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Original Article

Ischemia-modified albumin as a sensitive and practical biomarker of oxidative stress in patients with lower extremity peripheral arterial disease

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Abstract

Aim: We aimed to investigate the potential use of ischemia-modified albumin (IMA) as an indicator for oxidative stress in individuals with lower extremity peripheral vascular disease (PAD).
Material and Methods: This case-control study included 80 patients with lower extremity PAD as the study group and 80 individuals without PAD as the control group. Demographics, clinical characteristics, and laboratory data, including IMA, were compared among these groups.
Results: No notable differences were observed regarding the fundamental clinical characteristics among the groups. The study group exhibited a significantly higher median IMA level when compared to the control group. Receiver operating characteristic (ROC) curve analysis indicated that an IMA of 0.605 represented the optimal cut-off value, obtaining 87% sensitivity and 48% specificity.
Conclusion: This study suggests that IMA serves as a sensitive and practical biomarker for oxidative stress in patients with lower extremity PAD. However, further well-designed studies with larger patient participation are required in order to support the findings of this study and achieve more valuable scientific evidence.

Keywords: Ischemia-modified albumin, biomarker, oxidative stress, lower extremity peripheral arterial disease

INTRODUCTION

Peripheral arterial disease (PAD) is a progressive atherosclerotic condition which frequently develops in distal abdominal aorta and lower extremity arteries. Although the disease is also observed in young individuals, it is more commonly observed in older patients and related to increase in mortality and morbidity. Patients with PAD may be asymptomatic, especially in early periods of the illness, or they may also be admitted with symptoms such as intermittent claudication and critical leg ischemia in later periods of PAD [1-3]. The molecular processes of the pathophysiological scenario of this illness are complex, and a clear understanding of all its stages still remains difficult. Nonetheless, subclinical inflammation and oxidative stress have been documented to interact and significantly contribute to the pathophysiological mechanisms of PAD [4,5].

During the progression to an ischemia condition, the amino-terminal end of albumin undergoes modification, resulting in diminished capacity to bind transition metals. The modified form of albumin is referred to as ischemia-modified albumin (IMA) and is quantified through spectrophotometric methods, including

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the albumin cobalt binding test [6]. IMA is a biomarker primarily investigated in acute coronary syndromes and their early-term diagnosis [7,8]. Nonetheless, blood plasma IMA quantities have also been reported to change in other ischemic conditions such as acute ischemic stroke [9], pulmonary embolism [10], and mesenteric ischemia [11]. In addition, serum IMA level has been detected to increase in many diseases with systemic chronic inflammation, and it was thought that its levels might increase in reaction to oxidative stress and chronic hypoxia [12].

The current literature reveals a lack of studies focused on investigating IMA as a potential oxidative damage indicator in lower extremity PAD cases. Since the role of oxidative stress and chronic inflammatory processes are taken into consideration in PAD pathogenesis, we hypothesized that serum IMA levels could be significantly affected in cases with PAD. Hence, we aimed to study the possible value of IMA as an oxidative stress biomarker in patients with lower extremity PAD by comparing serum IMA levels in this patient groups with those in individuals without PAD.

MATERIAL AND METHODS

Study Design

The Bolu Abant İzzet Baysal University Medical Research Ethics Committee approved the trial (Approval number: 2021/83, date: April 13, 2021). This was a prospectively designed case-control research undertaken at a tertiary care hospital. The study included 160 adult participants, and they were categorized equally in two groups as the study group and control group. The study group consisted of 80 participants with lower extremity PAD while the control group consisted of 80 well-matched volunteers without lower extremity PAD. We performed this study on a total of 160 participants according to the findings of the power analysis (G Power 3.1.9.7); power=0.95, effect size was 0.931.

Participants in the study group were symptomatic at the time of admission, and had either intermittent leg claudication or critical limb ischemia (stage II-IV patients according to Fontaine classification). According to the Fontaine classification, in the study group, there were 33, 36, 8 and 3 cases in stages II a, II b, III and IV, respectively. After a detailed physical examination, ankle-brachial index (ABI) value was calculated to make the initial diagnosis of PAD. The initial diagnostic criterion for PAD was an ABI value less than 0.9. Definitive diagnosis of PAD was established by the color doppler ultrasonography and/or angiography of lower extremity arteries in individuals with an ABI value of less than 0.9. The subjects in the control group were selected from individuals who sought services at the hospital's outpatient clinic for various reasons, including routine examinations and regular surveillance. Individuals under 18 and over 80 years old, those who had a previous ischemic events such as myocardial, cerebral, mesenteric or skeletal muscle ischemia, or major surgical intervention in the last three months, pregnant women, patients with active infection, cancer, immunological or hematological disorders were excluded.

Clinical features, concomitant conditions, and laboratory findings were extracted by the hospitals' computerized database, documented for analysis, and thereafter subjected to statistical comparison between the two groups.

Laboratory Analysis

Samples of plasma were collected from peripheral veins of the upper extremities after a fasting period of 6-8 hours and placed in sterile standard blood tubes for examination. Following the determination of blood levels of hematocrit, hemoglobin, leukocytes, platelets, creatinine, urea, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, and albumin, the samples were spun at 1500 revolutions per minute for 10 minutes to isolate the serum. Subsequently, the serum was placed in freezers and preserved at –70°C till IMA measurements were performed.

Serum IMA levels were determined using the albumin cobalt binding test. The serum was mixed with cobalt chloride and incubated for 5 minutes. Cobalt was supplied to bind with albumin in this procedure. After the incubation, dithiothreitol (DTT) was added and mixed to allow DTT to a chromatic compound containing cobalt unbound to albumin. The synthesized colored composite was by spectroscopic analyzed at a wavelength that ranges of 500 nm.

Statistical Analysis

Data were examined utilizing the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA). The adherence of continuous metrics to a distribution that's normal was assessed using the Kolmogorov-Smirnov test. Student's T test and Mann-Whitney U test were utilized to compare continuous metrics with and without normal distribution, respectively. The Chi-square test was utilized for the comparison of categorical variables. Data were expressed as mean ± standard deviation for continuous variables with normal distribution, median (minimum-maximum) for continuous variables lacking normal distribution, and count (%) for categorical variables. A receiver-operating characteristic (ROC) curve analysis was performed to determine the cut-off value of IMA. P values were deemed statistically significant if they were below 0.05.

RESULTS

The average ages of individuals with and without PAD were 61.3 and 59.7 years, respectively. Seventy percent of patients with PAD and 67.5% of those without PAD were male. The mean systolic and diastolic blood pressures were found to be considerably elevated in patients with PAD compared to those without PAD. No significant differences in fundamental demographic and clinical parameters were observed between the groups, indicating similarity (Table 1).

Table 1. Demographic data and comorbidities of the groups

Variable		PAD group (n=80)	Control group (n=80)	p value
Age (years)		61.3±8.2	59.7±9.1	0.104
Gender (n)	**Male**	56	54	0.466
	Female	24	26	
Weight (kg)		77.2±9.8	78.3±11.5	0.505
Height (cm)		168.4±5.6	167.9±8.2	0.470
BMI (kg/m²)		27.2±3.4	27.5±3.7	0.456
Obesity (n)		13	15	0.208
DM (n)		24	19	0.082
HL (n)		22	20	0.443
Smoking (n)		28	22	0.196
SBP (mmHg)		128.8±16.0	118.2±15.2	**<0.001**
DBP (mmHg)		78.3±11.2	71.7±9.8	**<0.001**

BMI: body mass index, DBP: diastolic blood pressure, DM: diabetes mellitus, HL: hyperlipidemia, PAD: peripheral arterial disease, SBP: systolic blood pressure; Data are expressed as mean±standard deviation for continuous variables showing normal distribution, or number for categorical variables; Student's T test was used in the comparative analysis of continuous variables showing normal distribution whereas Chi square test was used in the comparative analysis of categorical variables

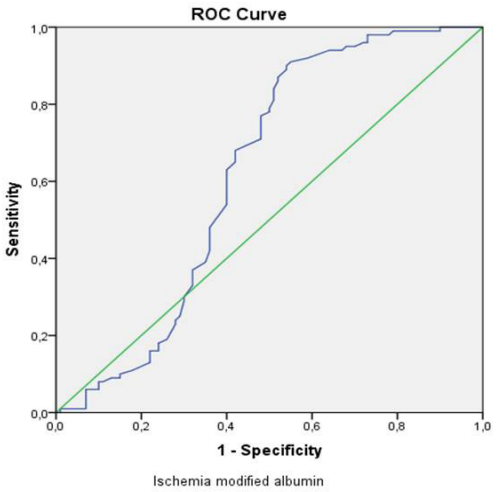
No significant changes were seen between the groups in all examined laboratory parameters, with the exception of IMA. Only the median IMA value was found to be significantly elevated in patients with PAD compared to those without PAD (Table 2).

Table 2. Laboratory data of the groups

Variable	PAD group (n=80)	Control group (n=80)	p value
Hemoglobin (g/dL)	13.7±2.1	13.1±2.0	0.388
Hematocrit (%)	40.8±6.0	40.0±5.4	0.690
Platelet count (10^3/µL)	231.8±74.7	223.8±76.4	0.335
WBC (10^3/µL)	10.1±3.7	9.3±3.5	0.272
Hemoglobin A1c (%)	5.8 (4.0-10.8)	5.4 (4.0-9.6)	0.258
LDL cholesterol (mg/dL)	123 (50-266)	120 (42-214)	0.834
Total cholesterol (mg/dL)	200 (106-388)	188 (94-315)	0.612
CRP (mg/L)	5 (1-83)	5 (1-33)	0.780
Urea (mg/dL)	45 (15-93)	40 (19-76)	0.096
Creatinine (mg/dL)	0.97 (0.58-2.87)	0.85 (0.52-2.26)	0.123
AST (U/L)	24 (8-255)	25 (9-98)	0.663
ALT (U/L)	22 (7-148)	20 (6-55)	0.124
Albumin (g/dL)	3.62±0.71	3.49±0.90	0.082
IMA (ABSU)	0.79 (0.33-2.28)	0.66 (0.04-2.38)	**0.003**

ABSU: absorbance unit, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, IMA: ischemia-modified albumin, LDL: low density lipoprotein, PAD: peripheral arterial disease, WBC: white blood cell; Data are expressed as mean±standard deviation for continuous variables showing normal distribution, or median (minimum-maximum) for continuous variables not showing normal distribution; Student's T test was used in the comparative analysis of continuous variables showing normal distribution whereas Mann-Whitney U test was used in the comparative analysis of continuous variables not showing normal distribution

ROC curve analysis indicated that an IMA of 0.605 was the ideal cut-off value, yielding sensitivity and specificity rates of 87% and 48%, respectively [AUC=0.622 (95% CI: 0.541-0.704), p=0.003] (Figure 1).



Optimum cut-off value	AUC	%95 CI	p value	Sensitivity (%)	Specificity (%)
0.605	0.622	0.541-0.704	0.003	87	48

Figure 1. Receiver operating characteristic (ROC) curve for ischemia-modified albumin (IMA)

DISCUSSION

This study examined fundamental clinical features and laboratory data, including IMA, between persons with and without lower extremity PAD. The study's most notable finding was that the median IMA value was considerably elevated in the PAD study group compared to the control group. Furthermore, it was determined that IMA, with an optimal cut-off value of 0.605, had a high sensitivity rate, albeit a low specificity rate, in predicting PAD.

IMA is a modified variant of serum albumin that arises under oxidative stress circumstances. It arises when the amino-terminal portion of albumin diminishes its binding affinity for transition metals like cobalt, nickel, and copper due to cellular processes induced by ischemia. An ischemia event results in hypoxia, acidosis, elevated free radicals, and subsequent degradation of Na/K pumps, culminating in the creation of IMA through the cleavage of the initial two amino acids (Asp-Ala) in the amino-terminal region of human serum albumin. IMA is recognized for its low binding affinity to transition metals. Oxidative stress occurs when there is an imbalance between reactive oxygen species and the antioxidant defense system, with elevated serum IMA levels indicating heightened oxidative stress [6,12,13]. Consequently, variations in serum IMA levels during ischemia settings have emerged as a prevalent subject of discourse in recent years.

Oxidative stress refers to the disparity between the production of reactive oxygen species (ROS) and the capacity of antioxidant defenses. Neutrophils, macrophages, fibroblasts, and endothelial cells are the primary sources of ROS. The inflammatory process induced by persistent ischemia persists. In PAD, the prolonged ROS burden results in persistent injury and inflammation. Furthermore, there is diminished redox capacity in antioxidant processes [4]. Consequently, an imbalance between the production of reactive oxygen species and antioxidant defense mechanisms has arisen.

Currently, IMA is recognized as a unique and highly sensitive measure of oxidative stress, serving as a crucial biomarker for the early detection of myocardial ischemia and acute coronary syndromes [7,8,13-15]. Moreover, serum IMA levels have been observed to be elevated in various conditions associated with vascular endothelial cell dysfunction, including diabetes mellitus [16], hypercholesterolemia [17], obesity [18], preeclampsia [19], and Behcet's illness [20]. In addition to these, a limited number of research with inconsistent results regarding serum IMA levels in individuals with lower extremity PAD may also be encountered. In a study by Roy et al. [21], 23 patients exhibiting typical leg claudication and confirmed lower extremity PAD underwent a treadmill exercise stress test to provoke leg ischemia, with serum IMA levels assessed at baseline, immediately post-peak exercise, and one hour following exercise. The authors established that serum IMA levels were markedly reduced immediately following exercise-induced limb ischemia and correlated with disease severity in patients with PAD. Montagnana et al. [22] investigated blood IMA levels in 35 patients diagnosed with lower extremity PAD and 20 control subjects without PAD, finding no significant elevation of serum IMA levels in PAD patients compared to controls. Conversely, Ma et al. [23] evaluated 290 participants with type 2 diabetes mellitus, categorizing them into a PAD group (n=110) and a non-PAD group (n=180), and discovered that the mean IMA value was considerably elevated in the PAD group compared to the non-PAD group. Furthermore, a recent study by Özsin et al. [24] examined a potential correlation between serum IMA levels and the existence and severity of PAD by comparing 100 patients with lower extremity PAD to 50 healthy volunteers. The authors observed that serum IMA levels were markedly elevated in the PAD group compared to the control group, and elevated IMA levels were indicative of the existence and severity of PAD. The findings of our research were analogous to those of Ma et al. [23] and Özsin et al. [24]. Nonetheless, our study exhibited certain methodological discrepancies compared to the aforementioned investigations. Ma et al. [23] conducted a study on patients with type 2 diabetes mellitus, revealing that the condition greatly influenced serum IMA levels, which were elevated in diabetic patients [16]. Conversely, the research conducted by Özsin et al. [24] examined both IMA levels and adjusted-IMA levels in

individuals with and without PAD. Adjusted-IMA levels were computed based on the median albumin values of the groups, revealing that elevated adjusted-IMA levels serve as a predictor for the existence of PAD. Furthermore, the scientists categorized patients with PAD into two subgroups: mild claudication and moderate-severe claudication, thereby elucidating the correlation between adjusted-IMA and the severity of PAD.

Our work considered atherosclerosis, inflammation, and oxidative stress, which contribute to the pathophysiology of PAD, and was designed with the hypothesis that the illness may be linked to IMA, a marker of oxidative stress. We established that serum IMA levels were markedly elevated in individuals with PAD compared to control persons. Elevated IMA levels may be attributed to heightened generation of reactive oxygen species in individuals with PAD. Our investigation indicated that in individuals with lower extremity PAD, IMA served as a biomarker with elevated sensitivity, albeit with diminished specificity. Consequently, we propose that IMA is not a viable diagnostic marker for PAD. In daily clinical practice, IMA may serve as a negative predictor of PAD in the absence of an other ischemic event.

Limitations

This study had multiple limitations. The principal limitations of the study included a relatively small sample size, restricted data processing, and an absence of comparative and correlational analysis of IMA with other oxidative stress biomarkers. Furthermore, a subgroup analysis based on the Fontaine classification was not conducted in the study cohort, as the study was designed as a case-control investigation, and the potential association between the Fontaine classification and impairment of IMA levels was not assessed.

CONCLUSION

Our studies have shown that IMA may serve as a sensitive and practical biomarker for assessing oxidative stress levels in individuals with lower extremity PAD, as well as a negative predictor of PAD. Nonetheless, more rigorously conducted prospective studies with a bigger participant cohort are essential to corroborate the findings of this study and acquire more substantial scientific data.

Ethics Committee Approval: Our study was conducted prospectively after obtaining ethical approval from The Bolu Abant İzzet Baysal University Medical Research Ethics Committee (Approval number: 2021/83, date: 13.04.2021).

Patient Consent for Publication: Written consents were obtained from all participants.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

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