Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1221793
J Health Sci Med 2023; 6(2): 244-249

The usefulness of arylesterase in predicting contrast-induced nephropathy in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention

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Cite this article as: Kalaycı S, Hamamcıoğlu AC, Kalaycı B. The usefulness of arylesterase in predicting contrast-induced nephropathy in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. J Health Sci Med 2023; 6(2): 244-249.

ABSTRACT

Aim: Oxidative stress is one of the causes of contrast-induced nephropathy (CIN). Paraoxonase1 (PON1), is one of the oxidative stress markers. The most sensitive method that has been in use to measure PON1 enzyme activity is the measurement of arylesterase (AREase) activity. To explore relationship between AREase activity and CIN development.

Material and Method: A total of 58 STEMI patients were included in our study. The patients were divided into two groups as CIN (+) and CIN (-). The success of AREase activity level in predicting the development of CIN was also examined by using ROC analysis.

Results: Out of the study patients, 13 were CIN (+) and 45 were CIN (-). AREase activity was found to be statistically significantly lower in the CIN (+) group (875 U/L vs 819 U/L, p= 0.004). In the regression analysis, diabetes mellitus, contrast volume and AREase activity were determined as independent risk factors in the development of CIN. As a result of the ROC analysis, we concluded that the AREase activity level <824.1 U/L predicted the development of CIN with 61.5% sensitivity and 86.7% specificity (AUC= 0.768, 95% CI= 0.638-0.868, p=0.001).

Conclusion: AREase level is an independent risk factor for the development of CIN and can be used for the prediction of CIN development.

Keywords: Acute myocardial infarction/STEMI, angiography, coronary, coronary artery disease, percutaneous coronary Intervention (PCI), renal disease, acute

INTRODUCTION

Contrast-induced nephropathy (CIN) is an iatrogenic acute kidney injury that develops after the intravascular administration of the contrast agent for diagnostic or therapeutic purposes and is associated with increased mortality (1). The three pathophysiological mechanisms most frequently accused in the development of CIN are direct tubular damage, intra-renal vasoconstriction, and increased production of reactive oxygen species (ROS) (2). In most patients, CIN can be cured spontaneously and renal replacement therapy is not being required. However, 15% of patients who develop CIN may need temporary haemodialysis, and end-stage renal disease may develop in 4% of patients whose renal functions do not improve (3). Chronic kidney disease, diabetes mellitus, congestive heart failure, intra-arterial interventions, high contrast volume, advanced age, hypertension, hyperuricemia, and multiple myeloma are the conditions that increase the prevalence of CIN (4).

Compared with fibrinolytic therapy, percutaneous coronary intervention (PCI) is the most selective treatment in ST-segment elevation myocardial infarction (STEMI) patients because of the presence of less ischemic complications, higher preserved myocardial mass, and lower mortality rates (5). However, one of the most important complications of PCI is CIN. The frequency of CIN is higher in STEMI patients than the other patients with acute coronary syndromes (6). The risk of CIN can be minimized by hydration during and after primary PCI, keeping the volume of contrast agent limited, and also by choosing a low-osmolar contrast agent (7).

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Received: 20.12.2022 **Accepted:** 14.01.2023

Various biomarkers have been in use to detect the elevated amount of ROS production that has been considered as one of the most important mechanisms responsible for the development of CIN. Paraoxonase-1 (PON-1) is the enzyme that binds to high density lipoprotein (HDL) and protects it from oxidative modification and hydrolysis by hydrogen peroxide (8). It is known that PON-1 activity decreases in systemic oxidative stress and atherosclerosis (9). One of the two substrates used for the measurement of PON-1 activity is arylesterase (AREase). It has been previously shown that oxidative stress increases in CIN and coronary artery disease (4, 10). However, the relationship between CIN and AREase activity in STEMI patients has not been studied before. In our study, we investigated whether there is a relationship between AREase, a marker of oxidative stress, and the development of CIN in STEMI patients undergoing primary percutaneous intervention and whether this relationship can be used for the prediction of CIN in STEMI.

MATERIAL AND METHOD

Study Population

This is a single centre, retrospective, cross-sectional study. Between October 2019 and January 2020, a total of 58 patients who met the study criteria were included in the study. The exclusion criteria of the study were determined as the presence of acute or chronic infection, malignancy, autoimmune disease, pregnancy, breastfeeding, known systolic heart failure and being under 18 years of age. Patients taking drugs with antioxidant effects were excluded from the study. Individuals who refused to be part of the study were also excluded.

STEMI was defined as chest pain together with the detection of new or presumed new ST segment elevation in ≥ 2 adjacent leads in 12-lead electrocardiography. Emergency coronary angiography was performed to all patients in this group, and as a standard, acetylsalicylic acid, clopidogrel or ticagrelor and heparin were given before angiography, also, if not contraindicated, beta-blockers, angiotensin-converting enzyme inhibitors, and statins were prescribed during hospitalization. Contrast-induced nephropathy has been characterized by an increase in serum creatinine level (≥ 0.5 mg/dL or ≥ 25%), within 48–72 hours after the administration of a contrast agent (11). According to this definition, patients were divided into two groups as CIN (+) and CIN (-). To all of the groups, iohexol, a low osmolar contrast agent, was administered during coronary angiography.

This study was retropesctively designed as a part of entitled "Oxidative stress parameters in patients with ST segment elevation myocardial infarction and the effects on in-hospital prognosis" which was a prospective study supported by Scientific Research Project Unit of Zonguldak Bülent Ecevit (BAP 2019-21664500-01). The study was carried out with the permission of Zonguldak Bülent Ecevit University Non-interventional Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 2022/09-8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Collection & Blood Sample Preparation

Demographic information, heart rate, systolic blood pressure, body mass index, smoking status, presence of hyperlipidaemia, hypertension and diabetes mellitus, as well as the medications of the patients were recorded for all patients included in the study. Hypertension was defined if an individual had systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg in more than two measurements in the hospital, previously diagnosed as hypertensive or if an individual was under the usage of any antihypertensive medications. Hyperlipidaemia was defined if an individual had serum triglyceride levels ≥200 mg / dl, low-density lipoprotein cholesterol levels ≥130 mg / dl, serum total cholesterol levels ≥240 mg / dl, previously diagnosed as hyperlipidemic, or if an individual was under the usage of lipid-lowering medication. Diabetes mellitus was defined as having fasting plasma glucose levels more than 126 mg / dL in multiple measurements or if an individual was already diagnosed as diabetic, or if a person was under the usage of antidiabetic medications. Both the active smokers and ex-smokers were included in the study as smokers.

Detection of infarct related artery (IRA) as spontaneous complete recanalized in coronary angiography performed before primary percutaneous coronary intervention (PCI) in patients with STEMI was defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

Transthoracic echocardiography was performed to the patients in the patient group within 24-48 hours after admission to the hospital, and to the patients in the control group at the outpatient admissions clinic. Left ventricular ejection fraction (LVEF) was measured and recorded with biplane images, and patients with LVEF < 50% was regarded as having early left ventricular systolic dysfunction. In-hospital mortality was also recorded in the patient group.

Blood samples of the study patients were taken from the antecubital veins while preparing the patients for coronary angiography and collected into the biochemistry tubes with K2EDTA. Hemogram analysis was performed with

LH 780 Analyser (Beckman Coulter, Miami, USA). Lipid parameters and routine biochemistry parameters were immediately measured with the ADVIA 2400 (Siemens, NY, USA) device. The blood samples were centrifuged at 3000 rpm for 10 minutes and the sera were separated. Separated sera were stored in eppendorf tubes at -80 degrees Celsius until AREase activities were measured.

Arylesterase (AREase) Activities

ELISA kits were used to determine serum PON-1 and AREase activities (Relassay, Turkey). PON-1 activity was measured spectrophotometrically at 37°C and 412 nm and AREase activity was measured at 37°C and 270 nm PON-1 activity was expressed as international units per 1 litre of sera (U/L) and AREase activity was expressed as kilo units per 1 litre of sera (KU/L) (12, 13).

Statistical Analysis

Statistical analyses were performed with SPSS 19.0 software. Distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum) and categorical variables as frequency and percent. Categorical variables were compared using Pearson Chi-square test. Continuous variables were compared with independent sample t test or the Mann-Whitney U test for two groups. The variables of age, hypertension, diabetes mellitus (DM), contrast volume, AREase value and LDL-C were used in Multivariate Binary logistic regression analysis with the backward elimination method to determine risk factors according to the presence of CIN. MedCalc 19.6.4 was used to calculate receiver operating characteristic (ROC) analyses, to determine the optimal cut-off value of AREase to predict the development of CIN. P value of less than 0.05 was considered as statistically significant for all tests.

RESULTS

Among 45 patients, 13 were CIN (+). The frequency of CIN was 22.4%. Both groups were similar in terms of age and sex. Not only diabetes mellitus but also hyperlipidaemia occurred more in CIN (+) patients and this was statistically significant (p= 0.043 and p= 0.038). Demographic and clinical characteristics of the study patients were shown in **Table 1**. No difference was recorded in terms of echocardiography parameters and the patient medications. Contrast volume used was significantly elevated (222 ± 25 ml vs 197 ± 8 ml, p= 0.004) in the CIN (+) group.

Routine biochemical and hemogram values as well as AREase activity levels were shown in **Table 2**. LDL-C was significantly decreased in CIN (+) patients (124 ± 38 mg/dL vs 103 ± 34 mg/dL, p= 0.043). AREase activity was also significantly decreased in CIN (+) group (875 [252-1007] U/L vs 819 [371-939] U/L, p= 0.004) as shown in **Figure 1**.

Table 1. Demographic properties and clinical characteristics of the study patients.

Variables	CIN (-) n= 45	CIN (+) n= 13	P
Age (years), mean±SD	59±12	61±12	0.608
Male, n (%)	32 (76)	14 (87)	0.346
Diabetes mellitus, n(%)	12 (26)	8 (61)	0.043
Hypertension, n(%)	15 (35)	8 (50)	0.324
Smoking, n(%)	30 (71)	11 (68)	0.843
Hyperlipidemia, n(%)	26 (61)	5 (31)	0.038
Body mass index (kg/m2)	26.1 [17-52]	26.9 [23-35]	0.300
Systolic blood pressure (mmHg)	128 ± 20	139 ± 22	0.070
Admission heart rate (beats/min)	79 ± 13	86 ± 12	0.093
Anterior MI presentation	23 (54)	5 (31)	0.101
TIMI 3 flow	13 (30)	3 (18)	0.357
Stent length (mm)	20 [12-41]	22 [9-42]	0.483
Contrast volume (ml)	222 ± 25	197 ± 8	0.004
Infarct related coronary artery (n,%)			0.673
LAD	23 (51)	5 (38)	
CX	7 (15)	2 (16)	
RCA	15 (33)	6 (46)	
Echocardiography parameters			
LA (mm)	37 [30-50]	36 [32-48]	0.588
IVS (mm)	12 [9-15]	12 [9-17]	0.879
PW (mm)	11 [9-14]	11.5 [9-16]	0.555
EDD (mm)	48 [42-65]	47.5 [42-61]	0.787
ESD (mm)	31 [25-40]	30 [26-41]	0.587
EF (%)	45 [30-60]	45 [30-60]	0.860
Drug use			
RAS blocker	14 (33)	5 (31)	0.881
Diuretic	6 (14)	2 (12)	0.861
Beta blocker	7 (16)	3 (18)	0.852
Alfa blocker	0 (0)	1 (16)	0.105
CCB	6 (14)	4 (25)	0.339
Anti platelet	8 (19)	1 (6)	0.233
Combine antihypertensive	10 (23)	5 (31)	0.566
Statin use	11(26)	2 (12)	0.268

Abbreviations: CCB: Calcium channel blockers, CIN: Contrast induced nephropathy, CX: Circumflex, EDD: End diastolic diameter, EF: Ejection fraction, ESD: End systolic diameter, IVS: Inter ventricular septum, LA: Left atrium, LAD:Left anterior descending, PW: Posterior wall, RAS: Renin angiotensin system, RCA: Right Coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Table 2. Laboratory findings and the studied oxidative stress markers.

Variables	CIN (-) n= 45	CIN (+) n= 13	P value
Urea (mg/dL)	33 [12-83]	40 [23-87]	0.085
Creatinin (mg/dL)	0.9 [0.6-1.2]	0.9 [0.5- 4.6]	0.724
TC (mg/dL)	190 [88-360]	155 [115-241]	0.059
LDL-C (mg/dL)	124 ± 38	103 ± 34	0.043
HDL-C (mg/dL)	39 ± 8.4	39 ± 5.2	0.778
Triglyceride (mg/dL)	151 [56-465]	136 [52-233]	0.100
Peak troponin-T (ng/mL)	5.5 [0.26-131]	2.5 [0.3-10]	0.263
Peak CK-MB (ng/mL)	142 [1.3-300]	116 [21-300]	0.807
WBC count (103/μL)	10.4 6-19	10 (7.9-22)	0.986
Hemoglobin (g/dL)	13.8 ± 2.0	14.1 ± 2.4	0.595
Platelet (103/μL)	245 (140-563)	213 (79-379)	0.409
AREase (U/L)	875 [252-1007]	819 [371-939]	0.004

Abbreviations: AREase: Arylesterase, AU: Arbitrary Unit, CIN: Contrast induced nephropathy, CK-M: Creatine kinase MB, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, OSI: oxidative stress index, TAS: Total antioxidant status, TOS: Total oxidant status, TC: Total cholesterol, U/L: Unit/ Liter, WBC: White blood cell.

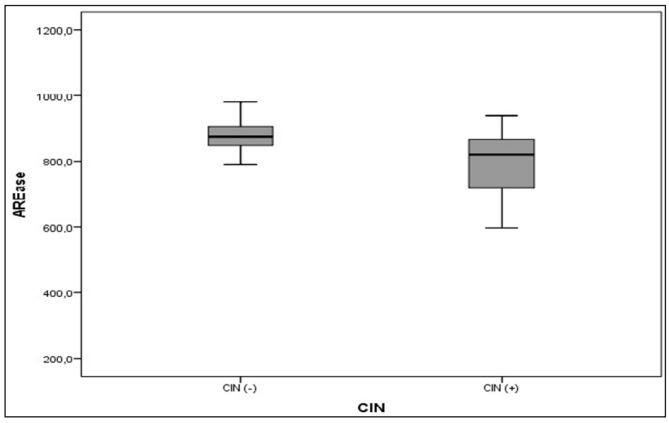

Figure 1. Box plot presentation comparison of arylesterase activity among CIN (+) and CIN (-) groups

In order to determine the independent risk factors in the development of CIN, a Multivariate Binary Logistic Regression analysis was performed by modelling age, LDL-C, hypertension, AREase activity, contrast volume and diabetes mellitus (**Table 3**). As a result of this analysis, diabetes mellitus, contrast volume and AREase activity were determined as independent risk factors for the development of CIN. With the ROC analysis, we concluded that the AREase activity level <824.1 U/L predicted the development of CIN with a sensitivity of 61.5% and a specificity of 86.7% (AUC= 0.768, CI= 0.638-0.868, p=0.001) (**Figure 2**).

Table 3. Multivariate binary logistic regression analysis of independent risk factors for the presence of contrast induced nephropathy in all study patients

Indicators*	Rank**	OR	%95 CI	P value
Hypertension	1	1.417	0.187-10.762	0.736
LDL-C	2	1.013	0.985-1.041	0.372
Age	3	0.937	0.853-1.029	0.171
AREase	4	0.992	0.986-0.998	0.015
DM	4	6.723	1.133-39.882	0.036
Contrast volume	4	1.078	1.025-1.134	0.002

*Abbreviations: ARE: Arylesterase, DM: Diabetes Mellitus, LDL-C: Low-density lipoprotein cholesterol. **Indicates the rank of elimination in stepwise backward LR method.

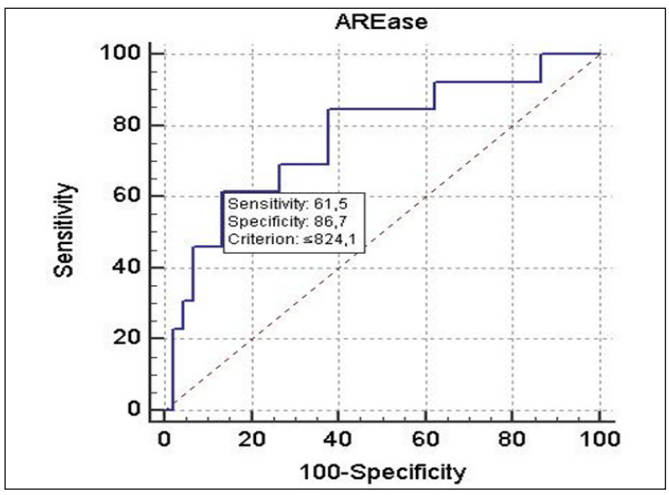

Figure 2. ROC curve analysis of the arylesterase activity level for the evaluation of CIN presence.

DISCUSSION

In this study, we found a significant relationship between AREase level and the development of CIN in STEMI patients who underwent percutaneous intervention. AREase level was significantly lower in patients with CIN (+), and we found a moderate negative correlation in the correlation analysis. After adjusting the other parameters, the presence of diabetes mellitus, contrast volume and AREase activity were found as independent predictors to determine of the development of CIN.

Paraoxonase-1 (PON-1) is an HDL-related enzyme ester with antioxidant and antiatherosclerotic properties. Paraoxonase activity (PONase) and AREase activity are used to measure PON-1 activity (14). AREase is defined as calcium dependent esterase/ lactonase like paraoxonase. However, AREase seems to be more sensitive than PONase in determining PON-1 activity as AREase activity is minimally affected by PON-1 polymorphisms and had lower inter-individual variability (15). For this reason, we decided to study AREase for the measurement of PON-1 activity. To our knowledge, there has been no previous study investigating the relationship between CIN and AREase activity. However, in one study, PON-1 activity was measured in STEMI patients by evaluating PONase, paraoxon hydrolysis (diethyl-p-nitrophenylphosphate), and it was found to be associated with CIN (16). In this study, the rate of diabetes mellitus patients was higher in the CIN (+) group, but no sub-analysis was performed. Similarly, also in our study, AREase activity values reflecting PON-1 activity were found to be associated with the presence of CIN.

AREase activity values reflecting PON-1 activity were found to be significantly lower in people with angiographic coronary artery disease than those with normal coronary arteries, and the low enzyme activities were also shown to be more pronounced in those with occlusion in all three coronary arteries (17). In a study performed by Tang et al. (14) it was found that the low serum AREase and paraoxonase activities in patients with stabile coronary artery disease were both associated with increased risk for major cardiovascular events. However, in this study, the prognostic value of AREase activity were reported to be much higher than the paraoxonase activity (hazard ratio 2.63; 95% CI, 1.97–3.50; P<0.01). In addition to this, it is known that PON-1 activity decreases in patients with chronic kidney disease (15).

In a meta-analysis study, the incidence of CIN in STEMI patients was reported to be closely related with hypertension, diabetes, presence of previous myocardial infarction, age, damaged left anterior descending artery, Killip class 2, decreased left ventricular ejection fraction, lower estimated glomerular filtration rate and

left ventricular ejection fraction <40% (18). In our study, no relationship was found between the responsible coronary artery or stent length and CIN. However, we concluded that the presence of diabetes, contrast volume and AREase activity are independent risk factors for the development of CIN.

Large randomized studies have demonstrated the relationship between high LDL-C and cardiovascular diseases as well as mortality (19). However, major adverse cardiovascular events (MACE) have been found to be associated with low LDL-C at admission stage in STEMI patients, and this situation has been expressed as lipid paradox (20). Although the underlying mechanism is unclear, low LDL-C levels at the admission stage was found to be associated with CD14++CD18+ monocytes in STEMI patients, moreover LDL-C levels less than 85 mg/dL at the admission stage was found to be associated with increased risk for MACE during a median follow-up of 2.7 years. (21). In our study, the LDL-C level was found to be lower in the patient group with CIN (+) than in the group with CIN (-). However, regression analysis failed to demonstrate LDL-C as an independent risk factor for CIN.

There is only one study evaluating the development of CIN and oxidative stress parameters in anterior STEMI patients who underwent percutaneous intervention. In this study, total antioxidant status (TAS), total oxidative status (TOS), and oxidative stress index (OSI) and paraoxon were used to evaluate PON-1 activity as oxidative stress markers (16). A significant correlation was found between all oxidative stress markers and CIN, and according to the regression analysis, PON-1 activity and OSI values were found to be the independent predictors. In our study, AREase, which was shown to be more sensitive to PON-1 activity, was used, and as a result, a significant correlation was found between AREase activity and CIN development in all STEMI patients who underwent percutaneous intervention.

Studies have been conducted on the administration of antioxidants to reduce the development of CIN associated with overproduction of reactive oxygen radicals. Meta-analyses have also shown that the administration of N-acetylcysteine along with hydration reduces the development of CIN (22, 23). Positive effects of ascorbic acid, another antioxidant, on coronary angiography-related nephropathy have also been demonstrated (24). On the other hand, in another study, prophylaxis administration with oral a- or g-tocopherol (vitamin E) was found beneficial in addition to hydration to reduce the development of CIN in patients with chronic kidney disease undergoing coronary angiography (25). It has been previously shown that statins prevent the development of CIN by reducing inflammation and oxidative stress with their pleiotropic effects (26).

Study Limitations

Our study had some limitations. Smoking and statin usage are conditions that affect oxidative stress. However, in our study, the two groups were similar in terms of smoking and statin usage. Therefore, no additional analysis was performed. Also, the patients taking antioxidant drugs such as zofenopril, captopril, and nebivolol were excluded from the study. The most important limitation of our study was the small sample size. In future, our knowledge on this subject will increase with prospective studies that will be conducted in a larger population by grouping and separating diabetic patients. Another limitation may be the seasonal period in which the study was conducted. The design of our study was cross-sectional and included patients over a three-month period, so the results may have been affected by seasonal differences.

CONCLUSION

Inspection of AREase activity in STEMI patients undergoing percutaneous intervention is an independent risk factor for the development of CIN and can be used for prediction. In summary, we can say that AREase activity measurement provides very valuable information in terms of CIN risk in STEMI patients who underwent percutaneous intervention.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zonguldak Bülent Ecevit University Non-interventional Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 2022/09-8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was supported by Scientific Research Project Unit of Zonguldak Bülent Ecevit University (BAP 2019-21664500-01) in Turkey.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Acknowledgement: We would like to thank Asisstant Professor Dr Fürüzan Köktürk (PhD) for the statistical analyses.

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