

## Levels of creatine kinase MB-mass in chronic kidney disease patients on maintenance hemodialysis without coronary complications

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### Abstract

**Introduction:** A triad of clinical evaluation, electrocardiography and biomarkers of acute cardio necrosis are basis for diagnosing acute coronary syndrome (ACS). Evaluation of ACS by electrocardiography can be inconclusive in patients on maintenance hemodialysis; thereby making cardiac biomarkers better indicators. Hemodialysis is known to alter troponin I values with studies suggesting high false positives but not for the values of CKMB mass.

**Aim:** The aim of the study was to estimate the levels of cardiac CKMB-mass in patients with stage IV/stage V renal failure on maintenance hemodialysis (MHD) with no evidence of cardiac disease, and to correlate these values with manufactures guidelines for healthy individuals (cut off of < 5 ng/ml).

**Materials and Methods:** The study was conducted on 23 patients between age group 20 to 70 years, diagnosed with stage IV or V Chronic Kidney disease (CKD) (confirmed biochemically and ultrasonographically). These patients were undergoing regular biweekly regime of maintenance hemodialysis for more than 3 months at dialysis unit PESIMSR, Kuppam. CKMB mass levels were measured in these patients.

**Results and Conclusion:** The kidney function tests and electrolyte values were deranged in patients with CKD, however as the patients were on calcium supplementation, mineral levels were within normal range. Liver function tests of these patients were found to be normal. The hemoglobin and RBC levels were lower due to CKD associated anemia. CKMB-mass levels of these patients were done in Biomerieux Vidas analyzer using Enzyme linked fluorescent assay (ELFA) method. The values were within manufacturer's cutoff range of 5ng/ml with mean value of 3.0±1.69 ng/ml. The patients were followed up either until death or for 24 months for any cardiac related events and follow up rate was 99%. The overall survival rates of the patients were found to be 77% and none of the patients were found to have developed cardiac related events and specifically myocardial infarction. The cause of death of the patients were also not related to cardiac related causes.

**Keywords:** Creatine kinase MB (CKMB) mass, CKD, MHD, ACS, hs-Troponin I.

### Introduction

A triad of clinical evaluation, electrocardiography and biomarkers of acute cardio necrosis are basis for diagnosing acute coronary syndrome (ACS). Inaccuracies in any one of the parameter may lead to delay in diagnosis, posing a prognostic risk to these patients.

However, patients of chronic kidney disease (CKD) on maintenance hemodialysis have been observed to have enhanced cardiovascular risk due to left ventricular hypertrophy (LVH) with hemodynamic overload due to increased plasma volume, arteriovenous (AV) fistula and anemia<sup>1,2</sup> Prevalence of atherosclerosis is high in kidney disease with high incidence of increased media thickness and calcified lesion.<sup>3</sup>

Difficulty in diagnosing ACS has also been frequently observed as typical clinical picture like chest pain and ECG findings may not be always present in the patients.<sup>4</sup> Evaluation of ACS by electrocardiography can be inconclusive; there by making cardiac markers better indicators. Hemodialysis is known to alter troponin I values with studies suggesting high false positives but not for the values of CKMB.<sup>5</sup> Manufacturer guidelines give CKMB cutoff values of < 5 ng/ml.

The aim of the study was to estimate the levels of cardiac

CKMB-mass in patients with stage IV/stage V renal failure on maintenance hemodialysis with no evidence of cardiac disease, and to correlate these values with manufactures guidelines for healthy individuals (cut off of < 5 ng/ml) In our present study we hypothesis that CKMB-Mass values in patients with chronic kidney failure on maintenance hemodialysis are within the manufactures cut off value of < 5 ng/ml.

### Materials and Methods

The study was conducted on available pool of 60 patients between age group 20 to 70 years diagnosed as stage IV or V CKD (confirmed biochemically and ultrasonographically) registered for maintenance hemodialysis at dialysis unit PESIMSR, Kuppam. These patients were undergoing regular biweekly regime of maintenance hemodialysis for more than 3 months. The study was approved by institutional ethical and research committee. Informed consent was taken from all patients included in the study. All patients not willing to take part, undergoing hemodialysis for more than 2 years, those with present or past history of chest pain or any cardiac events and patients with critical illness were excluded from the study. Hence out of 60 patients, 23 patients (13 males and 10 females) were included in the study based on our inclusion

and exclusion criteria. Main causes of kidney failure in these patients were hypertension followed by diabetes mellitus.

As per protocol, every month 3.5 ml blood collected in serum separator gel yellow vacutainer and K2-EDTA lavender vacutainer are sent to laboratory for routine biochemical and hematological evaluation of the patients. Blood is drawn just before initiation of first session of dialysis during the week from atriovenous (AV) fistula or internal jugular (IJ) catheter.<sup>6</sup> Therefore it was not necessary to prick the patient for second time for collecting blood sample for analyzing CKMB mass. Samples were immediately transferred to clinical biochemistry and hematology laboratory for analysis, all routine biochemical parameters were analyzed in vitros 250 autoanalyzer,<sup>7</sup> Cardiac marker Creatine kinase-MB mass was analyzed in Biomerieux Vidas analyzer using Enzyme linked fluorescent assay (ELFA) method.<sup>8</sup> Hematological parameters were analyzed in Bechman coulter LH 780 hematology analyzer.

Follow up of the patients were done after 18 months via telephonic contact and patient's survival and cardiac related events were enquired.

### Statistical Analysis

Results were analyzed in Microsoft excel and SPSS software version 16. Mean and standard deviations (SD) were obtained for all routine biochemical investigations.

### Results

The kidney function tests and electrolyte values were deranged in patients with CKD, however as the patients were on calcium supplementation, mineral levels were within normal range. Liver function tests of these patients were found to be normal. The hemoglobin and RBC levels were lower due to CKD associated anemia (Table 1).

CKMB levels of the patients were within manufacturer's cutoff range of 5ng/ml with mean value of  $3.0 \pm 1.69$  ng/ml and the results showed that there was no statistically significant gender specific biological variation of CKMB mass in these patient. Male patients had higher mean value of mass-CKMB when compared to female patients. One male patient had values higher than the cut of 5ng/ml, without obvious active cardiac event (Table 2). 82.4% patients had CKMB values below 4ng/ml, 56.52% below 3ng/ml and 30.4% of patients had values below 2ng/ml (Table 3).

**Table 1a:** An estimation of routine biochemical parameters

	<b>Males (Mean±SD) (n=13)</b>	<b>Females (Mean ±SD) (n=10)</b>	<b>Total (Mean±SD) (n=23)</b>
Serum Urea(mg/dL)	74.38 ± 17.79	80.5 ± 69.8	77.06 ± 14.8
Serum Creatinine(mg/dL)	6.30 ± 1.60	5.93 ± 1.19	5.9 ± 1.4
Serum Sodium (mmols/L)	140.92 ± 3.5	142.20 ± 3.12	141.47 ± 3.3
Serum Potassium (mmols/L)	4.95 ± 0.93	5.46 ± 0.48	5.16 ± 0.7
Serum Chloride (mmols/L)	103.77 ± 4.95	106.80 ± 6.2	105.08 ± 4.3
Serum Calcium mg/dl	8.18 ± 0.58	8.25 ± 0.75	8.21 ± 0.64
Serum Phosphorous mg/dl	4.15 ± 1.38	3.96 ± 1.27	4.06 ± 1.30
Serum Magnesium mg/dl	2.91 ± 0.78	3.48 ± 1.0	3.15 ± 0.9
Serum Bilirubin (mg/dl)	0.5 ± 0.23	0.4 ± 0.18	0.48 ± 0.2
Serum Conjugated Bilirubin (mg/dl)	0.02 ± 0.0	0.02 ± 0.0	0.02 ± 0.0
Serum Total proteins (g/dl)	6.6 ± 0.63	6.6 ± 0.34	6.6 ± 0.5
Serum Albumin (g/dl)	3.4 ± 0.51	3.5 ± 0.28	3.42 ± 0.42
Serum Globulin (g/dl)	3.2 ± 0.36	3.1 ± 0.21	3.19 ± 0.30
AG ratio	1.1 ± 0.19	1.1 ± 0.14	1.08 ± 0.16
Serum AST(U/L)	25.9 ± 25.07	20.2 ± 4.87	23.4 ± 19.45
Serum ALT(U/L)	37.2 ± 49.7	26.8 ± 10.71	32.65 ± 37.75
Serum ALKP(U/L)	141.8 ± 118	127.1 ± 77.23	135.39 ± 100

AG: albumin/globulin; AST: Aspartate transaminase; ALT: alanine transaminase; ALKP: Alkaline phosphatase;

**Table 1b:** Estimation of hematological parameters

	Males (Mean±SD)	Females (Mean±SD)	Total (Mean±SD)
Hb%	7.95±1.67	8.63±2.68	8.2 ±2.14
RBC (X103µL)	3.08±0.65	3.07±0.86	3.07±0.73
WBC (X103µL)	6.89±2.84	6.23±1.26	6.6±2.2
Platelets (X103µL)	201.6±54.2	240.6±113	218±85

Hb%: Hemoglobin percentage; RBC: Red blood cells; WBC: white blood cell; µL: microliter; ESR: erythrocyte sedimentation rate

**Table 1c:** Inflammatory parameters

	Males (Mean±SD)	Females (Mean±SD)	Total (Mean±SD)
WBC (X10 <sup>3</sup> µL)	6.89 ± 2.84	6.23 ± 1.26	6.6 ± 2.2
ESR (mm/hr)	101.2 ± 39.7	71.5 ± 51.2	65 ± 43

Hb%: Hemoglobin percentage; RBC: Red blood cells; WBC: white blood cell; µL: microliter; ESR: erythrocyte sedimentation rate

**Table 2:** Estimation of CKMB-Mass values

CKMB-mass (ng/ml)	Males (Mean±SD)	Females (Mean±SD)	p values	Total (Mean ± SD)
Serum	3.45±2.07	2.43±0.78	0.127	3.0±1.69

**Table 3:** Percentage of patients with different CKMB levels

S.No	CKMB-Mass	Percentage of Patients
1	5 ng/ml	98%
2	4 ng/ml	82.4 %
3	3 ng/ml	56.52 %
4	2 ng/ml	30.4 %

The patients were followed up either until death or for 18 months for any cardiac related events and follow up rate was 99%. The overall survival rates of the patients were found to be 77% at 24 months post biomarker evaluation. The cause of death of these patients was also not related to cardiac events (Table 4).

**Table 4:** Patients survival rate and cardiac relate events at 18 months follow up

Sl No	Parameters	Percentage of Patients
1	Survival rate	77%
2	Death rate	23%
3	Cardiac related death	0%
4	MI or other cardiac events	0%

MI: Myocardial infraction

**Discussion**

The biological variation for Troponin I was studied and high variation was observed in renal dysfunction.<sup>9</sup> Study by Ingec et al suggested significant difference in c-Troponin I values estimated before and after dialysis sessions.<sup>5</sup> Several previous studies suggest similar results.<sup>10-12</sup> An alternate cardiac marker is essential for the patients with acute cardiac events with deregulated kidneys as Troponins cannot accurately predict ACS in these patients. However CKMB has been studied and have found to be promising marker as the kidney function and hemodialysis was found to have no statistically significant effect on its values.<sup>5</sup> Study by Borja et al compared 3 different cardiac markers HS Troponin T, NT-pro-BNP and CKMB isoenzyme in patients with CKD on maintenance hemodialysis, and suggested normal levels CKMB when compared with other cardiac markers, study also suggest good correlation of higher normal values of CKMB of >2 ng/ml with increases risk of cardiovascular events on long term follow up of these patients. High CKMB levels were also associated with poor cardiovascular prognosis in CKD patients on maintenance hemodialysis<sup>13</sup> however all patients included in our study had normal values of CKMB-mass and none of the study subjects developed cardiac related events (Table 3) and specifically myocardial infarction.

Sensitivity of CKMB as a cardiac marker in general population is found to be inferior when compared to Troponin levels. But due to its short half life, it shows good correlation with acute coronary syndrome in cases of re-infarction especially after revascularization, current recommendations suggests its use in such cases.<sup>14,15</sup> However due to low enthusiasm among clinicians and researchers, studies related to CKMB have not gained much momentum as a cardiac biomarker; most studies involving CKMB exclude patients with CKD. Most of

the available studies estimated CKMB enzyme activity.<sup>14</sup> Not many studies are available in literature done for CKMB mass levels in CKD patients.

In our present study we observed normal values of CKMB Mass according to manufacturer's guidelines in the CKD patients as against the general findings of high cardiac marker Troponin levels observed in other studies. On follow up of these patients for 18 months none of the patients developed cardiac related illness. Survival rate of these patients was found to be low but no patients died of cardiac related causes and none of the patients developed myocardial infarction.

Hence we suggest use of baseline CKMB levels for all patients undergoing hemodialysis. Re-estimation of CKMB and its elevation can be a predictor of acute coronary events in cases of clinical suspicion among these patients.

Due to unavailability and low compliance of patients with CKD with biweekly regime on maintenance hemodialysis and financial constrains, a larger sample size could not be achieved. Further studies with larger sample size are required to establish CKMB mass as a better marker of acute myocardial infarction in patients suffering from CKD on maintenance hemodialysis. Echo-cardiographic correlation of the patients and comparison with cardiac Troponin I would be extremely helpful for elaborating the scope of the study.

## Conclusion

All the patients included in the study were found to have CKMB-mass levels within manufacturer guidelines for healthy adults. No patients developed cardiac related events when followed up for 18 months or until death. Hence we conclude that CKMB-mass evaluation can act as a marker for all patients with clinical suspension of acute coronary syndrome undergoing hemodialysis for CKD. However studies with larger sample size can make the clinical picture clearer.

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**Conflict of Interest:** None.

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