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# ASSOCIATION OF SERUM ISCHEMIA MODIFIED ALBUMIN LEVELS WITH LIPID PROFILE IN EARLY PHASES OF ACUTE CORONARY SYNDROME

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**ABSTRACT**

**Background:** Acute coronary syndrome (ACS) is a medical emergency where diagnosis and management of patient before onset of myocardial necrosis is beneficial in reducing morbidity and mortality of the patients. Convential cardiac markers are able to detect ischemia only after onset of necrosis. The present study was carried out to evaluate the sensitivity of Ischemia modified albumin (IMA) in detecting ACS and correlation of IMA with lipid profile.

**Method:** The study was carried out on 78 subjects (which included 38 cases of ACS and 40 controls). The diagnosis was made on the basis of clinical history, ECG, qualitative cTnI and estimation of CK-MB mass. Blood sample was collected for LFT, KFT, lipid Profile and Serum IMA.

**Result:** A highly significant difference was observed in serum IMA levels and serum HDL levels between ACS cases and controls. IMA alone as well in association with the currently known biomarkers had a diagnostic sensitivity of above >90 % for detecting ischemia in ACS. Serum IMA levels showed a significant positive correlation with serum triglyceride levels and significant negative correlation with serum HDL.

**Conclusion:**IMA is an early and highly sensitive marker, which can be utilized, for detection of myocardial ischemia before infarction sets in. Serum IMA levels have a positive correlation with dyslipidemia which needs further evaluation at molecular levels.

**KEYWORDS :**

## INTRODUCTION

Acute coronary syndrome (ACS) is an umbrella term used to describe a range of conditions associated with sudden, reduced blood flow to the heart. The ischemic process results in inadequate oxygen and nutrient supplies to the affected sites, which may cause irreversible damage resulting in death of cardiac myocytes. ACS is divided into ST elevation MI (STEMI) and non–ST elevation ACS, which includes unstable angina and non–ST elevation MI (NSTEMI), the latter two conditions are indistinguishable at the time of presentation [1].

It is a medical emergency that requires prompt diagnosis and care. It is essential to identify myocardial ischemia before the onset of irreparable myocardial cell damage.

According to the World Health Organization (WHO), the diagnosis of ACS may be based on three criteria: clinical symptoms, alterations in the electrocardiogram (ECG), and biochemical markers.

Identification of patients with myocardial ischemia can be problematic and time-consuming in hospital set up when routinely available biomarkers are used [2]. The clinical features are usually non-specific and include sudden onset chest pain, discomfort, and shortness of breath, light-headedness, nausea and vomiting. Diagnosis of STEMI is usually based on 12-lead ECG and includes ST segment elevation of 2 mm in men and 1.5 mm in women for leads V2 and V3; 1 mm for leads v1, V4-6, I, II, III, aVL and aVF and 0.5 mm for leads V7-9 (posterior leads) and V3R and V4R (in right-sided leads) [3].

NSTEMI may occur in 1% to 6% of patients without history of coronary artery disease and may present with normal or near-normal ECG [4] Abnormalities, such as atrial fibrillation, ventricular hypertrophy, and other bundle branch blocks, can conceal ischemic signs on ECG [5]. Serial ECG or continuous ST segment monitoring may be required for improving the detection of ischemic changes [6].

The traditional biomarkers for detection of ACS include- Creatine Kinase (CK)-MB, Cardiac Troponins and Myoglobin, all of which are associated with myocardial necrosis. The sensitivity of CK-MB for Acute myocardial infarction is only 50% if measured early at the time of presentation [7]. Elevation in Cardiac troponins (cTnI and cTn T) are considered gold standard for diagnosis of MI, as they are more sensitive and specific markers as compared to CK-MB [8].

Serum based biochemical test capable of detecting ischemia prior to cell damage was first proposed by Bar-Or [9,10]. This biomarker is based on serum albumin, the most abundant protein in the body [11]. The N-terminal region of albumin has the N-Asp-Ala-His-Lys sequence. The first three amino acids show greater metal-binding capacity and specificity for cobalt (Co), copper (Cu) and nickel (Ni). When exposed to ischemia, hypoxia and/or free radical damage, the N-terminal region undergoes degradation to form Ischemia Modified Albumin (IMA) showing reduced ability to bind to metals (Co, Cu and Ni). Ischemia modified albumin is detectable within six to ten minutes and remains elevated for up to several hours later, hence proposed as biomarker for myocardial ischemia [12]. Some of the recent studies have indicated the diagnostic importance of estimating serum Ischemia Modified albumin in patients of Acute Coronary Syndrome [13,14].

Since dyslipidemia is often linked to ACS, this study was planned to evaluate serum Lipid Profile and IMA levels in patients of ACS within 8 hours of onset and to evaluate correlation of ischemia Modified albumin with lipid profile.

## MATERIAL & METHOD

This hospital based case-control study was carried out in the Department of Biochemistry in collaboration with Department of Cardiology, at ESIC Postgraduate Institute of Medical Sciences and Research in New Delhi.

Thirty -eight suspected cases of ACS and forty age and gender matched healthy controls were included in the study.

**Inclusion Criteria-** Applying the purposive sampling technique, patients admitted to the ICCU in midnight and early morning with complain of chest pain and diagnosed as ACS by the attending physician were included in study group.

**Exclusion Criteria-** Subjects not willing to participate, patients with hypoalbuminemia (serum albumin level less than 3.5 g/dl), chronic kidney disease, history of ischemic stroke, advanced peripheral vascular disease, acute limb ischemia, liver cirrhosis, acute heart failure, and skeletal muscle injury were excluded from the study.

Provisional diagnosis was made on the basis of clinical history, ECG, qualitative cTnI and estimation of CK-MB mass, which were performed immediately as a part of standard of care and patient management protocol. An aliquot of serum sample drawn for CK-MB estimation was also used for estimation of Ischemia Modified Albumin (IMA). The sample for IMA estimation was stored at -20°C until batch analyzed by ELISA method (R& D Bio systems). Repeated freezing and thawing of samples was avoided.

As per the Institute protocol, fasting samples were sent to the lab next morning for routine biochemical tests (LFT, KFT, Lipid profile, sugar, serum electrolytes). At the time of sample collection, angiographic confirmation was not possible due to lack of facility. Final diagnosis was made retrospectively.

The results of IMA were not made available to the attending physicians at the time of diagnosis and management. Age and gender matched healthy volunteers were selected from the hospital employees.

Statistical analysis was carried out on SPSS version 17.0. Data is presented as Mean ±SD. The various statistical methods used for evaluation are shown against each table.

## RESULT

The age of patients ranged from 22 to 71 years in study group. Personal and medical history in ACS group revealed 50% as smokers, 51.3% alcoholic, 63.15% hypertensive, 44.7% diabetic and 26.3 % with positive family history of cardiac disease.

Among the ACS group, there were 16 cases of STEMI, 12 cases of unstable angina and 10 cases of NSTEMI. The baseline characteristics of both the groups is shown in Table I . A significant difference was seen between systolic and diastolic Blood pressure among cases and controls.

**Table 1 : Baseline Characteristics Of The Study Population**

| Variable | Control Group (n=40) | Study Group (n=38) | P-Value |
|---|---|---|---|
| Age (Years) | 44.56 ± 8.8 | 52.12 ± 15.31 | 0.041* |
| Male (%) | 57.5% | 57.9% | 0.523 # |
| SBP (mmHg) | 118.2 ± 10.5 | 134 ± 12.8 | 0.025* |
| DBP (mm Hg) | 82.4 ± 5.9 | 92.1 ± 8.2 | 0.01* |
| Mean S. Albumin (g/dl) | 4.8 ± 0.72 | 4.65 ± 0.78 | 0.676* |

*By Independent t-test and # by Chi-square test

No significant difference was seen between Serum Cholesterol and serum triglyceride levels among cases and control group as seen in Table 2. However, serum HDL was found to be significantly lower in ACS cases (43.21 ± 14.32 mg/dL) as compared to the control group (61.63 ± 8.57 mg/dL). Serum IMA levels were significantly raised in patients with ACS (75.57 ±71.99 ng/mL) as compared to control group (39.96 ± 17.52 ng/mL) (p<0.001).

**Table 2: The Differences In Lipid Profile, Creatine Kinase Levels And IMA Observed Between The Study And The Control Group**

| Variable | Control Group (n=40) | Study Group (n=38) | P-value |
|---|---|---|---|
| Serum Cholesterol (mg/dL) | 136.9 ± 49.65 | 158.14 ± 59.21 | 0.223 |
| Serum Triglycerides (mg/dL) | 133.92 ± 43.20 | 165.77 ±64.39 | 0.075 |
| Serum HDL (mg/dL) | 61.63 ± 8.57 | 43.21 ± 14.32 | 0.035 |
| Serum IMA (ng/mL) | 39.96 ± 17.52 | 75.57 ±71.99 | P<0.001 |
| Serum CK (T) (U/L) | 106.5 ± 10.8 | 319.4 ± 365.1 | P<0.001 |
| Serum CK-MB (U/L) | 13.9 ± 4.9 | 106.4 ± 25.7 | P<0.001 |

P-value calculated by Independent t-test

Serum IMA levels and lipid profile was compared in different sub-groups of ACS patients (Table 3). No significant difference was observed in serum Cholesterol, triglycerides, HDL and IMA levels between all the three groups

**Table 3: Difference In Lipid Profile And IMA In Different Subgroups Of ACS**

| Variable | STEMI (N=16) | Unstable Angina (n=12) | N STEMI (N=10) | p-value |
|---|---|---|---|---|
| Serum Cholesterol | 165.3 ± 62.18 | 149.16 ± 53.1 | 163.88 ± 52.67 | 0.426 |
| Serum triglycerides | 166.8 ± 67.92 | 158.87 ± 63.9 | 172.62 ± 59.7 | 0.239 |
| Serum HDL | 41.52 ± 10.6 | 44.68 ± 13.7 | 42.98 ± 9.5 | 0.225 |
| Serum IMA | 82.69 ± 67.8 | 73.97 ± 70.2 | 84. 29 ± 68.7 | 0.092 |

P-value calculation by ANOVA

Based on the data, the sensitivity of various diagnostic modalities in identifying the ischemic event in ACS was evaluated. It was found that IMA alone as well in association with the currently known biomarkers had a diagnostic sensitivity of above >90 % for detecting ischemia in ACS (as Shown in Figure I).

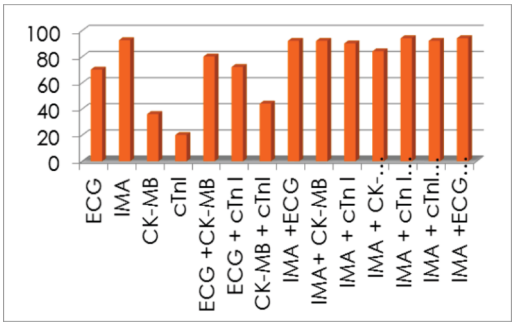


**Figure 1: Sensitivity of various diagnostic modalities in ACS**

Serum IMA levels showed a significant positive correlation with serum cholesterol and serum triglyceride levels in patients with ACS and a highly significant negative correlation with HDL levels (Table 4).

**Table 4: Correlation Of IMA With Lipid Profile In ACS Cases**

| VARIABLE | CORRELATION FACTOR | P-VALUE |
|---|---|---|
| Cholesterol | 0.607 | 0.028 |
| Triglycerides | 0.558 | 0.047 |
| HDL | -0.652 | 0.01 |

By Pearsons' Correlation

## DISCUSSION

Many patients admitted in Emergency Department may present with myocardial ischemia without the onset of myocardial necrosis. The traditionally known markers-ECG and cardiac markers are positive only after onset of myocardial necrosis. The accurate diagnosis of acute Coronary syndrome before onset of myocardial necrosis is a great challenge to the clinicians. IMA is a modified form of human serum albumin where N-terminal undergoes modification under the effect of ischemia. The modifications may result from acidosis, free-radical injury, hypoxia or energy- dependent membrane disruption [15].

In the present study, the age group of healthy controls was lesser than that of the cases, since the controls were selected from amongst the hospital employees and persons above 58 years of age were not available for participation. The systolic and diastolic blood pressure was found to be significantly higher in cases as compared to control group. The increased blood pressure is a result of sympathetic over-activity through a number of pathways involving G protein–coupled adrenergic receptors which may trigger an ACS episode [16].

Serum Cholesterol and serum triglycerides were found to be raised in ACS cases as compared to controls, however the difference in mean levels was not found to be statistically significant. However, serum HDL levels were significantly lower in ACS cases as compared to the controls. Changes in lipid metabolism have been reported during acute phase response in ACS, which may result in decrease in serum total cholesterol, LDL-cholesterol and serum HDL and increase in serum triglycerides [17]. Numerous and complex changes in HDL have been reported during acute phase response, which may result in remodeling of HDL and interfering with its anti-oxidant properties [18].

Serum lipid Profile and IMA levels were not found to be significantly different in the various subgroups of ACS (Table 3). Similar results were seen in the study by Gurumurthy etal , where the levels of Serum IMA were nearly similar in all the three subgroups of ACS but were significantly higher than the control group [19].

In the present study, IMA levels were significantly higher in the ACS group as compared to controls (p<0.001), thus supporting the fact that patients with evidence of myocardial ischemia and ACS have reduced cobalt binding to human serum albumin. Similar increase in serum IMA levels has also been reported in studies carried out in recent past [20-22].

IMA values when used alone, or along with CK-MB, cTnI and ECG

have nearly 90% sensitivity as compared to conventional diagnostic tools when used alone or in various combinations. These results are in conformity with previous reports, which had revealed that a combination of the IMA, ECG and the TnI results had improved the sensitivity to 96% for the detection of ACS [23]. In another study by Anwaruddin S et al., it was found that the combination of IMA, Myoglobin, CK-MB and TnI increased the sensitivity for detecting ischemia to 97%, with a negative predictive value of 92% [24].

In the current study, Serum IMA levels showed a significant positive correlation with serum Cholesterol and Serum triglyceride levels and a significant negative correlation with HDL Levels. Similar correlation with lipid profile has also been demonstrated by Han etal, in their study on acute cerebrovascular disease [25]. Dyslipidemia in ACS may be associated with increased blood viscosity, resulting in slowing of blood flow, platelet aggregation promoting the occurrence of ischemic events. A second possibility is that highly concentrated serum combines with albumin to reduce binding sites of albumin and cobalt ions, causing a decrease in the binding capacity of albumin for cobalt, which is manifested as increased levels of serum IMA [25].

## CONCLUSION:

IMA is an early and highly sensitive marker, which can be utilized for detection of myocardial ischemia before infarction sets in. Serum IMA levels have a positive correlation with dyslipidemia which needs further evaluation at molecular levels. HDL may prevent the rise in serum IMA levels because of its metabolic roles, anti-oxidant and anti-inflammatory properties.

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