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BIOCHEMICAL SIGNIFICANCE OF ISCHEMIA MODIFIED ALBUMIN: A NOVEL BIOCHEMICAL MARKER OF MYOCARDIAL ISCHEMIA IN THE EARLY DIAGNOSIS OF ACUTE CORONARY SYNDROME

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ABSTRACT **Introduction:** The term acute coronary syndrome (ACS) is used for a series of myocardial ischemia, from angina to acute myocardial infarction. Due to associated with high mortality diagnosis of ACS is important before the irreparable damage occurs to myocardium. **Aim:** To evaluate the role of IMA as a novel cardiac marker of myocardial ischemia in early diagnosis of ACS within 6 hours onset of symptoms. **Material & Methods:** Patients attending the emergency department (ED) within 6 hrs having ACS were selected. IMA was measured by Albumin cobalt binding test, Troponin I by I STAT cartridge and CK-MB by IFCC method. ROC cure was plotted to evaluate the diagnostic performance. **Results:** There was significant increase in IMA levels in ACS group (124.87± 19.48) than control (70.06±26.31). At the cut off value 92.12 sensitivity was 99% which was higher than Troponin I (84%) and CK-MB (78%), but specificity of IMA (87%) was less than CK-MB (93%) and Troponin I (82%). **Conclusion:** IMA appears to be a developing into a new marker for diagnosing of ACS in the initial hours after symptoms onset when the standard biomarkers may not be elevated.

KEYWORDS : ACS, Cardiac Biomarker, Ischemia Modified Albumin.

INTRODUCTION

Coronary heart disease is defined as acute or chronic cardiac disability arising from imbalance between the myocardial supply and demand for oxygenated blood.[1] In today's world about 17 million deaths occurred due to cardiovascular disease (CVD). Only 23% of CVD fatalities occur before the age of 70 in the western population; however, this number is 52% in India.[2] Acute coronary syndrome is an ischemic cardio manifestation which may result in myocardial damage and necrosis parallel to prolonged duration of ischemia resulting in myocardial infarction.[3] The manifestations of the myocardial ischemia are varied like chest pain, epigastric discomfort, breathlessness, nausea and vomiting. However, these symptoms may be subtle and are not easily recognized. Because of varied presentation and associated with high mortality, the early identification of patients with acute myocardial infarction is very critical.[4]

The Various Biomarkers like creatine kinase-MB, cardiac troponin I along with echocardiogram (ECG) is used in diagnosis of ACS. They are not providing reliable information when measured in the first 2-6 hrs. Moreover, the usual biomarkers may not rise during reversible myocardial ischemia and other diagnostic tools such as stress testing, echo cardiology are not routinely available.[5] Following an ischemic heart, Ischemia modified Albumin (IMA) has been recently introduced as a marker of Myocardial Ischemia. IMA is regarded as a new sensitive marker of myocardial ischemia in contrast to that of other cardiac markers. During an ischemic event structural changes occur in the amino terminus of albumin, rapidly reducing its capability to bind transition metal ions possibly as a result of acidosis, free radicals injury. The metabolic variant of albumin generated is referred to as ischemia modified albumin (IMA).[7,8]

The aim of our study was to compare the diagnostic utility of IMA with cardiac troponin I and CK-MB for early diagnosis of ACS patients presenting within 6 hours of onset of chest pain.

MATERIAL AND METHODS

The present diagnostic case control study was conducted at the department of biochemistry in collaboration with the department of cardiology at S.P. medical college, Bikaner. The study was approved by ethics committee of institution and informed consent was taken from all participants. A total of 100 ACS diagnosed case and 100 healthy individuals in the control group were enrolled.

Patients presenting in acute cardiac care unit (ACCU) with complain of chest pain within 6 hours of duration and diagnosed by the attending physician were included in ACS group. Diagnosis was made on the basis of clinical history, ECG, Cardiac markers of cell necrosis. Individuals without diagnosed medical condition, who visited hospital for their routine checkup, were recruited in the control group after following up their investigation's reports.

Exclusion criteria:
Patients with hypoalbuminemia, jaundice, chronic kidney disease, ischemic stroke, altered liver and renal functions test and pregnancy were excluded from the study.

The IMA assay procedure was based on the principle that myocardial ischemia leads to structural change in amino terminal (NH_2-Asp-Ala-His-Lys) of human serum albumin (HAS) determined by decrease cobalt (Co (II)) binding, followed by the measurement of unbound Co (II)) using dithiothretol (DTT) as a coloring agent. IMA concentration is directly proportional to the color intensity formed.[8]

IMA estimated on spectrophotometer by albumin cobalt binding test, cardiac troponin I by I STAT Cartridge and CK-MB by IFCC method.

Statistical analysis:
The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analyzed and statistically evaluated using SPSS-PC-25 version. Quantitative data was expressed in mean ±standard deviation and mean of two groups were compared by student t test. Receiver operating characteristic (ROC) curve was used to determine the optimal cut-off values which provided the maximum sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) of these parameters to predict ACS. P' value less than 0.05 was considered statistically significant.

RESULTS
Baseline demographic and clinical characterization of the patients and healthy controls groups are given in table 1. As shown in Table 1, the mean age of ACS group was significantly higher ($p<0.001$) than control group. The difference between gender of controls and cases were statistically insignificant. The IMA levels were significantly high ($p<0.001$) in ACS (124±87±19.48) subjects as compared to control subjects (70.87± 26.31). The mean values of cTnI ($p<0.001$) and CK-MB ($p<0.001$) were significantly higher in patients than control subjects.

Figure 1 show Receivers operating characteristics curve (ROC) showing comparison of IMA, cardiac troponin I and CK-MB, area under the ROC curve was observed to be 0.93, with 95% confidence interval (0.89-0.97) as shown in above figure at the optimum cut-off value of 92.19 U/ml for IMA. Thus we considered 92.19U/ml as an optimal diagnostic cut-off value for our study.

AUC of IMA, to predict ACS at cut-off value of 92.19 U/ml was 0.93 that was higher than CK-MB and Troponin I. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of IMA was 99.0%, 87.0%, 88.39%, 98.86% and 93.0% respectively to predict ACS, which was higher than cardiac troponin I and CK-MB. Specificity of CK-MB was higher than IMA and cardiac troponin I as shown in table 2.

Observation Tables
Table -1 Baseline characteristics of all subjects

Variables	Controls subjects (n= 100)	ACS subjects (n=100)
Age	44.12± 6.94	46.63±7.41 **
Gender (men/women)	82/18	80/20
IMA(U/ml)	70.87± 26.31	124±87±19.48 **
cTnI (ng/ml) ^	0.05 (0.03-0.06)	0.22 (0.08-1.21) **
CK-MB(U/L)	16.94 ± 4.07	34.55± 14.72**

Values were expressed in mean with standard deviation (Mean± SD)

^ Data represented in median IQR, Mann Whitney U test was applied
- Statistically significant ($p< 0.05$)
- ** statistically highly significant($p<0.001$)
- n= numbers

Table 2. Diagnostic value of IMA, cardiac troponin-I and CK-MB to predict ACS

	IMA	Cardiac troponin-I	CK-MB
Area under curve (AUC)	0.93	0.90	0.92
95% CI	0.89-0.97	0.85-0.94	0.88-0.95
Cut off value	92.12	0.06	23.35
Sensitivity	99.0%	84.0%	78.0%
Specificity	87.0%	82.0%	93.0%
PPV	88.39 %	82.35%	91.76%
NPV	98.86 %	83.67%	80.87%
Accuracy	93.0%	83.0%	85.5%

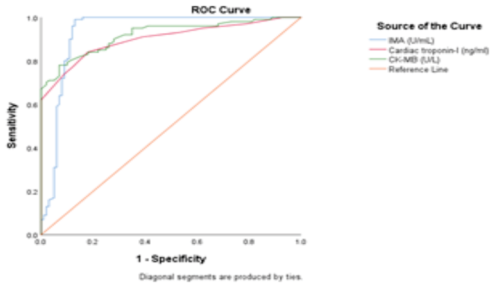

Figure 1: Receivers operating characteristics curve of IMA, cardiac troponin I and CK-MB

DISCUSSION
Determination of biomarker for myocardial injuries plays an important role in the diagnosis of ACS. At present determination of cardiac TnI and CK-MB have been well accepted as a marker of myocardial damage. But these makers are not suitable for assessing early myocardial ischemia particularly in first 2-6 hours of ischemia cellular markers are released into the circulation only after complete damage to the myocardium has already occurred.[9]

So rapidly detectable, highly sensitive markers would be desirable for myocardial ischemia. Prolong ischemia can lead to myocardial cell death it is a pre-condition to an infarction. Therefore, the identification of myocardial ischemia at the earliest stage is a must, for providing the devastating consequences of the disease.[10]

Ischemia modified albumin has been recently been evaluated as a new sensitive serum biomarker for cardiac ischemia in contrast to the cardiac enzymes which are released when a cardiac necrosis occurs. In present study, we assessed IMA, cTnI and CK-MB of patients who presented to acute cardiac care unit. The results of our study showed that the serum IMA level was significantly higher in ACS subjects than compared to control. The diagnostic appearance of serum IMA in ACS was maximum (AUC 0.93). The sensitivity and specificity were 99.0 % and 87.0 % respectively. Our result was supported by observations of Chawala et al, Sinha M.K. et al.[10,11] because ischemic events could cause as much as or more damage to serum albumin and the surrounding tissue. However, in our study IMA was less specific than CK-MB and troponin I.

CONCLUSIONS

Measurement of IMA as a marker of myocardial ischemia can be useful in early diagnosis of ACS. IMA appears to be a sensitive but not specific marker of myocardial ischemia in ACS patients presenting to the acute cardiac care unit (ACCU). So, IMA can be used as additional cardiac marker along with cardiac troponin I and CK-MB. Other non-myocardial ischemic conditions should be kept in mind while interpreting IMA values.

Disclosure Statement

This study is investigator initiated. The authors declare that they have no competing/conflict of interests in relation to this article.

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Consent For Publication

- Not applicable.
- Ethics approval and consent to participate.
- The study protocol was approved by the medical ethics committee of the Rajasthan University of Health Sciences, Jaipur, Rajasthan (State), India.

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