

Clinical Significance of Creatine Kinase-MB Elevation in Patients with Chronic Kidney Disease before initiation of Hemodialysis

ABSTRACT

Aim: To measure creatine kinase – myocardial band (CK-MB) concentration in stable patients with chronic kidney disease without cardiac symptoms who had not commenced hemodialysis and compare results with those of healthy control subjects.

Study Design: Cross-sectional study

Place and Duration of Study: Renal Unit, Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria from January 2014 to June 2015.

Methodology

Serum CK-MB, HDL-cholesterol, total cholesterol, triglyceride, fasting plasma glucose, urine and serum albumin, urine and serum creatinine concentrations were analysed in 83 diagnosed chronic kidney disease patients attending the renal clinic and 83 age- and sex-matched healthy control subjects. Estimated GFR (eGFR), urinary albumin-creatinine ratio (UACR) and LDL-cholesterol were calculated.

Results

CKD patients had higher CK-MB, higher blood pressure, higher serum creatinine, higher triglyceride, higher UACR, lower serum albumin, lower HDL and lower eGFR compared to controls. Sixteen (19.3%) patients versus 11 (13.3%) controls had elevated CK-MB. Among patients, CK-MB was positively correlated with UACR but not associated with other biochemical or clinical variables.

Conclusion

CK-MB elevation was associated with albuminuria, which is strongly linked with increased cardiovascular mortality and morbidity. Though non-specific elevations of CK-MB are common in CKD patients, high CK-MB levels may still be useful as predictors of adverse cardiovascular events and all-cause mortality.

Keywords: Creatine Kinase – MB, chronic kidney disease, cardiovascular disease, UACR, albuminuria

1. INTRODUCTION

Creatine kinase – myocardial band (CK-MB) is an isoform of creatine kinase (CK) that is mainly present in cardiac muscle with small concentrations (up to 3% of the total CK activity) in healthy skeletal muscle [1]. Smaller amounts are also found in the tongue, diaphragm, uterus and prostate gland [2]. CK-MB is a large molecule which is mainly cleared by the reticulo-endothelial system and is not excreted in the urine, and its concentration is not influenced by changes in renal or hepatic blood flow [3]. Determination of serum CK-MB has proven useful in most situations in the accurate diagnosis of cardiac injury, particularly acute coronary syndromes [4]. However, CK-MB levels can also be increased in patients with skeletal muscle injury or renal failure, complicating the accurate diagnosis of myocardial injury by routine methods [1]. Because skeletal muscle contains CK concentrations that are eightfold higher per gram of tissue than those in cardiac tissue, small areas of skeletal muscle injury or disease can result in relatively high serum CK-MB concentrations [5]. False positive elevations of CK-MB have been found to occur in patients with chronic kidney disease (CKD) and this elevation has been attributed to regeneration of myopathic or injured skeletal muscle fibers in renal patients [1,2,5]. For this same reason, certain diseases of skeletal muscle, such as Duchenne muscular dystrophy or polymyositis, often result in serum elevations of total CK and an abnormal increase in serum CK-MB concentrations often up to 5% to 15% of the total CK activity. In addition, CK-MB can form complexes with immunoglobulins. Thus, elevated CK-MB levels can occur in patients with renal failure, rhabdomyolysis, myopathies, muscle trauma, or because of analytical and biological interferences, macro-complexes or during the peri-partum period [5].

This lack of cardiac-specificity reduces the predictive value of a positive CK-MB result and it is particularly challenging for interpretation in patients with concomitant renal failure and myocardial injury. In this setting, cardiac-specific biomarkers such as cardiac troponins are more useful. CK-MB as a diagnostic and prognostic marker of myocardial damage has been predominantly replaced with cardiac troponins [5]. However, serial measurements of serum CK-MB are still useful for the diagnosis of acute myocardial

infarction (AMI), estimation of infarct size, diagnosis of re-infarction and prediction of in-hospital mortality risk. It has been recommended as an acceptable alternative to cardiac troponins [6]. Serum CK-MB concentrations can be affected by various demographic factors such as gender, race and age [7,8]. Higher serum CK-MB concentrations and higher CK-MB reference limits have been demonstrated in men compared to women and in Blacks compared to Caucasians [7,8]. Serum CK-MB activity also increases with age regardless of gender or race [8,9]. Apple et al observed a significant trend for increasing mean CK-MB concentrations by age across decades up to the seventh decade (60 – 69 years) [8]. These differences have been attributed to the larger muscle mass typically found in men versus women, Blacks versus Caucasians and in adults versus children and geriatric population [7,8]. CK-MB activity in serum is proportional to muscle mass, and therefore serum CK-MB activity characteristically increases as muscle mass enlarges and vice versa [7,8]. This study was undertaken to measure CK-MB concentrations in patients with chronic kidney disease, who did not have any history or symptoms of cardiovascular disease, and who had not commenced hemodialysis and compare results with those of healthy control subjects.

2. METHODOLOGY

2.1 Subjects

The target population included diagnosed chronic kidney disease patients (those with symptoms and signs of renal disease and/or $GFR < 60 \text{ ml/min/1.73 m}^2$ for ≥ 3 months, with laboratory or radiological evidence) of the renal unit of the University of Port Harcourt Teaching Hospital (UPTH) above the age of 18 years who were stable and ambulatory and had no symptoms of cardiac disease. Patients on dialysis and those with acute renal failure or other acute condition, symptoms or history of cardiovascular disease were excluded. A corresponding number of age- and sex-matched control subjects with normal renal function and no history of cardiovascular disease, diabetes, hypertension, or other acute or chronic condition were drawn from the general population. Approval was obtained from the Ethical Committee of UPTH and informed consent was obtained from all participants. Demographic, social and medical data of participants were assessed with the use of questionnaires.

2.2 Physical Examination

Blood pressure (BP) of each participant was measured with a mercury sphygmomanometer after ten minutes of rest on two occasions and hypertension was taken as a BP equal to or greater than 140/90 mmHg. Participants were weighed bare footed and wearing light clothing on a weighing balance placed on a flat surface. Their heights were measured on a portable collapsible stadiometer and body mass index (BMI = weight/height²) was calculated.

2.3 Specimen Collection

After 10-12 hours overnight fast and observing aseptic procedure, 10ml of venous blood was drawn from the antecubital fossa of each participant into a fluoride oxalate bottle for fasting plasma glucose analysis, an EDTA bottle for analysis of lipids and a plain bottle for the estimation of serum creatinine, albumin and CK-MB. Plasma/serum was separated from blood cells after centrifugation at 2500g for 10 minutes, harvested with a clean Pasteur pipette and stored at -20°C. Freshly voided spot mid-stream urine was also collected from each participant in a plain bottle for determination of urinary albumin-creatinine ratio (UACR).

2.4 Laboratory Analysis

Urine and serum creatinine concentrations were analysed using the modified Jaffe method and the serum value obtained was used to calculate the estimated glomerular filtration rate (eGFR) of each participant using the Abbreviated Modification of Diet in Renal Disease (MDRD) formula: $32788 \times (\text{serum creatinine in } \mu\text{mol/L})^{-1.154} \times (\text{Age})^{-0.203} \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)}$ [10]. Estimation of fasting plasma glucose was done using the colorimetric glucose oxidase method [11], urine and serum albumin by the BCG (Bromocresol Green) method [11], HDL-cholesterol by precipitation technique, total cholesterol and triglyceride by enzymatic method [11] and LDL-cholesterol was calculated using the Friedewald's formula [12]. CK-MB was determined using ELISA technique (Calbiotech). Reference ranges provided by the manufacturer for CK-MB was 0 – 9.0 ng/mL.

2.5 Statistical Analysis

Data obtained from this study was analysed using the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc. Chicago, Illinois, U.S.A.). Frequencies and percentages were obtained for

categorical variables. The means of continuous variables were compared using unpaired students t test and expressed as mean $\pm$ standard deviation (SD). Pearson correlation statistics was used to determine association between CK-MB and clinical and biochemical variables of patients and controls. P-values less than or equal to 0.05 were taken to be significant in all analyses.

2.6 Definition of Variables

CKD Stages: Stage 1: eGFR $\geq$ 90 ml/min/1.73 m² with kidney damage, stage 2: eGFR = 60 – 89.9 ml/min/1.73 m² with kidney damage, stage 3: eGFR = 30 – 59.9 ml/min/1.73 m², stage 4: eGFR = 15 – 29.9 ml/min/1.73 m², stage 5: eGFR < 15 ml/min/1.73 m² [13].

Albuminuria: UACR of < 30 mg albumin/g creatinine (3.4 mg albumin/mmol creatinine) was regarded as normal, UACR of 30 – 300 mg/g (3.4-33.9 mg/mmol) as microalbuminuria and UACR of > 300 mg/g creatinine (> 33.9 mg/mmol) as overt albuminuria (macroalbuminuria) [14].

3. RESULTS

There were 83 CKD patients made up of 41 (49.4%) males and 42 (50.6%) females and 83 age- and sex-matched control subjects consisting of 41 (49.4%) males and 42 (50.6%) females. CKD patients had higher systolic ($P < .001$) and diastolic blood pressure values ($P < .001$) than controls (Table 1). Serum CK-MB ($P = .04$), triglyceride ($P < .001$), creatinine ($P < .001$) and UACR ($P < .001$) of CKD patients were higher and their serum albumin ($P = .003$), HDL ($P = .001$) and estimated GFR ($P < .001$) were lower than that of controls (Table 2).

Sixteen (19.3%) patients versus 11 (13.3%) controls had elevated CK-MB ($P = .38$). Mean (SD) CK-MB was 11.4 (4.6) ng/ml for patients with elevated CK-MB and 3.0 (1.5) ng/ml for patients with normal CK-MB. There was a significant positive correlation between CK-MB and UACR ($P = .002$) among CKD patients but there were no significant correlations between CK-MB and age ($P = .74$), BMI ($P = .13$), serum albumin ($P = .19$), serum creatinine ($P = .95$) and eGFR ($P = .28$) (Table 3). CK-MB correlated positively with BMI ($P = .05$) among controls (Table 3).

135 **Table 1. Comparison of physical characteristics of CKD Patients and Controls**

CHARACTERISTIC	Mean (SD)		P
	CKD PATIENT (n=83)	CONTROLS (n=83)	
Age (years)	46.1 (15.3)	42.6 (9.6)	.09
Body mass index (Kg/m ²)	24.4 (4.2)	26.1 (5.9)	.06
Systolic blood pressure (mmHg)	129.9 (22.2)	119.9 (14.2)	<.001*
Diastolic blood pressure (mmHg)	81.0 (14.4)	75.1 (8.2)	<.001*

* P-values ≤ .05 significant

136 **Table 2. Comparison of Biochemical Parameters of Patients and Controls**

PARAMETER	Mean (SD)		P
	CKD PATIENTS (n=83)	CONTROLS (n=83)	
CK-MB (ng/mL)	6.7 (6.0)	4.6 (4.1)	.04*
Serum Creatinine (μmol/L)	292.8 (363.3)	95.2 (22.8)	<.001*
Estimated GFR (mL/min)	57.3 (35.3)	91.6 (32.4)	<.001*
Fasting plasma glucose (mmol/L)	5.2 (2.4)	4.7 (1.5)	.14
Triglyceride (mmol/L)	1.4 (0.8)	0.9 (0.3)	<.001*
High density lipoprotein (mmol/L)	0.8 (0.3)	1.0 (0.2)	.001*
Low density lipoprotein (mmol/L)	3.2 (1.0)	3.0 (0.6)	.09
Total cholesterol (mmol/L)	4.7 (1.2)	4.6 (0.5)	.63
Serum Albumin (g/L)	39.7 (7.8)	42.9 (2.0)	.003*
UACR (mg/g)	369.1 (719.2)	13.0 (26.3)	<.001*

137 * P-values ≤ .05 significant; CK-MB – Creatine Kinase Myocardial Band; GFR – Glomerular Filtration
138 Rate; UACR - Urinary Albumin: Creatinine Ratio

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142 **Table 3. Correlation of CK-MB with clinical and biochemical variables in patients and controls**

Variable	CKD Patients (n=83)		Controls (n=83)	
	r	P	r	P
Age	0.045	.74	0.075	.58
BMI	-0.203	.13	0.260	.05*
Albumin	-0.178	.19	0.130	.33
Creatinine	0.009	.95	0.007	.96
eGFR	0.146	.28	0.121	.37
UACR	0.406	.002*	0.038	.78

143 * P-values $\leq .05$ significant; r – correlation coefficient; BMI – body mass index; eGFR – estimated
 144 glomerular filtration rate; UACR – urinary albumin: creatinine ratio
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146 4. DISCUSSION

147 In this study, CKD patients had higher blood pressure values, higher serum CK-MB, higher triglyceride,
 148 higher creatinine and higher UACR than controls but their serum albumin, HDL and estimated GFR were
 149 lower. Sixteen (19.3%) patients had elevated CK-MB compared to 11 (13.3%) controls. Similarly,
 150 Kiranmayi et al found that patients with chronic renal failure had higher levels of CK-MB than healthy
 151 controls and this elevation was observed in 26% of patients [2]. Twenty percent to 30% of CKD patients
 152 tend to show higher-than-normal concentrations of CK-MB without evident cardiac disorder [15]. These
 153 elevations may occur as a result of increased production from injured skeletal muscle fibers undergoing
 154 regeneration, changes in the volume of extracellular fluid, demographic factors, biological and analytical
 155 interferences [1,2,15]. The increase is usually non-specific, persistent and the proportion of CK-MB
 156 generally remains low [16]. CK-MB elevations in controls may be related to higher muscle mass as
 157 indicated by the positive association observed between CK-MB and BMI [7,8].

158 Patients with CKD are a major cardiac risk population. Cardiovascular disease (CVD) accounts for much
 159 of their observed morbidity and mortality [15,17]. The incidence and severity of cardiovascular morbidity
 160 and mortality increase as glomerular filtration rate (GFR) declines [17,18]. Several studies have published
 161 correlations between CK-MB and GFR. Wang et al noted that CK-MB levels increased with the severity of
 162 renal dysfunction in CKD patients and correlated inversely with GFR [19]. However, in this study, there
 163 was no correlation observed between CK-MB and eGFR. Similarly, Sato et al did not observe any
 164 relationship between CK-MB levels and eGFR [3]. However, we observed a positive correlation between

CK-MB and UACR, which is a measure of albuminuria. Microalbuminuria is recognized as an independent risk factor for cardiovascular and renal disease [17,20]. Microalbuminuria can identify patients at risk of developing renal disease even before abnormalities of creatinine appear and may also signify severity of end-organ damage [17]. Microalbuminuria is strongly associated with increased cardiovascular mortality and morbidity and also with surrogate measures of CVD, including left ventricular hypertrophy (LVH), carotid intima media thickness, and myocardial ischemia [17]. Iliou et al observed that high CK-MB levels were significantly associated with LVH [4]. The HOPE investigators found that the presence of microalbuminuria was associated with a 61% increased risk for the composite endpoint of stroke, acute myocardial infarction, or CVD death, and a doubled increase in the risk for all-cause mortality [17]. UACR is able to predict both short-term and long-term mortality [20].

5. CONCLUSION

CKD patients had higher CK-MB, higher blood pressure, higher serum creatinine, higher triglyceride, higher UACR, lower serum albumin, lower HDL and lower eGFR compared to controls. Sixteen (19.3%) patients versus 11 (13.3%) controls had elevated CK-MB. CK-MB was positively correlated with UACR among patients but not associated with other biochemical or clinical variables. Though non-specific elevations of CK-MB are common in CKD patients, high CK-MB levels may still be useful as predictors of left ventricular hypertrophy, adverse cardiovascular events and all-cause mortality. Repeated measurements of CK-MB may be required for accurate assessment of cardiovascular outcomes in order to facilitate more aggressive treatment with the goal to reduce event rates.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for this study. A copy of the written consent is available for review by the editorial office/chief editor/editorial board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

None exists.

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