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Ischemia-Modified Albumin as a Predictor Tissue Ischemia Marker in Patients With Acute Coronary Syndrome

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ABSTRACT

Background: Ischemia-modified albumin (IMA) has gained attention as an important biochemical marker of oxidative stress in acute myocardial ischemia. This study assessed the screening ability of IMA in acute coronary syndrome and its correlation with the severity of obesity, arterial blood pressure, and lipid profile.

Methods: A cross-sectional study using a non-probability sampling technique with 200 patients was conducted at the Physiology Department of Liaquat University of Medical and Health Science (LUMHS) from 1st September 2021 to 1 May 2022. Obese patients from the general population who had a positive family history of cardiovascular disorders were recruited and a biophysical examination was conducted. Afterward, 5cc of blood was drawn and sent for laboratory assessment of IMA and Lipid profile by using ELISA-based assay kits. Using SPSS v.25, ANOVA and student's T-test were used to assess the quantitative data. The Chi-Square Test was employed to assess the qualitative data, and a $p<0.05$ was considered significant.

Results: Among 200 participants, 86 participants had increased IMA. Median body mass index (BMI), high-density lipoprotein, low-density lipoproteins, triacylglycerol, cholesterol and ischemia-modified albumin was 39.00(5.00)kg/m2, 29.00(22.25)mg/dL, 165.00(75.00)mg/dL, 189.00(94.25)mg/dL, 294.50(91.75)mg/dL and 111.00(35.00)IU/mL, respectively. A strong relationship of IMA was seen with low-density lipoproteins (r=0.608), triacylglycerol (r=0.680), and cholesterol (r=0.646). An even stronger correlation was observed between ischemia-modified albumin and both systolic and diastolic blood pressure (r=0.903 and 0.839, respectively).

Conclusion: : IMA levels are altered with changes in BMI, lipid profile, and arterial blood pressure. Thus, IMA can be utilized to predict the risk of cardiovascular diseases in high-risk patients.

Keywords: Myocardial Infarction, Cardiovascular diseases, Hypertension, Oxidative stress.

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INTRODUCTION

A novel tissue ischemia marker is called IMA (ischemia-modified albumin). These days, IMA is widely acknowledged as a sign of oxidative stress. Recently, IMA a new molecular marker for identifying cardiac damage has garnered a lot of interest. Particular attention has been paid to the evaluation of the IMA test for the detection and assessment of myocardial ischemia insult as well as other acute coronary syndromes in emergency patients. Since myocardial ischemia and the ensuing biochemical changes can occur in any artery, the IMA specificity for this condition is uncertain [1].

A kind of albumin known as "N-terminally modified" albumin (IMA) is the product of myocardial ischemia. IMA is diagnosed by looking for a decreased cobalt binding affinity, which is caused by a changed albumin N-terminus. With patients experiencing acute myocardial ischemia, the albumin cobalt binding test is ineffective because of the rapid rise in fatty acid levels in their blood, even though it might be a useful diagnostic tool for separating non-ischemic chest discomfort from acute coronary syndrome. Nearly all liberated fatty acids (FAs) attach themselves firmly to albumin, changing the protein's structure and decreasing its affinity for binding cobalt. Fatty acid levels in the blood and through albumin cobalt binding experiments, ischemia-modified albumin were identified, and are closely related both metabolically and chronologically. In summary, "FA-occupied albumin" is a more accurate representation of IMA in ACS [2, 3].

Human serum albumin's N-terminal residues are known to bind to transition metal ions such as nickel, copper, and cobalt. The N-terminal residues lose their capacity to bind in the presence of ischemia, most likely as a result of membrane rupture (energy-dependent), hypoxia, acidosis, and free radical damage. Because IMA estimation is so simple, it can be performed at the patient's bedside or in a laboratory using very little equipment. To measure the alterations, a predetermined quantity of cobalt can be introduced to the patient's serum. Due to a modification in the N-terminal binding residue, the amount of free cobalt that is still in the combination cannot bind to albumin. Instead, it binds to dithiothreitol (DTT), and a 470 nm colorimeter is used to identify the color that results from DTT and cobalt binding. Because of this, the amount of damage in the N-terminal residue affects how well albumin binds to cobalt; it is commonly recognized that human albumin is not as stable as that of other animals. Because of this, trying to replicate the same conditions as in the ischemia process with albumin from various species would not provide the same results [4, 5]. Ischemia-modified albumin increases at the early stages of vascular damage and remains high for several hours, enabling diagnosis before the development of myocardial necrosis. Myoglobin, troponin, and isoenzyme creatine kinase (CK-MB) all demonstrate this necrosis. In ischemia individuals, IMA rises to a greater quantity of 8% from its typical circulating value of 2% [6, 7].

Several people with high IMA had their albumin's N-terminal segment sequenced, and no evidence of N-terminal degradation was found. There have been several theories put out to explain the sharp rise in IMA. They saw how fatty acids are created during ischemia coronary events, and how they interfere with albumin at the binding sites to stop albumin from attaching to cobalt, which causes IMA to appear even while IMA is absent. While the elevations were thought to be a clear biomarker for the ischemia process in AMI and ACS, it is undeniable that they occur in a wide range of other situations where ischemia is common. Systemic illnesses including diabetes and hypertension are linked to IMA. An increase in IMA has been associated with smokers, as well as individuals suffering from cirrhosis of the liver, systemic sclerosis, end-stage renal illness, peripheral vascular disease, and ischemia of the skeletal muscle, to mention a few ailments [4, 8].

Patients with acute ischemic chest pain, those undergoing continuous ambulatory peritoneal dialysis, and those experiencing deep sepsis are among the conditions for which IMA is a valid predictor of the severity and prognosis [9]. It will be a major advancement in early diagnosis and help lessen the burden of cardiac mortality in our society if IMA can be used as a cardiovascular disease prediction in a susceptible group. Therefore, this study's goal was to evaluate the relationship between IMA, the degree of obesity, arterial blood pressure, and lipid profile.

METHODS

The cross-sectional study was carried out from September 1, 2021, to May 1, 2022, at the Physiology Department of LUMHS in cooperation with the Medicine Ward, other clinical wards, and DR Lab LUMHS. The sample size of 200 was calculated using Epi Info software, and a non-probability type of sampling technique was deployed to gather data.

The study included obese individuals from the general population with a positive family history of cardiovascular disease. Both genders were included in the study. The exclusion criteria were individuals with a prior history of taking medicines for cardiovascular disease, lipid-lowering drugs, and a history of cardiac disease. Before the commencement of the research, the Ethical Review Committee approved the project under the grant number LUMHS/REC/144/2021. All study participants provided written agreement, and data confidentiality was upheld throughout the investigation. Data collec-

tion was performed by asking the study population a series of questions and conducting a physical examination that included measuring blood pressure, pulse, height, and weight. Following the physical examination, five milliliters of blood were drawn, and the laboratory used ELISA-based microplate test kits to analyze the blood for lipid profile and ischemia-modified albumin.

To analyze the data, IBM SPSS Statistic version 27 was used. To check normality, the Kolmogorov-Shapiro test was employed. The interquartile range and median for quantitative variables were computed. Reports were given for frequency and percentages of qualitative factors. Quantitative factors were compared using the Mann-Whitney U test. The association between the quantitate variables was investigated using Spearman's rank correlation. To examine the association between the qualitative variables, the Chi-Square test was employed. P-values < 0.05 were regarded as statistically significant.

RESULTS

Of the total 200 patients, 77 (38.5%) were female and 123 (61.5%) were male. The median age was 41.00 years ranging from 35 to 50 years. Median BMI, high-density lipoprotein, low-density lipoproteins, triacylglycerol, cholesterol, and ischemia-modified albumin was 39.00(5.00) kg/m2, 29.00(22.25) mg/dL, 165.00(75.00) mg/dL, 189.00(94.25) mg/dL, 294.50(91.75) mg/dL and 111.00(35.00) IU/mL. Substantial differences we identified in elevated ischemic modified albumin for systolic blood pressure (p=0.000), diastolic blood pressure (p=0.000), high-density lipoproteins (p=0.000), low-density lipoproteins (p=0.000), triacylglycerol (p=0.000), and cholesterol (p=0.000) as presented in Table-1.

Table 1: Comparison of lipid profile according to elevated ischemia-modified albumin.

Variables	Median (IQR)			p-value
	Overall	Elevated Ischemia Modified Albumin		
		Elevated	Reduced	
Gender				
Male		56(65.1%)	67(58.8%)	0.361
Female		30(34.9%)	47(41.2%)	
Age (years)	41.00(9.00)	43.00(8.00)	41.00(9.00)	0.911
Body mass index (kg/m^2)	39.00(5.00)	39.00(5.00)	39.00(5.00)	0.824
Systolic blood pressure (mmHg)	154.00(31.00)	176.00(17.00)	145.00(14.25)	<0.001*
Diastolic blood pressure (mmHg)	105.00(20.00)	117.00(15.00)	98.00(14.00)	<0.001*
High-density lipoprotein (mg/dL)	29.00(22.25)	27.00(5.00)	41.00(23.25)	<0.001*
Low-density lipoproteins(mg/dL)	165.00(75.00)	187.00(41.00)	132.00(70.25)	<0.001*
Triacylglycerol(mg/dL)	189.00(94.25)	252.50(70.25)	178.00(35.00)	<0.001*
Cholesterol (mg/dL)	294.50(91.75)	356.00(52.00)	277.00(40.75)	<0.001*

*IQR: inter-quartile range, Mann-Whitney U test was applied.*Significant at 0.05 level.*

Among 200 patients, 86(43%) were found to have increased ischemia-modified albumin as presented in Figure 1. We found a strong positive relationship with low-density lipoproteins (r=0.608), triacylglycerol (r=0.680), and cholesterol (r=0.646) with ischemia-modified albumin while a very strong positive relationship with ischemia modified albumin and both systolic and diastolic blood pressure (r=0.903 and 0.839, respectively).

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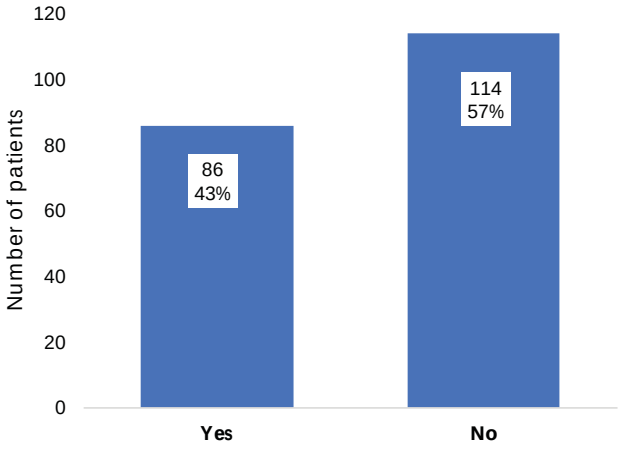

Figure 1: Number of patients with elevated ischemia-modified albumin.

Additionally, we discovered a substantial and negative correlation (r=-0.674) between ischemia-modified albumin and high-density lipoprotein as shown in Table 2.

Ischemia modified albumin	Correlation coefficient (r)
Systolic blood pressure (mmHg)	.903**
Diastolic blood pressure (mmHg)	.839**
High-density lipoprotein (mg/dL)	-.674**
Low-density lipoproteins(mg/dL)	.608**
Triacylglycerol(mg/dL)	.680**
Cholesterol (mg/dL)	.646**

*Spearman's rank correlation was applied. *Significant at 0.05 level.*

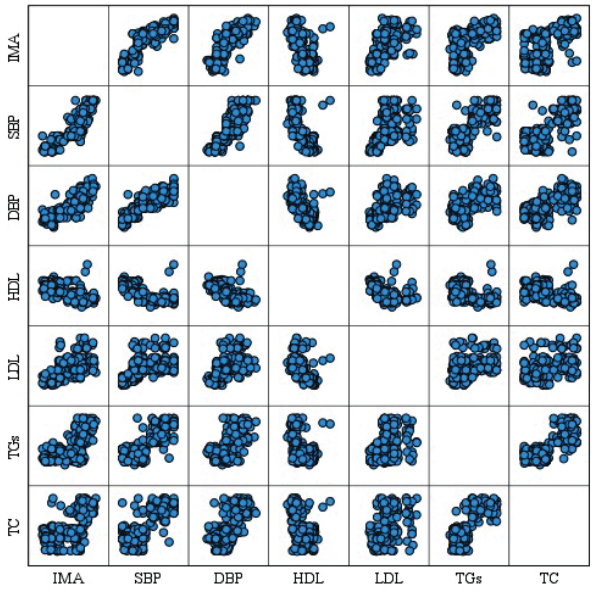

Figure 3: Scatter diagram, presenting the relationship of ischemia-modified albumin with lipid profile

DISCUSSION

IMA is useful in the early diagnosis of cardiogenic ischemic diseases since it was recently demonstrated to be a marker for acute myocardial ischemia. Acute coronary syndrome (ACS) patients can use IMA as a diagnostic indicator of early coronary ischemia, which has been authorized by the FDA (Food and Drug Administration). This can reduce the number of patients with cardiovascular illness who do not receive a proper diagnosis. In recent years, several additional studies have found that non-cardiogenic ischemia diseases can also cause a substantial elevation in the blood level of IMA. The subjects of the current study were obese individuals with elevated blood pressure and a positive family history of heart disease. A previous study found that, in comparison to cases of coronary artery disease undergoing diagnostic angiography, IMA was significantly higher in chronic patients with stable angina undergoing percutaneous coronary intervention because of single artery involvement [9].

IMA is a novel marker of ischemia brought on by low oxygen levels and an increase in hydroxyl free radicals. Additionally, it has been approved for use in clinical cardiology as a significant cardiovascular event indicator [10]. It is necessary to investigate the role of IMA in people with dyslipidemia and hypertension within a broader treatment framework. Similar to this study, another investigation discovered favorable associations between BMI and serum IMA levels [11]. One study found that individuals who are obese had elevated levels of IMA, which increases their risk of cardiovascular disease. However, the study did not quantify IMA levels based on the degree of obesity. As a result, it must routinely include the IMA measurement to track obese people [12]. Research has demonstrated that elevated IMA levels coexist with hypertension (HTN). According to his findings, which are also supported by the current study, individuals with hypertension had greater levels of oxidative stress and IMA [13]. IMA may be used as a routine diagnostic variable in obese people with high blood pressure to stop acute coronary events in the future.

In one research, 50 age- and sex-matched controls and 50 stroke patients' blood IMA levels were shown to be significantly greater in the former group than in the latter [14]. In ischemic lesions of all shapes and sizes, there was a rise in IMA levels, suggesting that "IMA levels increase in attack regardless of size and area.". The degree of the stroke remained unchanged, as did the IMA levels. This outcome is consistent with recent studies, which suggest that IMA has a predictive and deciding role in the early detection of ischemia alterations in hypertensive and obese individuals. As per the research, "stroke patients, especially those with ischemic stroke, have higher IMA levels" [15]. Reduced oxygen delivery to the brain leads to the development of free radicals and localized acidity. Copper and zinc ions, which normally circulate as free ions, are released via protein-binding sites in the plasma [16].

Research has demonstrated that tissue hypoxia is the source of oxidative stress and that IMA is a biomarker of ischemia [15, 17]. The IMA value in the serum was markedly raised due to the OS's role in the development of several diseases. An increasing amount of data suggests that IMA is associated with peripheral atherosclerosis and hyperlipidemia, obesity, metabolic syndrome, ischemic stroke, cerebral hemorrhage, and ischemia of the skeletal and mesenteric muscles. In addition, IMA has been connected to severe renal illness, liver cirrhosis, ovarian torsion, hepato-steatosis, preeclampsia, fetal distress, thalassemia, and diabetes stroke is the leading cause of mortality globally; symptoms need to be recognized and addressed as soon as possible[18]. According to our research, this leads to a reduction in the level of oxidative stress and a subsequent drop in IMA levels. Therefore, it is essential to have a biomarker at the primary care level to make a diagnosis and get the patient to the hospital within the allotted time. Biomarkers will surely lead to new data being included in the diagnostic process, which will help with the timely referral of the patient to a specialist for treatment. In conclusion, our findings suggested that, especially in rural areas, the IMA may be a dependable, efficient, and reasonably priced biomarker for early hypertension screening. More systematic validation studies are needed to create blood biomarkers that can enhance hypertension patients' care [19, 20, 21].

Additional studies are needed to establish the IMA biomarker's predictive significance across a wider sample size population and to develop a future research strategy on molecular levels.

CONCLUSION

Our findings demonstrate the predictive value of hyperlipidemia and IMA in morbidly obese individuals with Acute coronary syndrome. Since IMA is a predictor of ACS and correlated IMA is a predictive sign in obese ACS patients as opposed to healthy persons, detecting it early in these patients would help clinics with early prediction, diagnosis, monitoring, and therapy. This will help fill up the research gap and provide future scientists with the information they need.

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None.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

ETHICAL APPROVAL

Before the commencement of the research, the Ethical Review Committee approved the project under the grant number LUMHS/REC/144/2021.

PATIENT CONSENT

All study participants provided written agreement, and data confidentiality was upheld throughout the investigation.

AUTHORS CONTRIBUTION

The authors contributed equally to the development of the manuscript.

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