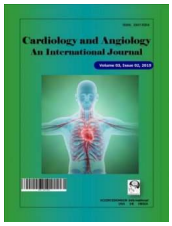

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Clinical Significance of Creatine Kinase-MB Elevation in Patients with Chronic Kidney Disease before Initiation of Hemodialysis

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Authors' contributions

This work was carried out in collaboration between both authors. Author VCW designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors VCW and EPO managed the analyses of the study. Author EPO managed the literature searches and performed the statistical analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: To measure creatine kinase – myocardial band (CK-MB) concentration in stable patients with chronic kidney disease who had not commenced hemodialysis and determine its relationship with cardiac Troponin I and cardiovascular risk factors.
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 December 2015.
Methodology: Blood pressure, serum CK-MB, cardiac Troponin I, 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. Body mass index (BMI), estimated GFR (eGFR), urinary albumin-creatinine ratio (UACR) and LDL-cholesterol were

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calculated.
Results: CKD patients had higher CK-MB, higher cardiac troponin I, 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 associated with UACR, low HDL and dyslipidemia but not associated with cardiac Troponin I.
Conclusion: CK-MB elevation was associated with albuminuria, low HDL and dyslipidemia. However, CK-MB lacked association with cardiac troponin I, which is a more cardiac-specific biomarker. This shows that serum CK-MB levels may not be suitable for diagnosing myocardial injury in CKD patients.

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 [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 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 ml/min/1.73 m^2 for ≥ 3 months, with laboratory or radiological evidence) above the age of 18 years who were stable and ambulatory and attending the Renal Clinic of the University of Port Harcourt Teaching Hospital (UPTH). Patients on dialysis and those with acute renal failure or other acute illness 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 or use of antihypertensive drugs. 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/height^2) was calculated.

2.3 Specimen Collection

After 10-12 hours overnight fast and observing aseptic procedure, 10 ml 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, cardiac troponin I and CK-MB. Plasma/serum was separated from blood cells after centrifugation at 2500 g for 10 minutes, harvested with a clean Pasteur pipette and stored at -20℃. 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 x (serum creatinine in µmol/L)$^{-1.154}$ x (Age)$^{-0.203}$ x 1.210 (if black) x 0.742 (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: (Total cholesterol) – (HDL-C) – (Triglyceride/2.2) in mmol/L [12]. Cardiac troponin I and CK-MB were 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. Differences in proportions were analysed using the Chi-squared test. The means of continuous variables were compared using unpaired students t test and expressed as mean ± 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 ≥ 90 ml/min/1.73 m^2 with kidney damage (persistent albuminuria), stage 2: eGFR = 60 – 89.9 ml/min/1.73 m^2 with kidney damage, stage 3: eGFR = 30 – 59.9 ml/min/1.73 m^2, stage 4: eGFR = 15 – 29.9 ml/min/1.73 m^2, stage 5: eGFR < 15 ml/min/1.73 m^2 [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].

Obesity: Defined as BMI ≥ 30 Kg/m^2 [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), cardiac troponin I (P < .001), 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)

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 did not correlate with cardiac troponin I among patients (*P* = .80) or controls (*P* = .74)

Table 1. Comparison of physical characteristics of CKD patients and controls

	Mean (SD)		
Characteristic	**CKD patient (n=83)**	**Controls (n=83)**	***P***
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*

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*
Cardiac Troponin I	1.0 (0.6)	0.3 (0.1)	<.001*
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*

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

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

	CKD Patients (n=83)		**Controls (n=83)**	
Variable	**r**	***P***	**r**	***P***
Age	0.045	.74	0.075	.58
BMI	-0.203	.13	0.260	.05*
Cardiac Troponin I	-0.034	.80	-0.045	.74
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

** P-values ≤ .05 significant; r – correlation coefficient; BMI – body mass index; eGFR – estimated glomerular filtration rate; UACR – urinary albumin: creatinine ratio*

but correlated positively with BMI (*P* = .05) among controls (Table 3).

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. Prevalence of cardiovascular risk factors was similar among patients with high and normal CK-MB (Table 4) except for dyslipidemia (*P* = .02) and low HDL (*P* = .03) which had higher prevalence among patients with high CK-MB.

4. DISCUSSION

In this study, CKD patients had higher blood pressure values, higher serum CK-MB, higher cardiac troponin I, higher triglyceride, higher creatinine and higher UACR than controls but their serum albumin, HDL and estimated GFR were lower. Sixteen (19.3%) patients had elevated CK-MB compared to 11 (13.3%) controls. Similarly, Kiranmayi et al found that patients with chronic renal failure had higher levels of CK-MB than healthy controls and this elevation was observed in 26% of patients [2]. Twenty percent to 30% of CKD patients tend to show higher-than-normal concentrations of CK-MB without evident cardiac disorder [15]. These elevations may occur as a result of increased production from injured skeletal muscle fibers undergoing regeneration, increase in the volume of extracellular fluid, left ventricular hypertrophy, congestive heart failure, demographic factors, biological and analytical interferences [1,2,13,15]. The increase is usually non-specific, persistent and the proportion of CK-MB generally remains low [16]. CK-MB elevations in controls may be related to higher muscle mass as indicated by the positive association observed between CK-MB and BMI [7,8].

Patients with CKD are a major cardiac risk population. Cardiovascular disease (CVD) accounts for much of their observed morbidity and mortality [15,17]. The incidence and severity of cardiovascular morbidity and mortality increase as glomerular filtration rate (GFR) declines [17,18]. Several studies have published correlations between CK-MB and GFR. Wang et al noted that CK-MB levels increased with the severity of renal dysfunction in CKD patients and correlated inversely with GFR [19]. However, in this study, there was no correlation observed between CK-MB and eGFR. Similarly, Sato et al did not observe any 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 disease and end-stage renal disease [17,20].

Patients with high CK-MB were observed to have a higher prevalence of low HDL and dyslipidemia, which are traditional cardiovascular risk factors. However, no association was observed between CK-MB and cardiac Troponin I, which is a more specific biomarker of myocardial injury. Several studies suggest that CK-MB has relatively low sensitivity and specificity for identifying myocardial injury in patients with uremia and thus, may not be suitable to diagnose acute coronary syndromes in CKD patients [21,22]. It has been proposed that the assessment of CK-MB in CKD is not only influenced by renal status but also other comorbid conditions that are prevalent in CKD patients, including

Table 4. Prevalence of cardiovascular risk factors in patients with high and normal CK-MB

Risk factor	Frequency (%)		*P*
	High CK-MB (n=16)	Normal CK-MB (n=67)	
Hypertension	9 (56.3)	37 (55.3)	1.0
Diabetes Mellitus	3 (18.8)	14 (20.9)	.89
Obesity	2 (12.5)	10 (14.9)	.97
Dyslipidemia	9 (56.3)	11 (16.4)	.02
Hypercholesterolemia	4 (25.0)	12 (17.9)	.19
Hypertriglyceridemia	5 (31.3)	8 (11.9)	.12
Low HDL	8 (50.0)	12 (17.9)	.03
High LDL	6 (37.5)	9 (13.4)	.09

** P-values ≤ .05 significant*

skeletal muscle damage, extracellular fluid overload, oxidative stress and inflammatory conditions. Hence, its rise cannot be exclusively correlated with cardiac involvement [23,24].

5. CONCLUSION

CKD patients had higher CK-MB, higher cardiac Troponin I, 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. High CK-MB was associated with high UACR and a higher prevalence of low HDL and dyslipidemia but not correlated with cardiac Troponin I among CKD patients. These findings suggest that CK-MB lacks adequate sensitivity and specificity for use in the diagnosis of myocardial injury in patients with CKD.

6. LIMITATION

This study was a cross-sectional study, so patients were not followed up over a period of time to ascertain cause and effect. Longitudinal studies are required to determine outcome.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for this study.

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

Authors have declared that no competing interests exist.

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