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The diagnostic value of ischemia-modified albumin in the diagnosis of aortic pathology

Oğuz EROĞLU[1], Süha TÜRKMEN[2], Ahmet MENTEŞE[3], Gökalp ALTUN[4], Süleyman TÜREDİ[2], Umut ERYİĞİT[2,*], Süleyman Caner KARAHAN[3], Abdülkadir GÜNDÜZ[2]

[1]Akçaabat Haçkalı Baba State Hospital, Trabzon, Turkey
[2]Department of Emergency Medicine, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
[3]Department of Biochemistry, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
[4]Department of Cardiovascular Surgery, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

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Aim: To investigate the diagnostic value of ischemia-modified albumin (IMA) in the diagnosis of patients with aortic aneurysm.

Materials and methods: The study group consisted of 98 patients who presented to our university hospital emergency department with aortic pathology and were definitively diagnosed using spiral tomography. The control group consisted of 101 healthy individuals with similar demographic characteristics.

Results: Mean IMA values were 0.89 ± 0.21 absorbance units (ABSU) in the aortic aneurysm group ($P < 0.001$), 0.70 ± 0.12 ABSU in the aortic dissection group ($P < 0.001$), 0.98 ± 0.23 ABSU in the aneurysm and dissection group ($P < 0.001$), 0.84 ± 0.16 ABSU in the aneurysm and rupture group ($P < 0.001$), and 0.87 ± 0.27 ABSU in the aneurysm, dissection, and rupture group ($P < 0.001$). Mean IMA value for the subjects in the control group was 0.62 ± 0.17 ABSU. All the differences between the aortic pathology groups' IMA values and those of the control group were statistically significant ($P < 0.001$).

Conclusion: On the basis of the findings from this study, serum IMA levels are higher in patients with aortic pathology compared to healthy individuals. This finding suggests that IMA may help to diagnose aortic pathology, but it requires confirmation by additional clinical studies.

Key words: Ischemia-modified albumin, aortic aneurysm, aortic dissection, aortic rupture

1. Introduction

Aortic pathologies such as aortic aneurysm, dissection, and rupture are emergent vascular conditions. Aneurysms sometimes require emergency surgery because of rupture risk. The risk of rupture is related to aneurysm size and increases with a size of 5.5 cm and above (1).

There are significant difficulties in the diagnosis of patients with aortic aneurysm or dissection in emergency practice. There is, as of yet, no biochemical marker suitable for use in the diagnosis of patients with aortic aneurysm. In aortic dissection, the arteries emerging from the aorta may be partly or completely obstructed. Total or partial vascular obstruction may be seen with the spread of hematoma. This can also affect the coronary arteries. Vascular obstruction creates ischemia in the region nourished by blocked vessels. The resulting ischemia may be expected to cause a rise in ischemic parameters in the body (2).

Recently, the most frequently investigated marker for use in such pathology is a D-dimer measurement. Studies have shown that aortic dissection increases D-dimer levels by triggering a series of hematological reactions involving vascular tissue and including the extrinsic pathway of the coagulation chain (3,4).

Ischemia-modified albumin (IMA) is a marker that has recently been much investigated and shown in studies to increase in acute ischemic conditions. Albumin's metal-binding capacity in the N-terminal is reduced under acute ischemic conditions, and a metabolic protein forms. This alteration in metal-binding capacity can be measured and is known as IMA.

The literature contains only one study of IMA values in aortic pathology. The present study, a pioneering one from that perspective, compared IMA levels determined in aortic aneurysm, dissection, or rupture patients with those in healthy individuals. The objective was to determine, from the results obtained, whether serum IMA levels could serve as a guide for future research in the diagnosis of aortic pathology.

* Correspondence: umuteryigitacil@gmail.com

2. Materials and methods

2.1. Patient inclusion and exclusion criteria

The study was planned as a prospective case-control study. Patients with aortic pathology presenting to our university hospital emergency department with suspected aortic aneurysm, dissection, or rupture and definitively diagnosed using spiral tomography, and patients in whom aortic pathology was identified after coincidental administration of spiral tomography for other reasons, were included. The requisite approval was obtained from the Ethics Committee of the Karadeniz Technical University Faculty of Medicine.

The average age of the patient group was 67.91 ± 12.91 years. Patients' demographic data, complaints, previous diseases, and physical examination findings were recorded on a study form. All patients enrolled were administered 12-derivation electrocardiogram (ECG), pulmonary imaging, and spiral tomography, and diagnosis was confirmed. Additionally, biochemistry, hemograms, prothrombin time/partial thromboplastin time, D-dimer levels, and cardiac enzymes were investigated in order to exclude other ischemic pathology, and the results were again recorded.

Exclusion criteria were other ischemic diseases, such as acute coronary syndrome, acute myocardial infarction, acute ischemic cerebrovascular disease, or pulmonary embolism (PE); an abnormal serum albumin level making the determination of IMA levels impossible (normal level: 3.5–5.5 mg/dL); advanced liver, kidney, or heart insufficiency; troponin-T and ECG variations evaluated from the point of view of nonovert acute coronary syndrome (ACS); age of <18 years; or refusal to participate in the study. A control group of 101 nonhospitalized emergency department patients (mean age ± SD: 53 ± 7 years) served as a reference for biochemical parameters. The exclusion criteria for the control group were the same as those for the patient group.

2.2. Laboratory analysis

Blood samples were drawn on admission. Serum samples were prepared by 15 min of centrifugation at 3000 rpm. Specimens to be used for measuring IMA serum concentrations were pipetted into Eppendorf tubes and stored at –80 °C.

Reduced cobalt-to-albumin binding capacity (IMA level) was analyzed using the rapid and colorimetric method of Bar-Or et al. (5). Two hundred microliters of patient serum was placed into glass tubes and 50 µL of 0.1% $CoCl_2.6H_2O$ (Sigma) was added. After gentle shaking, the solution was left for 10 min in order to ensure sufficient cobalt-albumin binding, and then 50 µL of 1.5 mg/mL dithiothreitol (DTT) was added as a coloring agent. After waiting 2 min, 1 mL of 0.9% NaCl was added in order to halt the cobalt-albumin binding process. A colorimetric control specimen was prepared for every limb ischemia and control patient specimen. For the colorimetric control samples, 50 µL of distilled water was substituted for 50 µL of 1.5 mg/mL DTT. Specimen absorbencies were analyzed at 470 nm using a spectrophotometer (Shimadzu UV1601). The color of the DTT containing specimens was compared with that of the colorimetric control tubes. The results were reported as absorbance units (ABSU).

2.3. Data analysis

All data were entered into SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and analyzed in the same program. Kruskal–Wallis analysis of variance was used in group comparison variance analysis (Mann–Whitney U test and corrected Bonferroni test) and Friedman's test in the analysis of changes in IMA levels (Wilcoxon test and corrected Bonferroni test). Means are shown as mean ± standard deviation. Receiver operating characteristic (ROC) curve analysis was performed to determine sensitivity and specificity of cut-off values for all patients. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patients' demographic characteristics

There were 199 individuals included in the study; 98 constituted the patient group with aortic pathology and 101 the healthy control group. Demographic characteristics for the patient and control groups are shown in Table 1.

The most common complaint at presentation was chest pain, in 64 (65.3%) patients. Other complaints, in order of frequency, were abdominal pain in 48 (49%), back pain in 41 (41.8%), lower back pain in 29 (29.6%), dyspnea in 32 (32.7%), syncope in 17 (17.3), palpable pulsatile mass in 5 (5.1%), and hematuria in 4 (4.1%) (Table 1).

Looking at the diseases in the patients' histories that might have led to aortic pathology, hypertension was observed in the histories of 89 (90.8%) patients. Hypertension was the most important risk factor for aortic aneurysm and dissection. Cigarette use was also observed in 24 (24.5%) of the patient group, all of these patients being male. Four (4.1%) members of the patient group had no previous complaints or diseases. Diabetes, bronchitis, benign prostate hypertrophy, and hyperthyroid were present in the histories of 36 (36.7%) patients (Table 1).

3.2. Patients' IMA values

The mean IMA value in the aortic aneurysm group was 0.89 ± 0.21, while it was 0.70 ± 0.13 ABSU in the aortic dissection group, 0.98 ± 0.24 ABSU in the aneurysm and dissection group, 0.84 ± 0.17 ABSU in the aneurysm and rupture group, and 0.87 ± 0.28 ABSU in the aneurysm, dissection, and rupture group. Mean IMA level for all aortic pathology was 0.88 ± 0.21 ABSU. Mean IMA levels in the control group were 0.62 ± 0.18 ABSU. All differences between the aortic pathology groups' IMA values and

Table 1. Patient and control group demographic characteristics.

Variables	Control group (n = 101)	Patient group (n = 98)
Sex		
Male, n (%)	78 (77.3)	61 (62.3)
Female, n (%)	23 (22.7)	37 (37.7)
Presentation complaints, n (%)		
Chest pain		64 (65.3)
Abdominal pain		48 (49)
Back pain		41 (41.8)
Lower back pain		29 (29.6)
Dyspnea		32 (32.7)
Hematuria		17 (17.3)
Syncope		4 (4.1)
Pulsatile mass		5 (5.1)
Past history characteristics, n (%)		
Hypertension		89 (90.8)
Cigarettes		24 (24.5)
None		4 (4.5)
Other		36 (36.7)

those of the control group were statistically significant ($P < 0.001$). Mean IMA levels in aortic pathology are compared individually with the control group in Table 2 and Figure 1.

The prognostic value of serum IMA levels was evaluated with the use of a ROC curve (Figure 2). The area under the ROC curve was obtained as 0.80 ± 0.03 (95% CI: 0.73–0.85). The optimum cut-off point maximizing sensitivity and specificity was 0.69 ABSU, with a sensitivity of 84.7% and a specificity of 60.4%.

The patient group's IMA values were statistically significantly higher compared to those of the control group ($P < 0.001$). Further examination of the patient group's IMA results showed the highest level in the combined aortic aneurysm and dissection group. However, the differences in IMA results among the aortic pathology subgroups were not statistically significant ($P = 0.126$).

4. Discussion

There are significant difficulties in the diagnosis of patients with aortic aneurysm or dissection in emergency practice. In differential diagnosis, laboratory tests for diagnostic purposes may provide useful clues regarding the presence of aortic regurgitation, aortic stenosis, myocardial infarct, myocarditis, pericarditis, cardiac tamponade, pulmonary embolism, pancreatitis, gastroenteritis, hernias, pleural effusion, thoracic outlet syndrome, myopathies, and mechanical back aches. In laboratory tests run for this purpose, there may be a rise in leukocyte numbers; elevated blood urea nitrogen and creatinine; a rise in troponin and creatinine kinase; the presence of hematuria, oliguria, or anuria; or a fall in hemoglobin level in the event of leakage from a blood vessel. In addition, D-dimer, which has recently been investigated in a great many studies,

Table 2. Comparison of patient and control group IMA values.

	AA	AD	AA + AD	AA + AR	AA + AD + AR	Average aortic pathology	Control group
n (number)	49	7	13	15	14	98	101
IMA (mean ± SD, ABSU)	0.89 ±0.21	0.70 ± 0.13	0.98 ± 0.24	0.84 ± 0.17	0.87 ± 0.28	0.88 ± 0.21	0.62 ± 0.18
P*	0.001	0.001	0.001	0.001	0.001	0.001	

AA: Aortic aneurysm, AD: aortic dissection; AR: aortic rupture.
*: Statistical significance was found when all subgroups were compared with the control group ($P = 0.001$). No statistical difference was found when subgroups were compared among themselves ($P = 0.126$).

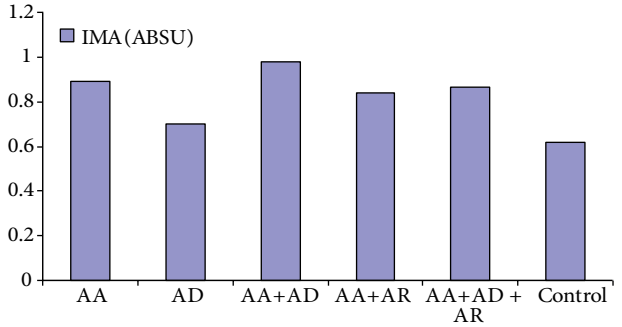

Figure 1. Comparisons of IMA levels from individual aortic pathology and the control group. AA: Aortic aneurysm, AD: aortic dissection; AR: aortic rupture.

has been shown to rise particularly in aortic dissection patients (6).

In a study by Weber et al. with patients diagnosed with aortic dissection in the emergency department, a D-dimer cut-off value of 0.5 μg/mL was taken and a sensitivity of 100% and a specificity of 68% were determined. D-dimer levels were shown to rise from the moment of onset of symptoms and a correlation was determined between dissection course and D-dimer increase, and it was seen that the level of patients lost in the hospital was very high (5).

Sbarouni et al. compared patients with acute aortic dissection and chronic aneurysm alone with a healthy control group and determined elevated D-dimer levels. A D-dimer cut-off value of 700 ng/mL was set and sensitivity was determined at 94%. Patients with aneurysm and acute aortic dissection not defined as chronic were compared with a healthy control group in that study and plasma brain natriuretic peptide (BNP) levels were significantly higher compared to the control group. In contrast, it has also been reported that, unlike BNP, D-dimer can be used as an excluding test in the diagnosis of aortic dissection and can also be employed in the differential diagnosis of dissection and chronic dilatation (7).

The first 3 amino acids of human serum albumin contain binding regions for cobalt, nickel, and copper, and these regions are very sensitive compared with other albumin regions (8). In acute ischemic conditions, albumin's metal-binding capacity in the N-terminus region declines and a metabolic protein forms. This change can be measured and is known as IMA. Studies have determined a normal value for IMA of 85 U/mL (ELISA results) (4).

IMA distribution levels between races and sexes have been investigated, and while no difference in terms of sex has been observed, a difference between races has been determined (blacks and Caucasians). In addition, IMA levels can rise in some conditions (end-stage kidney disease, certain neoplasms and liver diseases, and even

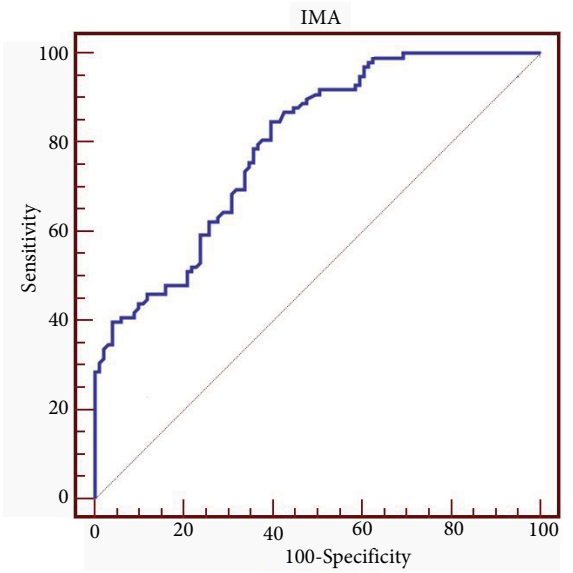

Figure 2. ROC curve of IMA levels.

in marathon runners) (9). A scan of the literature shows that elevated IMA levels have been reported in such acute ischemic conditions as cerebral ischemia, myocardial ischemia, mesenteric ischemia, muscular ischemia, and pulmonary ischemia, for which reason it has been thought that IMA can be used as a diagnostic marker (10–12).

IMA has been investigated for use in the diagnosis of several diseases. IMA measurement is recommended in the diagnosis of myocardial ischemia in patients with acute chest pain. One broad study determined that IMA had a high negative predictive value of 90% in excluding acute coronary syndrome in patients presenting to the emergency department with chest pain, and that the negative predictive value rose to 97.1% when evaluated together with negative cardiac troponins and nondiagnostic ECG results (12).

Bar-Or et al. determined by angiography that IMA concentrations in the blood of patients developing temporary ischemia began rising within a few minutes, and that blood IMA concentrations began decreasing to the values found in individuals with no ischemia approximately 6 h after reperfusion with angioplasty (13). Turedi et al. concluded that IMA can be an alternative marker in excluding a diagnosis of PE. That study examined IMA levels in 30 subjects diagnosed with PE using spiral computerized tomographic angiography and 30 healthy volunteers. IMA levels were significantly higher in the PE group compared to the healthy group (14). In another study, D-dimer was compared with IMA. That study consisted of 130 patients with suspected PE and 59 healthy controls, and IMA sensitivity in the diagnosis of PE was 93%, with specificity of 75%. D-dimer was determined to be 98.9% sensitive and 62.7% specific (8).

These studies suggest that IMA can be an assistant marker in the exclusion of PE. The rise in IMA level was attributed to direct tissue hypoxia-induced ischemia, the formation of infarct tissue, and especially tissue hypoxia arising following massive embolism-associated hypotension (14).

In another study, IMA levels in patients with mesenteric ischemia were significantly higher compared to those of the control group. The elevated IMA here was ascribed to ischemia developing as a result of cytosis (15).

Aortic dissection and ruptures can lead to a direct increase in IMA levels. IMA can also rise in connection with an endothelial response to aneurysmatic developments. Endothelial tissue releases vasodilator substances such as prostaglandin I2, nitric oxide, and prostaglandin E for the establishment of hemodynamics and vein tonus regulation (16). However, as the secretion of vasodilator substances declines because of the damaged endothelium, that of vasoconstrictor substances such as endothelin and thrombocyte-associated growth factor rises. Vasospasm occurs as a result, and there is a decrease in blood flow to many organs of the body. In addition, the manufacture of anticoagulant substances decreases as a result of endothelial damage and thrombocyte aggregation, and clotting takes place in the damaged endothelial region. Vasospasm and thrombocyte aggregation take place as a result of the release of the activated thrombocytes, thromboxane A2, and serotonin. This further increases the endothelial damage, and a vicious circle develops with the release of mitogen substances from the damaged endothelium. The vasospasm arising increases malperfusion and impairs the blood supply in many organs. The mediator and reactive oxygen radicals released in connection with endothelial damage further enhance that damage and the accumulated thrombus material makes coagulation cascade and the associated rising biochemical parameters measurable (17).

IMA is one of the measurable markers developing in association with this vicious circle. In the same way that IMA can rise in any aortic pathology that may give rise to endothelial damage, so the hypotension or hypovolemic shock arising after dissection and rupture will cause perfusion damage in the tissues and ischemia development, with an associated rise in IMA.

In a paper published in 2008, Sbarouni et al. determined similar IMA levels in acute dissection, chronic aneurysm, and healthy control groups, with no statistically significant difference among them. The findings in that study are diametrically opposed to our own (18).

IMA is thus a marker whose use has been investigated in the diagnosis of many diseases, such as coronary ischemia, PE, deep vein thrombosis, and hemorrhagic and ischemic stroke (19). Our study compared IMA levels in aortic pathology with a healthy control group. We investigated aortic pathology in 5 separate categories: aortic aneurysm, aortic dissection, aortic aneurysm and dissection, aortic aneurysm and rupture, and aortic aneurysm, dissection, and rupture. All of our findings, measured both separately and for the average of all pathologies, were significant when compared to the healthy control group ($P < 0.001$). Compared among themselves, aortic pathology had the highest average in the aortic aneurysm and dissection group (0.98 ABSU), while the lowest value was in the aortic dissection alone group (0.70 ABSU). However, in terms of IMA levels the difference among aortic pathologies was not significant ($P = 0.126$). We estimated that the highest IMA level in our study would be in the combined aortic aneurysm, dissection, and rupture group, but this group's mean IMA level (0.87 ABSU) was actually in third place. We thought this might be attributed to time of presentation at the hospital and the patient's existing clinical status, blood pressure levels, and renal functions.

The main limitation in this study is that the average age of the control group subjects was lower than that of the patient group. That stemmed from the relatively small number of patients meeting the inclusion criteria in the control group compared to the older patient group. It should also be considered that the levels of IMA are significantly influenced by a wide range of physiological variables. While some of these are known, not all have yet been fully identified. We were unable to check for all variables that could possibly influence the IMA levels. We were unable to calculate the positive and negative predictive values of IMA in aortic conditions because we lacked the prevalence data for these conditions.

On the basis of the findings from this study, serum IMA levels are higher in patients with aortic pathology compared to healthy individuals. If confirmed by other studies, this finding suggests that a negative IMA value may be used to rule out aortic pathology.

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