ROLE OF ISCHEMIA MODIFIED ALBUMIN AND TOTAL OXIDATIVE STRESS AS A BIOMARKER IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION IN PAKISTANI POPULATION

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ABSTRACT

Objective of study was to evaluate the serum level of Ischemia Modified Albumin (IMA) and total oxidative stress as a biomarker for diagnosis of ischemic heart disease prone to myocardial infarction. The present study was conducted in the Department of Biochemistry, University of Karachi with assistance of Liaquat National Hospital and National Institute of Cardiovascular Diseases, Karachi-Pakistan. Subjects were grouped according to selection criteria, three case group and control group. Total of 250 subjects, 100 in control group and 150 in case group (50 subjects in each group A, B and C) was included. Mean age (years) in control group was 47.41 ± 5.91, in group-A was 49.1 ± 5.8, in group-B was 49.0 ± 5.69 and in group-C was 51.1 ± 6.68. High mean ± SD values of IMA (µm/L) were observed for group C (97.58 ± 14.13) followed by group B (89.12 ± 5.48) and group A (84.68 ± 16.38) as compare to control group (22.49 ± 11.05). Statistically significant results were observed for IMA, troponin-I, SOD and TAC between group A, B, C and control group.

Key-words: Ischemia Modified Albumin, Cardiac Troponin-I, Ischemic Heart Diseases, Percutaneous Coronary Intervention, Myocardial Infarction

INTRODUCTION

World Heart Federation (WHF) reported that 17.9 million deaths occur each year worldwide are due to cardiovascular diseases (CVDs). Surprisingly, 82% of these deaths happen in the developing world (https://www.who.int/cardiovascular_diseases/en/) [Last assessed on 12-12-18]. The situation is very alarming in Pakistan as cardiac disease contributes about 30-40% of deaths in the country. (https://www.shifa.com.pk/chronic-disease-pakistan/)[Last assessed on 12-12-18].

Acute coronary syndrome (ACS) is an umbrella term to present a wide range of clinical signs as well as symptoms of myocardial ischemia. Latest clinical implication of ACS can vary from benign to potentially fatal doubt. For risk stratification history, physical examination and ECG are traditionally used clinical tools which may be insufficient in most cases (Chacko*et al*., 2017). Biochemical biomarkers in view of the desirability and feasibility, for example CK-MB (creatine kinase-muscle/brain), myoglobin and troponin estimation are utmost significant markers in early detection of IHD (Pan *et al*., 2014). In diagnosis of myocardial infarction associated with CK-MB, troponin produces greater specificity. After cardiac injury it takes 12 hours to reach peak, reducing its sensitivity in early detection of IHD (Biswas*et al*., 2014). In ischemic patient diagnosis is not easy, with acute chest pain, especially with non-interpretable baseline ECG, and there is no quick and definitive test that can be termed as a gold standard to rule out myocardial ischemia (Vijaya and Gayathri, 2014). Oxidative stress is considered as one of the primary contributory mechanism for myocardial injury during ischemia along with reperfusion. Extracellular superoxide dismutase (SOD) is linked to the heparin sulfate proteoglycans on the surface of the cell, which act as scavenger of superoxide ions in the external cell (Can *et al*., 2015). The increase in oxidative stress is mediated by antioxidant defense mechanism imbalance (Chawla*et al*., 2016). The total antioxidant state (TAS) in human plasma shows the balance between oxidants and antioxidants in each system. For the given plasma antioxidant levels, increased ROS production will result in a reduced level of TAS (Bahinipati and Mohapatra, 2016)

Modified form of albumin is an ischemia modified albumin (IMA), created by diminished ROS in oxygen stress circumstances which may leads to hypoxia and acidosis. The exact mechanism is not known how the IMA formation occurs but it seems that it is related to the production of ROS which change metallic binding positions (Reddy *et al*.,

2017). It is desirable to identify myocardial ischemia prior to the onset of myocardial cell injury (Vijaya and Gayathri, 2014). The IMA has been determined as a new serum biomarker for myocardial ischemia and oxidative stress (Patil*et al*., 2013). The IMA has become a cardiac biomarker test accessible and licensed for routine clinical application marked in Europe besides accepted through the Food and Drug Administration (FDA) in trade united states (US) (Mythili and Malathi, 2015). After the onset of myocardial ischemia, IMA rises in few minutes and within six hours returned to baseline after restoration of perfusion. It is paying increasing attention to detect a sensitive myocardial ischemia biomarker before reaching clinical decision limit for cardiac troponin test (Pan *et al*., 2014).

Therefore, the aim of this study is to assess the role of serum level of IMA and total oxidative stress as a biomarker in quick diagnosis of ischemic heart disease prone to myocardial infarction.

MATERIALS AND METHODS

This retrospective study was carried out in the Department of Biochemistry, University of Karachi (UoK) with the assistance of Liaquat National Hospital (LNH) Karachi, National Institute of Cardiovascular Diseases (NICVD), Karachi-Pakistan. The duration of study was from August 2014 to October 2017. Study was approved by Ethics committee of University.

Patients attended the Cardiac Emergency Department of LNH and NICVD with complaint of chest pain. Patients who developed myocardial ischemia admitted for monitoring, patients with percutaneous coronary intervention (PCI) and patients diagnosed as myocardial infarction (MI) with increased cardiac troponin-I (cTnI) level were included in this study. Subjects were grouped according to the selection criteria as case group and control group. Case group was further categorized as group A, group B and group C. In group A, subjects with diagnosed Ischemic Heart Disease (IHD), in group B, subjects performed PCI and in group C, subjects with diagnosed MI were included. In control group, normal, healthy subjects with same age as matched to case groups were selected for comparison. Known cases of liver disease, renal disease, peripheral vascular disease, brain ischemia, taking any lipid lowering drugs and women with pregnancy, were excluded from the study.

About 8 milliliters of blood was drawn from the antecubital vein from each subject, collected in clean centrifuge tube. The blood sample centrifuged for 5–10 minutes at 2500 – 3000rpm. The serum stored in clean, plastic dry cups at -80 degrees. IMA assayed by using colorimetric method using dithiothreitol (DTT). Troponin-I was determined by using ELISA kit method. Superoxide Dismutase (SOD) and total antioxidant capacity (TAC) were determined by spectrophotometer. To determine triglycerides (TAG), GOD- PAP method on selectra Pro Sa fully automated analyzer was used. Serum total cholesterol was analyzed by Chod-Pap method on selectra Pro Sa fully automated analyzer. Homogeneous enzymatic colorimetric method was used for estimation of high-density lipoprotein (HDL)–cholesterol and direct method was used for low density lipoprotein (LDL)-cholesterol measurement. All the controls were also subjected to measurement of above biochemical parameters along with estimation of serum IMA (Biswas *et al*., 2014)

Height was calculated to the nearest of 0.1cm while patients standing straight, and weight was calculated with a moveable weighing machine with zero error of 0.1 kilogram (kg). Body mass index (BMI) was measured as the ratio of weight (kg) to height squared (m^2).

Statistical Analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS), version 20.0. Continuous variables were presented as Mean ± SD. One-way ANOVA was employed for comparative analysis of groups. P value <0.05 was considered as statistically significant.

RESULTS

Total of 250 subjects were included in this study, 100 in control group and 150 in case group. Of case group, 50 subjects each were included in group A, B and C.

Table 1 shows the comparison of baseline and biochemical parameters between control group with different study groups. The mean age in control group was 47.41 ± 5.91 years, in group-A was 49.1 ± 5.8 years, in group-B was 49.0 ± 5.69 years and in group-C was 51.1 ± 6.68 years. Mean BMI in control group and group A, B, and C were found to be 22.02 ± 2.42 kg/m^2, 23.75 ± 2.76 kg/m^2, 23.24 ± 1.60 kg/m^2 and 24.88 ± 2.79 kg/m^2, respectively. Statistically significant results were observed for total cholesterol (p=0.001), HDL (p=0.001) and LDL (p=0.001), while results for TAG were insignificant.

Comparison of IMA, Troponin-I, SOD and TAC in control group with case groups were shown in Table 2.

High mean ± SD values of IMA (u/ml) were observed for group C (97.58 ± 14.13) followed by group B (89.12 ± 5.48) and group A (84.68 ± 16.38) as compare to control group (22.49 ± 11.05). Mean ± SD of troponin-I, SOD and TAC values were 0.11 ± 0.09, 3.10 ± 0.035 and 1.47 ± 0.029 in control group, 0.14 ± 0.09, 2.43 ± 0.07 and 0.98 ± 0.02 in group A, 0.19 ± 0.055, 2.53 ± 0.061 and 1.02 ± 0.058in group B and 0.65 ± 0.076, 2.35 ± 0.067 and 1.07 ± 0.055 in group C, respectively. Statistically significant results were observed for IMA, troponin-I, SOD and TAC between group A, B, C and control group.

Table 1. Comparison of baseline and biochemical parameters between control and different study groups.

Variables	**Control group** (n=100)	**Group-A (IHD)** (n=50)	**Group-B (PCI)** (n=50)	**Group C (MI)** (n=50)	P-value
Age (years)	47.4 ± 5.91	49.1 ± 5.8	49.0 ± 5.69	51.1 ± 6.68	0.096
BMI (kg/m^2)	22.02 ± 2.42	23.75 ± 2.76	23.24 ± 1.60	24.88 ± 2.79	0.068
Total Cholesterol (mg/dl)	167.1± 1.97	184.14± 4.23	195.36 ± 4.95	188.48± 3.87	0.001
TAG (mg/dl)	136.94±1.59	138.12± 3.53	141.54± 3.99	139.84± 5.14	0.748
HDL-c (mg/dl)	45.11± 0.48	42.28± 0.78	41.26 ± 0.867	39.36± 0.82	0.001
LDL-c (mg/dl)	94.26±1.7	102.54 ±1.68	104.82 ± 1.139	115.62± 3.42	0.001

Data presented as mean ± SD: P-value<0.05 considered to be statistically significant.

Table 2.Comparison of IMA, Troponin-I, SOD and TAC in control and case groups.

Variables	**Normal Control** (n =100)	**Group-A (IHD)** (n =50)	**Group-B (PCI)** (n =50)	**Group-C (MI)** (n =50)	**P-value**
IMA(U/mL)	22.49 ± 11.05	84.68±16.38	89.12± 5.48	97.58± 14.13	0.001
Troponin-I (ng/mL)	0.11 ± 0.09	0.14± 0.09	0.19 ± 0.055	0.65± 0.076	0.001
SOD (U/mL)	3.10±0.035	2.43±0.07	2.53±0.061	2.35±0.067	0.001
TAC (mmol/L)	1.47±0.029	0.98±0.02	1.02±0.058	1.07±0.055	0.001

Data presented as mean ± SD; P-value <0.05 considered to be statistically significant.

DISCUSSION

FA In present study, significant elevated levels of IMA in group C followed by group B and A were observed as compare to control group. Our results are comparable with Sahin *et al*., who reported that IMA levels amongst patients assessed in the emergency department by pre-diagnosis of ACS was significantly greater than values in healthy control group (Sahin *et al.,* 2018).

Levels of IMA were also found to be in chest pain high in another study (Güldoğan *et al.,* 2017). Few studies also recommended that instead of injury and cellular necrosis markers, such as total CK, CK-MB and Tn-I, IMA is a marker for the early prediction of myocardial ischemia (Chacko *et al.,* 2017). However, total CK, CK-MB were not determined in our present study. Nevertheless, IMA displayed no significant difference and correlation between IMA and the cardiac markers in Bonorino *et al*., (2015) study. It was found that IMA cannot be used unaccompanied

for the identification of MI because outcome may hinge on the concentration of serum albumin, which could not be detected in our patients (Bonorino *et al.,* 2015). In addition, Reddy *et al.* (2014) demonstrated that IMA can be an early predictor of Tn-I results after 6-24 hours in patients with ACS, suggesting an association between IMA and Tn-I. To the best of our knowledge, this is the first report of its kind from this region of world highlighting that the novel biomarker has several possible utilities including the diagnosis of many conditions, differentiating IHD from non-ischemic and even prognostic value. Increased levels of IMA evidently forecasted adverse results in patients and increased the hospitalization days (Nepal *et al.,* 2017).

The TG within all Apo lipoprotein B and most HDL particles were associated with higher risk of MI. In present study, TG was non-significantly increased in group B followed by group C and A. While, significantly low HDL was observed for case groups (mainly in group C) as compared to control group. To decrease risk for MI and cardiovascular events, focusing on targeting treatment for low serum levels of HDL was required. In this study, significant results were observed for troponin-I, SOD, TAC and IMA as a biomarker for the diagnosis of MI, IHD and PCI. Higher IMA level by Guntas *et al.* 2017 is a marker of oxidative stress in diseases with inflammation. When reperfusion of MI occurs, recognized as an alternative to AMI develop an inflammatory reaction in tissues (Guntas *et al.,* 2017). However, the restoration of blood flow in ischemic tissue extends the related tissue damage to ischemia**.** Present study used SOD and TAC as safeguard to MI, IHD and PCI to defend the oxidative stress. Hence, IMA seems to be a valuable marker to be used in patients at initial or late stages of ACS and coming to emergency department (Topaloglu *et al.,* 2015). However, further clinical trials with larger number of patients are required to address the utility, outcomes, and cost-effectiveness of IMA prior to its integration into clinical practice (Pan and Li, 2016).

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CONCLUSION

This study concludes that serum IMA at emergency department admission facilitates the early diagnosis of IHD. It should be regularly estimated in combination with other cardiac biomarkers.

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