

Original article:

Creatine Kinase MB: An important point of care diagnostic biomarker for cardiovascular disease

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Abstract

Background: Inflammation and oxidative stress is one of the important of mechanisms proposed for cardiovascular disease (CVD). Early diagnosis of CVD is critically important for successful treatment and recovery of patients. Creatine Kinase MB (CK-MB) is an example of earliest biomarker of cardiac dysfunction.

Aim: To evaluate the diagnostic role of CK-MB in patients with CVD.

Methods: A total 150 clinically diagnosed CVD patients belonging age group 40-60 years and admitted to medicine wards and ICUs were included in the study. Additionally, a total of 150, age matched healthy individuals with no clinical or family history of CVD were recruited as controls. CK-MB test was done by an automated VIDAS instrument using ELFA technique (Enzyme Linked Fluorescent Assay). Other biochemical parameters studied included renal function tests, HbA1c and lipid profile.

Results: CVD was found to be significantly associated with male gender compared to female. The BMI of CVD patients (29.05 ± 2.01) was significantly high as compared to healthy individuals (23.10 ± 2.38). Dyslipidemia was significantly associated with CVD patients. CK-MB level was significantly increased in CVD patients compared to healthy individuals.

Conclusion: Early detection and treatment of CVD is very important to prevent death associated with it. Various biomarkers have been identified for early and accurate diagnosis of CVD. CK-MB can be effectively utilized as an important biomarker for diagnosis of CVD.

Key words: Biomarker, cardiovascular disease, creatine Kinase MB, dyslipidemia

Introduction.

Only few decades back cardiovascular disease (CVD) was considered as a disease of wealthy, industrialized societies.¹ In recent years, it is witnessed that the epidemic of CVD has migrated from westernized societies to developing countries.² Nearly 80% of deaths due to CVD occur in developing countries. Hypertension, hyperlipidaemia, smoking, obesity and genetic predisposition are identified as important risk factors for CVD.³ In addition to these, emotional factors like stress and anxiety and the environmental issues play a significant role to increase the rates of CVD in developing countries.⁴ As overall mechanism of CVD is complex with multiple of biological pathways involved, several mechanisms are considered to be involved in its pathophysiology.⁵ Inflammation and oxidative stress is one of the important of mechanisms proposed for CVD. Early diagnosis of cardiovascular disease (CVD) is critically important for successful treatment and recovery of patients.⁶

In recent years multitudes of biomarkers are used for rapid and precise diagnosis of CVD. As per definition biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”.⁷

Creatine Kinase MB (CK-MB) is an example of earliest biomarker of cardiac dysfunction. Approximately 30% of myocardial CK is CK-MB and a rise of > 5% of the total CK activity indicates damage to the cardiac muscle.⁵ CK-MB appears in the bloodstream 4-6 h after onset of angina and peaks between 10-12 h after the myocardial infarction (MI).⁵ The present was conducted in a tertiary care teaching hospital with aim to evaluate the diagnostic role of CK-MB in patients with CVD.

Material and methods.

Study setting: The present study is a part of a Ph.D. thesis carried out in the Department of Biochemistry, J K Hospital and L N Medical College and Research Center, Bhopal Madhya Pradesh. **Study design and duration:** Descriptive cross-sectional study was conducted for a period of one year. A total 150 clinically diagnosed CVD patients belonging age group 40-60 years and admitted to medicine wards and ICUs were included in the study. Patients presenting with systemic inflammatory disease, liver disease, cardiomyopathy, malignancy, or any other disease were excluded.

Additionally, a total of 150, age matched healthy individuals with no clinical or family history of CVD were recruited as controls. The purpose and protocol of the study were explained to all participants in local language and informed consent to participate in the study was obtained. The protocol of the study was approved by Institutional Ethics Committee. **Sample collection and biochemical parameters:** A 5 mL of blood sample was aseptically collected by venipuncture from both CVD patients and healthy individuals for performing investigations like lipid profile, renal function test (RFT), HbA1c and CK-MB. Lipid profile, RFT and HbA1c were performed by fully automated analyser Siemens Dimension. CK-MB test was done by an automated VIDAS instrument using ELFA technique (Enzyme Linked Fluorescent Assay).

Statistical analysis:

Data was processed using SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, NY, USA). The values were represented in Number (%) and Mean \pm SD. Appropriate statistical test was applied. P value of <0.05 was considered as significant.

Results.

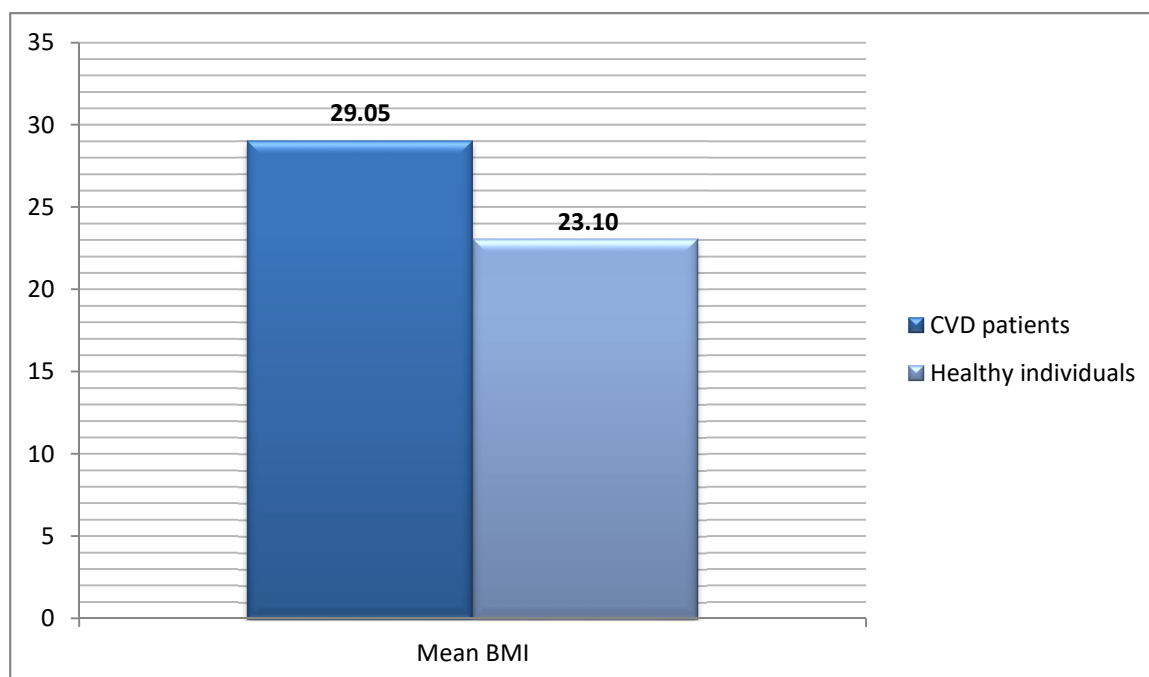
The study involved a total of 300 participants (150 CVD patients and 150 healthy individuals) belonging to age group 40-60 years. The gender wise distribution of CVD patients and healthy individuals is shown in table 1.

Table 1: Gender wise distribution of CVD patients and healthy individuals.

Gender	CVD patients (%)	Healthy individuals (%)	Chi square test, P value
Male	118 (78.7)	123 (82)	0.46
Female	32 (21.3)	27 (18)	
Total	150	150	

In the present study, CVD was found to be significantly associated with male gender compared to female (Z test, *P* value 0.0001). When the gender wise distribution of CVD patients and healthy individuals was compared there was no significant difference observed (Chi square test, *P* value 0.46). The mean age of CVD patients was 53.45±7.11 whereas for healthy individuals it was 54.08±7.11. There was no significant difference observed between the age of CVD patients and healthy individuals (T test, *P* value 0.27).

The mean ±SD body mass index (BMI) of CVD patients and healthy individuals is shown in figure 1. The BMI of CVD patients (29.05 ± 2.01) was significantly high as compared to healthy individuals (23.10 ± 2.38) (T test, *P* value 0.001*).



The mean± SD of renal function test of CVD patients and healthy individuals is shown in table 2. The mean blood urea level in CVD patients was 22.24 ± 6.32 mg/dl whereas mean creatinine level was 0.95 ± 0.15. There was no significant difference observed between RFT in CVD patients and healthy individuals.

Table 2: Renal function test (RFT) in CVD patients and healthy individuals.

Variable	Healthy individuals (Mean ±SD)	CVD patients (Mean ±SD)	T test, <i>P</i> value
Urea (mg/dl)	18.92 ± 6.49	22.24 ± 6.32	0.48
Creatinine (mg/dl)	0.88 ± 0.21	0.95 ± 0.15	0.51

Table 3: Lipid profile test in CVD patients and healthy individuals.

Variable	Healthy individuals (Mean ±SD)	CVD patients (Mean ±SD)	T test, P value
Cholesterol (mg/dl)	164.52 ± 28.98	227.66 ± 27.74	< 0.001***
Triglycerides (TG) (mg/dl)	124.86 ± 33.33	217.88 ± 30.91	< 0.001***
High density lipoprotein (HDL) (mg/dl)	46.23 ± 10.20	35.50 ± 6.72	< 0.001***
Low density lipoprotein (LDL) (mg/dl)	97.22 ± 28.53	158.03 ± 21.26	< 0.001***
Very low density lipoprotein VLDL (mg/dl)	24.97 ± 6.64	43.79 ± 6.38	< 0.001***

Lipid profile of CVD patients and healthy individuals is shown in table 3. The concentration of total cholesterol, triglycerides and LDL was found significantly higher in CVD patients compared to healthy individuals. The HDL values were significantly lower in diseased group (CVD patients) as compared to healthy individuals.

Table 4: HbA1c in CVD patients and healthy individuals.

Variable	Healthy individuals (Mean ±SD)	CVD patients (Mean ±SD)	T test, P value
HbA1c (%)	5.1 ± 0.37	5.3 ± 0.56	0.7

The mean HbA1c level of diseased group is shown in table 4. The HbA1c level was 5.3 ± 0.56 in CVD patients whereas it was 5.1 ± 0.37 in healthy individuals. There was no statistically significant difference observed between HbA1c level of patients with CVD and healthy individuals (T test, P value, 0.7).

Table 5: CK-MB level in CVD patients and healthy individuals.

Parameter	Healthy individuals (Mean ±SD)	CVD patients (Mean ±SD)	T test, P value
CK-MB (ng/ml)	6.05 ± 2.52	75.88 ± 9.48	< 0.0001***

The mean CK-MB level in CVD patients and healthy individuals is shown table 5. CK-MB level was significantly increased in CVD patients compared to healthy individuals (T test, P value < 0.0001 ***).

Discussion.

CVD, principally ischemic heart disease (IHD) and stroke are the leading cause of mortality and morbidity worldwide.⁸ Prevalence of CVD has nearly doubled from 271 million in 1990 to 523 million in 2019.⁹ Similarly the number of deaths due to CVD has steadily increased from 12.1 million in 1990 to 18.6 million in 2019.⁹ Rapid diagnosis along with effective treatment is a key determinant of outcomes for CVD events.¹⁰

In the present study, diagnostic role of CK-MB was evaluated for CVD patients belonging to age group 40-60 years. In Indians, CVDs strike at least a decade earlier than the western population.¹¹ Onset at early age, rapid progression and high mortality rate are particular causes of concern of CVD in Indian population.¹¹

Morbidity and mortality due to CVD is higher in individuals with high BMI.¹² Obesity is generally associated with factors like hypertension, hyperlipidemia, diabetes mellitus and elevated levels of fibrinogen and C-reactive protein (CRP), which increase the risk of CVD.¹² In this study, BMI of CVD patients (29.05 ± 2.01) was significantly high as compared to healthy individuals (23.10 ± 2.38). Similar to our observation, Akil *et al* (2011) also reported the associations between the high BMI and the increase rates of CVD.¹² Khan *et al.* (2018) concluded that overweight status and obesity to be significantly associated with high long-term risk for CVD morbidity compared with normal BMI.¹³

Dyslipidemia is defined as increased levels of serum total cholesterol, LDL and TG, or a decreased serum HDL concentration.¹⁴ It is an established risk factor for CVD. In the current study, the BMI of CVD patients (29.05 ± 2.01) was significantly high as compared to healthy individuals (23.10 ± 2.38). This finding was in accordance to that of [Hedayatnia et al.](#) (2020) who reported dyslipidemia to be significantly associated with risk of myocardial infarction in men.¹⁴ Dyslipidemia plays a significant role in endothelial dysfunction which predisposes to atherosclerosis, thrombosis, insulin resistance and hypertension.¹⁵ Triglyceride rich lipoproteins and LDL are known to be toxic to endothelial cells. However HDL is protective.^{15,16}

Diabetes mellitus increases the risk for CVD. Risk factors like obesity, hypertension, dyslipidemia, increased oxidative stress, increased coagulability, endothelial dysfunction and autonomic neuropathy are often common in diabetic patients.¹⁷ These risk factors directly contribute to the development of CVD. In the present study, although, 46 (30.7%) out of 150 CVD patients were diabetic, there was no significant difference observed between HbA1c level of CVD patients and healthy individuals.

Biomarkers are commonly used for detection, diagnosis, and management of various diseases including CVD.¹⁹ Creatine kinase and its CK-MB isoenzyme are used as a conventional biomarker for detection of CVD.²⁰ It catalyses the reversible transformation of creatine and adenosine triphosphate (ATP) to creatine phosphate and adenosine diphosphate (ADP). It is involved in mitochondria and cytosol in muscle cells. CK-MB is found in various organs like heart, skeletal muscle, small intestine, diaphragm, uterus, tongue, and prostate.²⁰ In this study, CK-MB level was significantly increased in CVD patients compared to healthy individuals. Similar finding was reported by Wu *et al* (2020).²¹ CK-MB has specificity of 97% just 10–12 hrs. after appearance of symptoms.²⁰

Conclusion.

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Early diagnosis of CVD is of paramount importance. Biomarkers are utilized in every step of patient care. CK-MB can be utilized as a point of care diagnostic biomarker for diagnosis of CVD.

References:

1. Aje TO, Miller M. Cardiovascular disease: A global problem extending into the developing world. *World J Cardiol.* 2009; 1(1):3-10.
2. Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. *Circulation.* 2005; 112:3547-3553.
3. Ramaraj R, Alpert JS. Indian poverty and cardiovascular disease. *Am J Cardiol* 2008; 10:102-106.
4. Rehan F, Qadeer A, Bashir I, Jamshaid M. Risk factors of cardiovascular disease in developing countries. *International Current Pharmaceutical Journal* 2016; 5(8): 69-72.
5. Dhingra R, Vasani R. Biomarkers in cardiovascular disease: Statistical assessment and section on key novel heart failure biomarkers. *Trends Cardiovasc Med* 2017; 27:123-133.
6. Leila F, Mojtaba S, Leila S, Shahab S. Recent advances in designing nanomaterial based biointerfaces for electrochemical biosensing cardiovascular biomarkers. *Journal of Pharmaceutical and Biomedical Analysis* 2018; 161: 344-376.
7. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001; 69:89-95.
8. Roth G, Mensah G, Johnson C, Addolorato G, Ammirati E, Baddour L *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *J American College Cardiology* 2020; 76: 2982-3021.
9. Meyer KA, Decker K, Mervis CA, Louder D, Bradshaw J, DeVader S, Wigand D. Emergency medical services data for cardiovascular disease surveillance, program planning, and evaluation in Maine. *Prev Chronic Dis.* 2008 Apr; 5(2):A54.
10. Gaze D. Rapid Cardiovascular Diagnostics. In: Saxena, S. K., editor. *Proof and Concepts in Rapid Diagnostic Tests and Technologies* [Internet]. London: IntechOpen; 2016 [cited 2022 Apr 15]. Available from: <https://www.intechopen.com/chapters/51063> doi: 10.5772/63910.
11. Sreenivas Kumar A, Sinha N. Cardiovascular disease in India: A 360 degree overview. *Med J Armed Forces India.* 2020; 76:1-3.
12. Akil L, Ahmad HA. Relationships between obesity and cardiovascular diseases in four southern states and Colorado. *J Health Care Poor Underserved.* 2011; 22(4 Suppl):61-72.
13. Khan SS, Ning H, Wilkins J. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. *JAMA Cardiol* 2018; 3:280-287.
14. Hedayatnia M, Asadi Z, Zare-Feyzabadi R, Yaghoobi-Khorasani M, Ghazizadeh H, Ghaffarian-Zirak R, et al . Dyslipidemia and cardiovascular disease risk among the MASHAD study population. *Lipids Health Dis.* 2020 Mar 16; 19(1):42.
15. Nayak P, Panda S, Thatoi PK, Rattan R, Mohapatra S, Mishra PK. Evaluation of Lipid Profile and Apolipoproteins in Essential Hypertensive Patients. *J Clin Diagn Res.* 2016; 10:BC01-04.
16. Albuquer JF, Ferrieres J, Ruidavets JB, Guiraud-Chaumeil B, Perret BP, Chollet F. Serum lipids in young patients with ischaemic stroke: a case-control study. *J Neurol Neurosurg Psychiatry.* 2000; 69:29-33.

17. Matheus A, Tannus L, Cobas R, Palma C, Negrato C *et al* Impact of diabetes on cardiovascular disease: an update. *Int J Hypertens* 2013; 2013:653789.
18. Robinson DJ, Christenson RH. Creatine kinase and its CK-MB isoenzyme: the conventional marker for the diagnosis of acute myocardial infarction. *J Emerg Med.* 1999; 17:95-104.
19. McLeish MJ, Kenyon GL. Relating structure to mechanism in creatine kinase. *Crit Rev Biochem Mol Biol.* 2005; 40(1):1-20.
20. Knudsen J, Steenstrup B, Byrjalsen I, Hildebrandt P, Sørensen S. At what level of serum total creatine kinase activity can measurement of serum creatine kinase MB isoenzyme activity be omitted in suspected myocardial infarction? *Scand J Clin Lab Invest.* 1989; 49:661–665.
21. Wu, YW, Ho, S.K., Tseng, WK., Yeh H. Potential impacts of high-sensitivity creatine kinase-MB on long-term clinical outcomes in patients with stable coronary heart disease. *Sci Rep* 2020;10: 5638.