTnI is more likely than the other markers to leak into circulation with minor pathologic changes. Approximately 2-3% of cTnI is present in the cytoplasm of cardiomyocytes<sup>2,18</sup>. Troponin I is only identified in intact TnT:I:C complex and TnI:C. As a result of its hydrophobicity, free TnI may bind to other surfaces and/or proteins, thus potentially masking its antigenic epitopes<sup>17</sup>. It was speculated that TnI, may adsorb onto the dialysis membrane because of its hydrophobicity. These findings have been confirmed by some authors<sup>29,30</sup>, but

refuted by others<sup>25</sup>.

The increased mortality seen with increased cTnI, in nonischemic settings supports our findings. Two recent studies<sup>21, 31</sup> in dialysis patients have shown similar associated mortality.

This now can be explained by cTnI reflecting subclinical myocardial pathology rather than acute coronary ischemia. Furthermore, we found a higher mortality risk associated with increased cTnI in the ESRD patients. Increased cTnI in this group of patients therefore indicates the presence of cardiac disease and a poorer outcome.

In CHF patients prognostic values of increased cTnI have also been reported recently<sup>10,24,32</sup> and cTnI may be a useful prognostic indicator even in cardiac disease including MI. Thus, increasing cTnI may be indicative of non-infarct-related myocyte pathologies.

Our present findings involving the mechanisms of myocardial injury in ESRD patients, continue to demonstrate the prognostic power of cardiac troponin testing for predicting mortality in these patients. Patients with acute coronary syndromes required using serum troponins measurements, and could be necessary to reexamine the interpretation of the many risk-stratification studies of unstable angina and non-Q-wave MI patients<sup>4, 9, 13, 15, 16, 20, 26, 34</sup>. In these studies an increased mortality was attributed to ischemic disease. The presence of microinfarcts and other myocardial pathologies should be considered as factors for mortality. In another study, patients with low grade or atypical angina showed a greater than twofold difference in event-free survival at 6 months between cTnI-positive and -negative groups despite very similar incidences of positive angiographic abnormalities (64% vs 47%)<sup>26</sup>. Increased cTnI, even in the absence of acute ischemia are indicative of compromised myocardium and a poor prognosis.

Recent studies have shown degradation of cTnI complexes, which is the predominant

form in serum. Oxidation or phosphorylation of the cTnI molecule can produce changes in immunoreactivity, leading to increased or decreased concentrations with storage and the poor specificity of cTnI in end-stage renal disease patients<sup>33</sup>. We believe that these increases could indicate a cardiac pathology. cTnI is superior in detecting minimal cardiac disease. Also, cTnI it is very important in the management of patients with acute coronary syndromes. In these groups of patients may be a better predictor of risk.

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