www.jmscr.igmpublication.org
Impact Factor 5.244
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: http://dx.doi.org/10.18535/jmscr/v4i7.68

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Ischemia Modified Albumin –An Early Marker of Myocardial Ischemia

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ABSTRACT
Introduction: *Coronary heart disease (ischemic heart disease-IHD) is projected to be the leading cause of death by 2030, accounting for 25-30% of deaths in industrialized countries.*
Aim and objective: *To estimate serum Ischemia Modified albumin in myocardial ischemia patients and to correlate it with Ck-MB and lipid profile.*
Materials and Methods: *The present study was conducted to estimate serum Ischemia modified albumin by* ***Albumin Cobalt Binding Assay*** *in fifty subjects who were admitted in the Intensive Coronary Care Unit with complaints of chest pain of less than 6 hours duration along with ECG showing S-T,T changes. This was compared with fifty healthy subjects.*
Results and Observation*: Statistical analysis in the study group showed the mean value of Ischemia modified albumin as 88.52 Iu/ml and sensitivity of 78% which revealed a significant raise than Ck-MB [mean value of 56.50 U/Land sensitivity of 69%] during the early hours of ischemia. With an area under the curve of 0.921 and a standard error of 0.028, it also showed an asymptomatic significance of 0.001 proving it as a better predictor over Ck-MB in diagnosing myocardial ischemia.*
Conclusion: *Values obtained suggested a significant correlation between ischemia modified albumin and CK-MB,and also with age, total cholesterol and low density lipo protein. Analysis of Ischemia modified albumin helps to diagnose myocardial ischemia at an Earlier stage in the first 2-6 hours following an ischemic event before it progresses to irreversible myocardial cell damage and necrosis, unlike other previous laboratory parameters that identify myocardial damage only after it is well established*
Keywords: *IHD-ischemic heart disease, ACS-Acute coronary syndrome, IMA- ischemia modified albumin,*

INTRODUCTION

Ischemic Heart Disease (IHD) [CHD – Coronary Heart Disease - synonym] has been defined as impairment of heart function due to inadequate blood flow to the heart muscles, compared to its needs, caused by obstructive changes in the Coronary circulation to heart.

Global burden of CHD depend on its mortality risk, decrease in life expectancy, increase in age specific death rates and proportion of death. WHO predicted that by 2030, 25 million deaths worldwide will occur due to CVD annually[1]. Many prospective studies like Framingham Study established the Coronary Heart Disease Risk factors (i.e.) factors that make the occurrence of the disease more probable.

Among the Non- modifiable risk factors Age has a dominant influence. The peak period is between

40 to 60 years but also occurs earlier when other risk factors co- exist[2]. Males are more affected by IHD than females. Clinical IHD in pre-menopausal women is very low due to estrogenic effects. The familial predisposition to atherosclerosis and Coronary Heart Disease is polygenic. Type Abehaviour doubles the risk of Coronary Heart Disease in otherwise healthy men. Under modifiable risk factors Hypertension accelerates the atherosclerotic process especially if hyper lipidemia is also present. The degree of risk of developing CHD is related to the number of cigarettes smoked per day. Smoking accelerates atherosclerosis and promotes acute ischemic events[3].Greater the weight gain greater is the risk of hyper tension, CHD and insulin resistance diabetes mellitus. Presence of hyper cholesterolemia is sufficient to initiate the disease process by inducing an endothelial injury in the coronary arteries. Serum cholesterol concentration associated with low density lipoprotein which serves as a vehicle for the delivery of cholesterol to peripheral tissues play a major role in precipitating CHD[3].CHD is 2-3 times higher in diabetics than in non-diabetics. Sedentary life style with reduced physical activity leads to an early development of CHD. High alcohol intake defined as 75g or more per day becomes an independent risk factor for CHD [3].

Clinical types of IHD

Patients with IHD fall into two large groups.

1) Patients with chronic coronary artery disease.
2) Acute coronary syndromes.

Chronic coronary artery disease:

These patients commonly present with ANGINA PECTORIS where the ischemia causes pain but is insufficient to lead to death of myocardium.

Acute coronary syndrome (acs) -

Acute Coronary Syndrome comprises of a spectrum of disease that encompasses ischemia with minimal myocardial damage (i.e.) unstable angina and Myocardial Infarction. This infarction may be

1) STEMI – (ST elevation myocardial infarction)
2) NSTEMI – (Non ST elevation myocardial infarction) [4.]

Pathogenesis of atherosclerosis:-

Atherosclerosis is a complex disease that involves lipoprotein influx and modification, increased prooxidant stress and inflammatory angiogenic and fibro proliferative responses intermingled with extra cellular matrix and smooth muscle cell proliferation resulting in the formation of atherosclerotic plaque [5].

Acute changes of plaque:-

The initiating events that disrupts a plaque are

1) Rupture, fissuring or ulceration of plaques exposing highly thrombosed plaque constituents or underlying sub endothelial basement membrane.
2) Hemorrhage into the core of plaques with expansion of plaque volume and worsening of the limited occlusion [6].

Role of thrombus:-

Rupture of plaques fibrous cap causes thrombosis that leads to episodes of unstable angina [6].

Patho physiology of IHD :-

The extent of damage to myocardium and the irreversibility of the ischemic cardiac muscle depend on

1) The metabolic needs of the under perfused tissue.
2) Degree of existing collateral vessels.
3) Location, severity, duration and rate of development of arterial occlusion[7].

ISCHEMIA MODIFIED ALBUMIN

In ischemia of the myocardium, within seconds of vascular obstruction, aerobic glycolysis ceases in the myocytes, leading to inadequate production of adenosine triphosphate and depletion of creatine phosphate resulting in the accumulation of lactic acid, NADH and fall in pH [3.]Reduced pHleads to release of bound copper and iron from protein and intracellular stores. Ischemia also reduces the electron carriers, thereby leading to the formation of reactive oxygen species like super oxide anions [8].

These free radicals oxidatively damage the histidine present in the amino terminal region of albumin. This albumin which has a damaged amino terminal is called Ischemia Modified Albumin (IMA) [9,10].

Normal albumin has a binding affinity for transitional metals like cobalt at its amino terminal. But Ischemia Modified Albumin lacks its ability to bind to cobalt which forms the basis for Albumin cobalt binding assay in measuring Ischemia Modified Albumin in myocardial ischemia [11].IMA starts increasing within 6 to 10 minutes of ischemia, reaches a peak by 4 hrs and returns to baseline after 6 hrs in transient ischemic conditions, like after Percutaneous transluminal angioplasty. Whereas the N-Terminal oxidative damage to albumin is cumulative and the repair is slow in cardiac ischemia, and the level also will not raise after 6 hours [12,13].

AIM OF THE STUDY

Aim of the study is to measure the Ischemia Modified Albumin by Albumin Cobalt Binding assay in patients, within 6 hours of onset of chest pain.

Objective

1) To correlate the IMA values with CK-MB
2) Correlation of other markers of atherosclerosis like

(a) Total cholesterol
(b) Triacylglycerol
(c) High density lipoprotein
(d) Low density lipoprotein
(e) Very low density lipoprotein with IMA

3) To prove the use of IMA as an early marker of myocardial ischemia.

MATERIALS AND METHODS

The study was conducted after getting the approval from the ethical committee of Stanley Medical College. Hundred subjects were chosen for the study. Both males and females in the age group of 30-70 years were included and an informed consent was obtained from all of them.

Fifty subjects with normal, clinical, biochemical parameters and with normal ECG served as the control group. They were selected from the master health checkup outpatient department of Stanley Medical College.

Fifty subjects who were admitted in Intensive coronary care unit [ICCU] with complaints of chest pain (of < 6 hours duration), with Electro cardio graphic findings showing ST changes formed the study group and they were selected from the department of cardiology, Stanley Medical College.

INCLUSION CRITERIA

1) Patients admitted with complaint of chest pain within 6 hours of onset.
2) Electro cardio graphic findings showing abnormal ST-T wave changes (ST segment elevation or depression or deep symmetrical T wave inversion).

EXCLUSION CRITERIA

1) Presence of renal diseases.
2) Presence of cirrhosis,
3) Presence of stroke, skeletal muscle injury, malignancy, trauma.
4) Critically ill patients.
5) Ongoing infectious diseases.
6) Serum albumin < 2 gms/dl , Serum creatinine> 3 mgs/dl.

BLOOD COLLECTION

5ml of blood samples were collected by vene puncture with strict aseptic precaution as soon as the subjects got admitted as per the inclusion criteria.

The samples were centrifuged and serum separated. One part of the sample was taken and analysis of CK-MB, albumin and creatinine were done immediately. Remaining part of the sample was stored for analysis of Ischemia Modified Albumin at 20^{o} C.

12-14 hours fasting sample was also collected from all subjects during their hospital stay and analysis of total cholesterol, triacylglycerol and high density lipoprotein were done.

Lab methods:

Ischemia modified albumin was estimated by chemical method using albumin –cobalt binding assay. Rests of all analytes were analyzed by ERBA-Transasia kit using Cobas Mira auto analyzer.

RESULTS AND STATISTICAL ANALYSIS

A total of 100 patients were included in the present study. Out of the 100, 50 were study group [IHD patients within 6 hours of onset of Chest pain] and other 50 were controls [Normal individuals].

AGE DISTRIBUTION AMONG THE STUDY AND CONTROL GROUP:-

Male and Female patients in the age group of 35 years to 70 years were taken in the study. Both the study and control group were age matched.

The mean age of the control group is 51.48 and the mean age of the study group is 52.04.

TABLE – I

Group	N	Minimum age	Maximum age	Mean	Standard Deviation	Student independent 't' test
Control	50	35	67	51.48	8.853	P=0.09
Study	50	35	68	52.04	9.178	Not Significant

The serum levels of IMA & CK-MB total cholesterol, Triacylglycerol and High density lipoprotein were estimated for all the patients taken for the study. Very low density lipoprotein and low density lipoprotein values were calculated. Mean and standard deviation were calculated for the quantitative variables, Total cholesterol, Triacylglycerol, High density lipoprotein, very low density lipoprotein and low density lipoprotein, IMA & CK-MB, in both study and control group. The values were analysed and the results are presented in table-2

Correlation between IMA and Ck-MB were analyzed using pearson's correlation analysis. The results are presented in table 3.

The Receiver operating characteristic [ROC] Curvesare plotted for IMA and CK-MB and presented in figures I .and II

COMPARISON OF BIOCHEMICAL PARAMETERS IN THE STUDY AND CONTROL GROUP

TABLE – 2

Parameter	Group	Mean	Standard deviation	'P' value
IMA	Control Study	38.35 88.52	13.95 26.57	P=0.001 Significant
CK-MB	Control Study	12.32 56.50	4.23 49.21	P=0.032 Significant
Total Cholesterol	Control Study	166.12 208.44	17.67 37.29	P=0.04 Significant
Triacyl glycerol	Control Study	125.45 128.38	24.25 16.94	P=0.058 Significant
High density lipoprotein	Control Study	44.04 34.44	9.53 8.43	P=0.01 Significant
Low density lipoprotein	Control Study	96.00 148.26	22.64 35.18	P=0.032 Significant
Very low density lipoprotein	Control Study	24.96 25.70	4.91 3.40	P=0.05 Significant

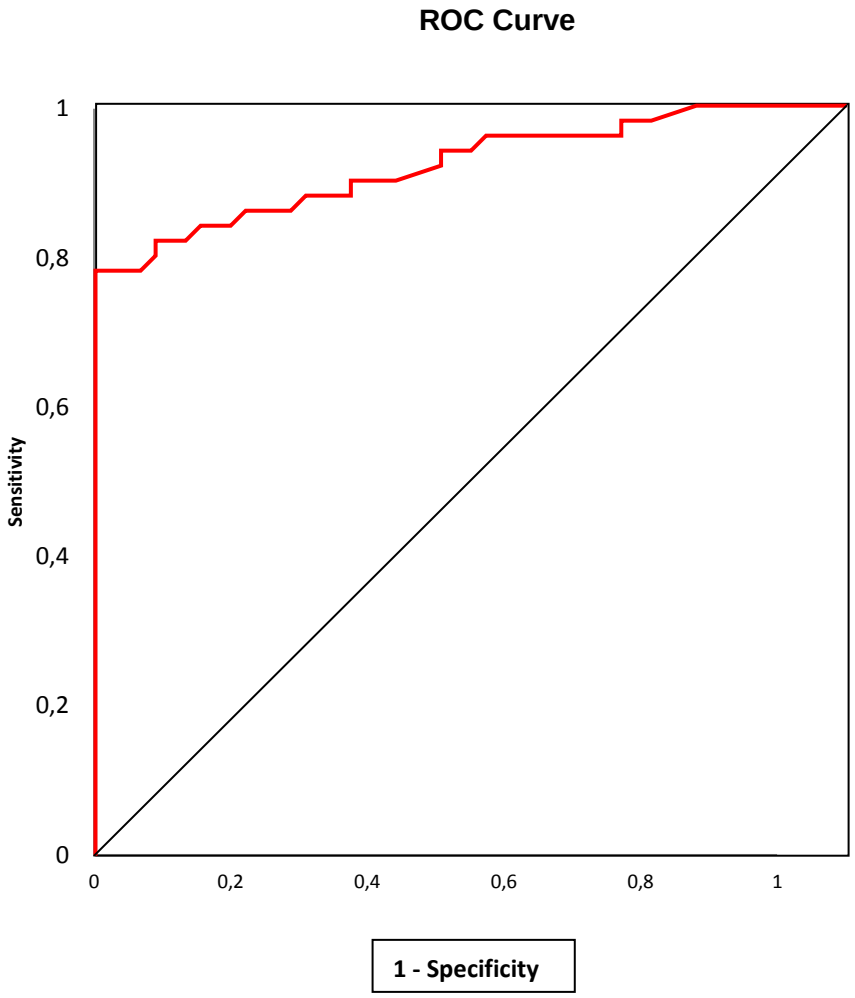
PEARSON'S CORRELATION ANALYSIS IMA WITH OTHER VARIABLES

TABLE – 3

IMA	Age	CK-MB	TC	TAG	HDL	LDL	VLDL
Correlation 1	0.132	0.53	0.482	0.062	0.374	0.55	0.459
Significance [2 tailed]	0.031	<0.001	0.004	0.06	0.001	0.002	0.56
	S	S	S	NS	S	S	NS

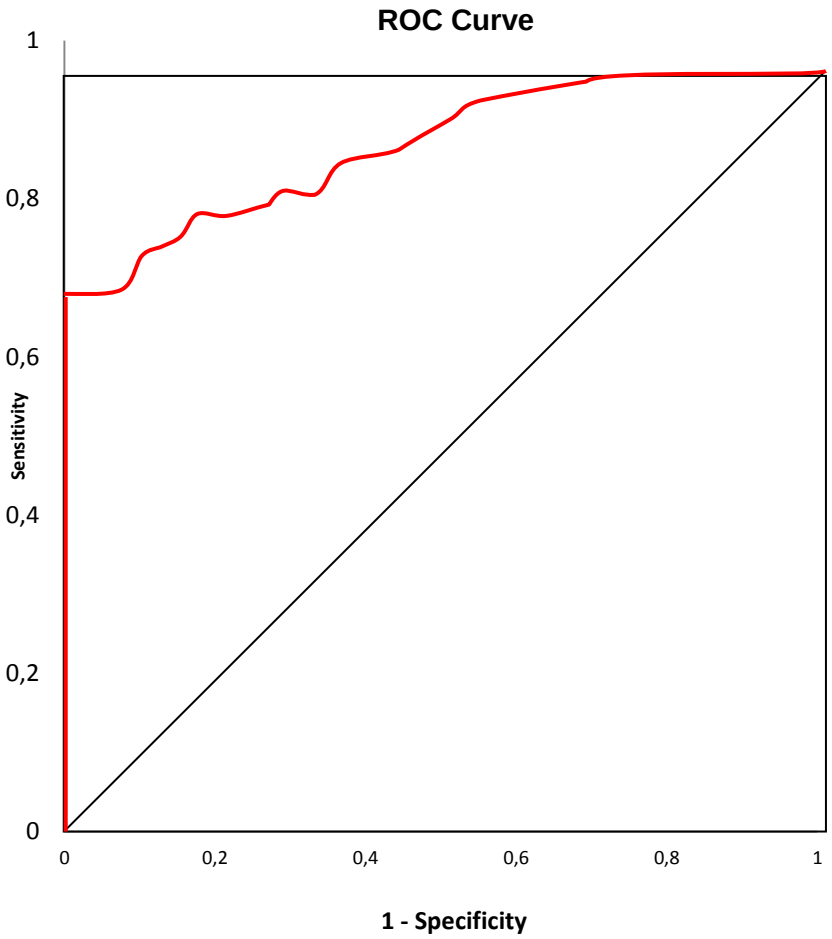
Figure I

RECEIVER OPERTING CHARACTERISTIC CURVE FOR ISCHEMIA MODIFIED ALBUMIN (IMA) and CK-MB



DIAGONAL SEGMENTS ARE PRODUCED BY TIES

Figure II



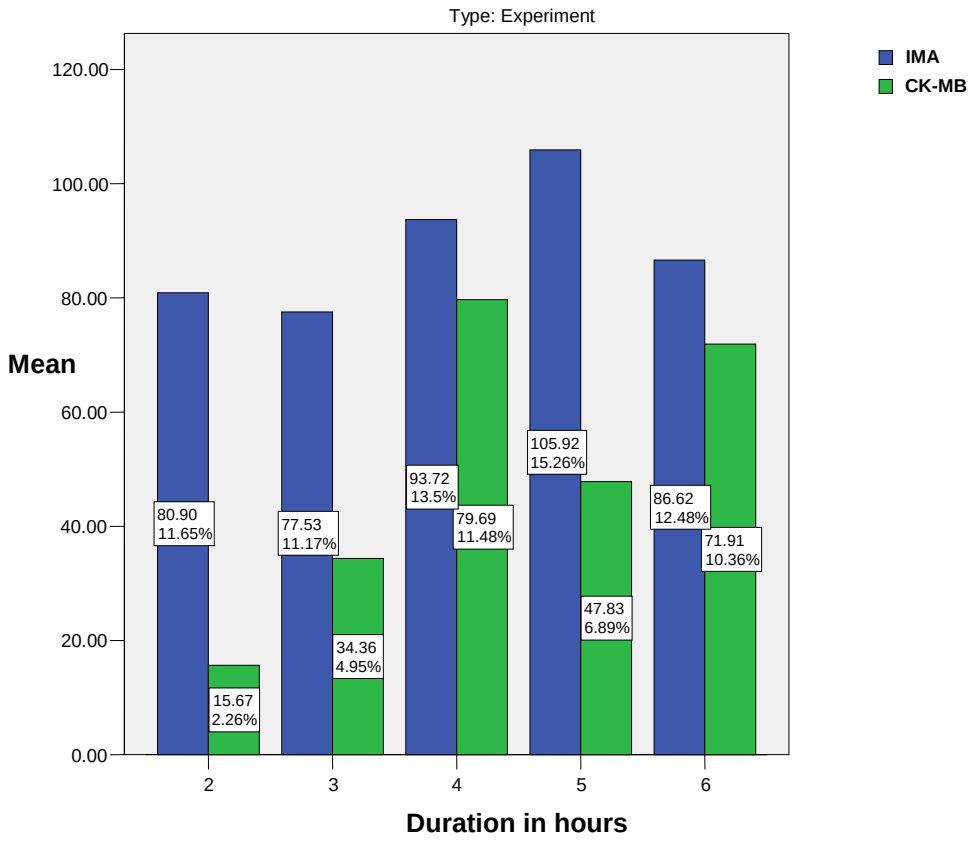
DIAGONAL SEGMENTS ARE PRODUCED BY TIES

DISCUSSION

The present study establishes the characterization of the IMA test for its association in the early diagnosis of Myocardial Ischemic patients and its comparison with CK-MB, the common biochemical marker of Coronary Heart Disease.

In the present study, the mean value of IMA of 88.52units/ml in the study group showed a significant rise than CK-MB during the early hours of ischemia with a sensitivity of 78%. This study also correlates with the data given in previous studies on Ischemia Modified Albumin- as a novel marker of Acute Coronary Syndrome[14].

IMA / CK-MB LEVELS WITH DURATION OF CHEST PAIN



BAR DIAGRAM FIGURE - 1

Various epidemiological and clinical studies have shown strong relationship between IMA and CK-MB levels increase in relationship to duration of chest pain [15].

The present study also shows a strong positive correlation with duration of chest pain which is depicted in the bar diagram in (Fig-1). There is significant serial elevation in IMA levels from 2 hours to 6 hours of onset of chest pain compared to the percent increase in CK-MB levels.

ROC curve of IMA and CK-MB reveal that the IMA curve is above the assay curve of CK-MB [16].

AREA UNDER THE CURVE

Test result variable (IMA)

Area	Std error	Asym sig	Asymptomatic 95% confidence interval	
			Low bound	Upper bound
0.921	0.28	0.000	0.866	0.976

With an area under the curve of 0.921 and a standard error of 0.028, IMA showed an asymptomatic significance of 0.000 proving it as a better predictor over CK-MB, in diagnosing myocardial ischemia. Hence IMA is a better assay for evaluating ischemia before CK-MB.

When the mean values of IMA and CK-MB are compared in the study and control groups, a significant relationship exists between both the study and control groups in all age group especially in the age group of < 40 years, 41-50 years and > 60 years Comparing the presence of

risk factors, myocardial ischemia in <40 years can be attributed to smoking and alcohol consumption in this age group.

Onset of HT and Diabetes in addition, contributed to the precipitation of myocardial ischemia in patients over the age group of 40 years.

In the Pearson's correlation analysis, there is a significant correlation noticed between IMA and CK-MB with age, Total cholesterol and LDL. Progressive atherosclerosis with increasing age leads to ischemia with super added risk factors precipitating the development of atherosclerosis at an early age.

Alteration in food habits and life style changes can decrease the effects of modifiable risk factors over atherosclerosis which can delay the onset of ischemia.

LIMITATIONS OF THE STUDY

1) Albumin Cobalt binding (ACB) assay which is utilized to estimate IMA levels in ischemic patients is based on the modification in the amino terminal region of albumin produced by extra cellular hypoxia, acidosis, and a free radical injury disruption[17]. Therefore ischemia in the absence of necrosis may cause bias towards apparent false positive Albumin Cobalt binding data.
2) The currently used colorimetric Albumin Cobalt binding assay is an indirect measurement of IMA production. New assay platforms (Immuno assays) are expected to be available in future which may improve the specificity of IMA [17,18].
3) Currently no reference standard exists for cardiac ischemia. A combination test of IMA with CK-MB and Troponin I can increase the sensitivity in the early diagnosis of Acute Coronary Syndrome [14, 19].

CONCLUSION

Biochemical markers such as CK-MB, Cardiac Troponin-I and Myoglobin are suitable only for assessing myocardial infarction. The results of the present study confirm the findings of previous studies, that reported that the Albumin Cobalt colorimetric assay distinguishes myocardial ischemic patients from non- ischemic patients ($p<0.001$)

Introduction of IMA assay for the first time provides emergency physicians with an objective diagnostic study to determine the presence of myocardial ischemia completely within the control of the emergency department.

IMA assay presents a quantitative accurate laboratory determination of the occurrence of an Ischemic myocardial event, Angina of various types.

Unlike the previous laboratory parameters that identify myocardial damage, only after it is well established, this test (Albumin Cobalt binding assay) helps to determine which patients will go in for severe occlusion.

The introduction of IMA is a welcome event and based on the results obtained, the present study supports the hypothesis that Ischemia Modified Albumin is a useful marker for the early diagnosis of myocardial ischemia before any significant increase in CK-MB levels.

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