Increased serum asymmetric dimethylarginine level is an independent predictor of contrast-induced nephropathy

Artmış serum asimetrik dimetilarjinin düzeyi kontrast nefropatisinin bağımsız bir öngördürücüsüdür

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ABSTRACT

Objectives: The aim of our study was to evaluate whether serum asymmetric dimethylarginine (ADMA) level is an independent predictor of contrast-induced nephropathy (CIN).

Study design: The study involved 90 consecutive patients with stable angina pectoris who underwent coronary angiography and ventriculography. Baseline serum creatinine (SCr) levels ranged between ≥1.2 and <2 mg/dl. All patients were hydrated with intravenous isotonic saline at a rate of 1 ml/kg per hour for 6 hours before and 12 hours after the procedure. The primary end point was the occurrence of CIN. The secondary end point was the change in SCr levels at day 2 after the contrast exposure. Serum ADMA was determined by the ELISA method.

Results: The CIN rate was 11.1%. We detected a statistically significantly higher serum ADMA level in the CIN(+) group compared to that of the CIN(–) group [210.6 ng/ml (115.6-217.2) *vs.* 91.5 ng/ml (65.2-122.1), p=0.01]. Mehran risk score and diabetes mellitus (DM) ratio were higher in the CIN(+) group compared to those values in the CIN(-) group [8 (5.75-10) *vs.* 5 (5-7), p=0.01 and 70% *vs.* 26.3%, p=0.01, respectively]. Serum ADMA level, Mehran risk score and DM were independent predictors of CIN (odds ratio (OR) 1.030, 95% confidence interval (CI) 1.011-1.050, p=0.002; OR 1.565, 95% CI 1.102-2.223, p=0.012; OR 9.422, 95% CI 1.441-61.598, p=0.019, respectively). A serum ADMA level of >124.7 ng/ml had 80% sensitivity and 76% specificity in predicting the development of CIN. In addition, we found a positive correlation between SCr change and serum ADMA level (p=0.001, r=0.35).

Conclusion: Our study demonstrates that increased serum ADMA level is an independent predictor of CIN.

ÖZET

Amaç: Bu çalışmada, serum asimetrik dimetilarjinin (ADMA) düzeyinin kontrast nefroptisinin (KNP) bağımsız bir öngördürücüsü olup olmadığı araştırıldı.

Çalışma planı: Çalışmaya koroner anjiyografi ve ventrikülografi yapılan kararlı anjina pektorisli 90 hasta alındı. Hastaların bazal serum kreatinin düzeyi ≥1.2 mg/dl – <2 mg/dl arasında idi ve tümü işlemden 6 saat önce başlanıp 12 saat sonraya kadar devam edecek şekilde intravenöz izotonik salin ile hidrate edildi. Çalışmanın birincil son noktası KNP gelişimi idi. İkincil son noktası kontrast sonrası ikinci günde serum kreatinindeki değişimdi. Serum ADMA düzeyi ELISA yöntemi ile ölçüldü.

Bulgular: Olguların %11.1'inde KNP gelişti. KNP(+) grupta KNP(–) gruba göre istatistiki olarak anlamlı olarak daha yüksek serum ADMA düzeyi saptandı (210.6 ng/mL [115.6-217.2]ve 91.5 ng/mL [65.2-122.1], p=0.01). Aynı zamanda Mehran risk skoru ve diabetes mellitus oranı KNP(+) grupta KNP(–) gruba göre daha yüksekti (sırasıyla, 8 [5.75-10] ve 5 [5-7], p=0.01 ve %70 ve %26.3, p=0.01). Serum ADMA düzeyi, Mehran risk skoru ve diabetes mellitus KNP'nin bağımsız öngördücüleriydi (sırasıyla, odds oranı [OO] 1.030, %95 güven aralığı [GA] 1.011-1.050, p=0.002; OO 1.565, %95 GA 1.102-2.223, p=0.012; OO 9.422, %95 GA 1.441-61.598, p=0.019). Bu çalışmada 124.7 ng/mL üzerindeki serum ADMA düzeyi KNP'yi öngördürmede %80 duyarlılık ve %76 özgüllüğe sahipti. Ek olarak serum kreatinindeki değişimle serum ADMA düzeyi arasında pozitif bir korelasyon saptandı (p=0.001, r=0.35).

Sonuç: Çalışmamız artmış serum ADMA düzeyinin KNP'nin bağımsız bir öngördürücüsü olduğunu göstermiştir.

Received: January 26, 2013 *Accepted:* May 05, 2013

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Contrast-induced nephropathy (CIN) is a serious complication of iodinated contrast media exposure. Regardless of the patients' baseline characteristics, such as creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), coronary artery disease, diabetes mellitus (DM), and hemodynamic status, the development of CIN correlates with increased in-hospital morbidity and mortality rates attributable to CIN.[1] Not only the patients with CIN requiring dialyses but also those developing mild renal impairment have poor outcomes.[1] In addition, CIN worsens long-term prognosis and is associated with late cardiovascular events.[2] Because the pathogenesis of CIN is dependent on a complex interplay of multiple factors and this syndrome is an independent predictor of potential adverse outcomes, numerous studies have focused their investigations on the risk stratification for CIN. Both patient- and procedure-related characteristics were evaluated in these studies to most accurately identify the population at risk for CIN.[1,3]

Abbreviations:

ADMA	*Asymmetric dimethyl-l-arginine*
CIN	*Contrast-induced nephropathy*
CrCl	*Creatinine clearance*
DM	*Diabetes mellitus*
LVEF	*Left ventricular ejection fraction*
NGAL	*Neutrophil gelatinase-associated lipocalin*
NOS	*Nitric oxide synthase*
ROC	*Receiver operating characteristic*

The pathophysiology of CIN is still poorly understood; however, it is clear that the patients with higher atherosclerotic burden and endothelial dysfunction are more vulnerable to contrast agents.[4,5] Previous studies have demonstrated that the patients with hypertension, DM, hypercholesterolemia, acute coronary syndrome, advanced age, multivessel disease, and peripheral vascular disease had higher risk for the development of CIN.[3,6-8] Asymmetric dimethyl-l-arginine (ADMA), an endogenous nitric oxide synthase (NOS) inhibitor, is a surrogate marker of endothelial dysfunction.[9,10] In many studies, ADMA levels were found to be elevated in various conditions associated with atherosclerosis and endothelial dysfunction.[9-11] Further, elevated ADMA levels have been demonstrated to be associated with increased oxidative stress and impaired NO production, some of the proposed mechanisms for the development of CIN.[9,12]

To our knowledge, no study in the literature thus far has investigated the presence or not of a relation between CIN and serum ADMA levels. The aim of our study was to evaluate whether or not serum ADMA level could be used as an independent marker in the prediction of CIN.

PATIENTS AND METHODS

Study population

The study involved 90 consecutive patients with stable angina pectoris who underwent coronary angiography and ventriculography. Baseline serum creatinine (SCr) levels of all subjects ranged between ≥1.2 and <2 mg/dl. Exclusion criteria included current infection, neoplasm, acute coronary syndromes, contraindications to iodinated contrast agents (e.g., history of allergic reactions against contrast media), need for urgent percutaneous coronary intervention, and recent exposure to contrast media or nephrotoxic agent (within 7 days before the study). Any patients requiring theophylline/aminophylline or dopamine throughout the study were also excluded. Each subject was questioned about the confirmed risk factors for atherosclerotic heart disease and CIN including hypertension, hyperlipidemia, DM, smoking status, and medications.

Study design

All patients were hydrated with intravenous isotonic saline at a rate of 1 ml/kg per hour for 6 hours before and 12 hours after the procedure. Before coronary procedures, echocardiographic examination was carried out in all patients by a cardiology specialist using Vingmed System 7 echocardiography machine and a 2.5 MHz probe. LVEF was measured by two-dimensional echocardiography via the modified Simpson method. Left and right coronary angiography was performed in multiple projections by the Judkins or Sones technique via the right femoral artery using Philips Integris 5000 equipment (Philips Medical Systems, Best, The Netherlands). Iopromide, a low-osmolar, nonionic contrast agent, was used in all procedures. SCr concentration was measured in venous blood at baseline (before initiating preprocedure hydration) and on day 2 after the procedure. The primary end point was the occurrence of CIN. We defined CIN as an increase ≥0.5 mg/dl and/or ≥25% in SCr concentration at day 2 of the procedure. The secondary end point was the change in SCr levels at day 2 after the contrast exposure.

Creatinine clearance was estimated by the Cockcroft-Gault formula.[13] We also estimated Mehran risk score[3] in all patients. Mehran risk score was de-

termined according to patient- and procedure-related variables. The patient-related variables consisted of renal failure (4 points for SCr >1.5 mg/dl or 2, 4, or 6 points for estimated glomerular filtration rate of 40-60 ml/min/1.73m^2, 20-40 ml/min/1.73m^2, and <20 ml/min/1.73 m^2, respectively), anemia (3 points), congestive heart failure (5 points), DM (3 points), hypotension (5 points), and age >75 years (4 points). The procedure-related variables included the need for an intraaortic balloon pump within 24 hours periprocedurally (5 points) and contrast media volume (1 point for each 100 cc^3).

The study was approved by the local ethics committee, and a written informed consent was obtained from all patients enrolled in the study.

ADMA

Serum samples for the measurement of ADMA level were drawn between 800-1000 hours and were preserved at -70°C. Serum ADMA was determined using enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm, Hangzhou) based on the principle of double-antibody sandwich technique.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS) for Windows version 15.0 software (Chicago, IL, USA) was used as the statistical software program. Kolmogorov-Smirnov test was used to determine whether the parameters fit with the normal distribution. Data within the normal distribution were expressed as mean±standard deviation (Mean±SD). Results of data without normal distribution are shown by median (interquartile range) expression. Mann-Whitney U-test was used to compare data that did not fit with the normal distribution between two groups. Unpaired Student t-test was used for comparing data within the normal distribution between two groups. Chi-square test was used for comparison of categorical variables. We performed multivariate logistic regression analyses to determine independent associations between the potential risk markers and CIN. The receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of serum ADMA level and the optimal cut-off value for predicting CIN. The association between change in SCr levels and ADMA values was evaluated by calculating the Spearman's correlation coefficient. A *p* value under 0.05 was accepted as the level of significance.

RESULTS

Our study population comprised 90 consecutive patients with stable angina pectoris who underwent coronary angiography and ventriculography. CIN occurred in 10 patients according to our CIN definition. CIN rate was 11.1%. Mehran risk score of the entire population was 6 (5-8).

Table 1 shows baseline demographic, clinical characteristics and medications in both the CIN(-) (80 patients) and CIN (+) (10 patients) groups. There was no significant difference between the CIN(+) and CIN(-) groups with regard to age, sex, hypertension, smoking, body mass index (BMI), LVEF, baseline Cr, baseline CrCl, contrast agent dose, lipid profile, hemoglobin, and medications (Table 1).

However, we detected a statistically significantly higher serum ADMA level in the CIN(+) group compared to that of the CIN(-) group (210.6 ng/ml (115.6-217.2) *vs.* 91.5 ng/ml (65.2-122.1), p=0.01) (Table 1, Fig. 1). The Mehran risk score and DM ratio were higher in the CIN(+) group compared to those of the CIN(-) group (8 (5.75-10) *vs.* 5 (5-7), p=0.01 and 70% *vs.* 26.3%, p=0.01, respectively) (Table 1).

For CIN, serum ADMA level, Mehran risk score and DM were analyzed using a multivariate logistic regression model. Serum ADMA level, Mehran risk score and DM were independent predictors of CIN (odds ratio (OR) 1.030, 95% confidence interval (CI) 1.011-1.050, p=0.002; OR 1.565, 95% CI 1.102-2.223, p=0.012; OR 9.422, 95% CI 1.441-61.598, p=0.019, respectively) (Table 2).

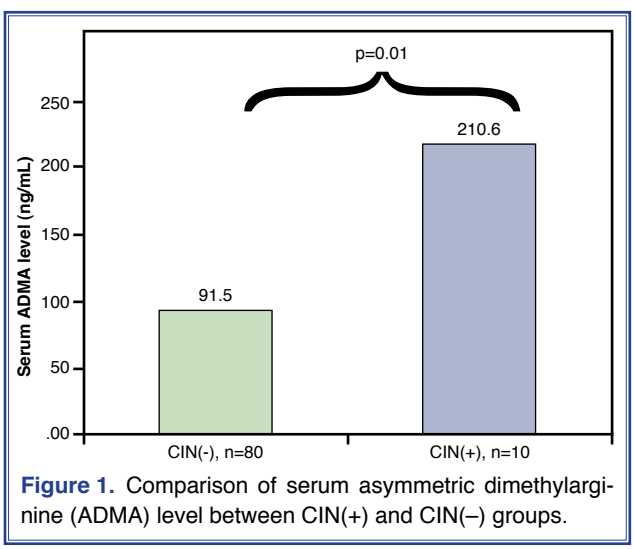

Figure 1. Comparison of serum asymmetric dimethylarginine (ADMA) level between CIN(+) and CIN(–) groups.

Table 1. Comparison of baseline characteristics, laboratory parameters and asymmetrical dimethylarginine (ADMA) levels between contrast-induced nephropathy (CIN)(+) and CIN(-) groups

Baseline characteristics	CIN(–) (n=80)			CIN(+) (n=10)			*p*
	n	%	Mean±SD / Median (range)	n	%	Mean±SD / Median (range)	
Age (y)			64.4±10.1			69.5±9.8	0.13
Sex (Male/Female)	57/23			6/4			0.46
Hypertension	54	67.5		9	90		0.14
Diabetes mellitus	21	26.3		7	70		0.01
Current smoker	31	38.8		1	10		0.07
BMI (kg/m^2)			27.4±4.0			25.2±4.2	0.10
LVEF (%)			51±9.8			48.6±12.0	0.47
Baseline creatinine (mg/dl)			1.42±0.13			1.34±0.12	0.07
Baseline CrCl (ml/min)			49.7±8.2			46.9±9.8	0.32
CA dose (ml)			61.5 (53-68)			58.5 (51-73.2)	0.96
CA dose/BMI (ml/BMI)			2.2 (1.9-2.5)			2.3 (1.9-3.1)	0.29
Total cholesterol (mg/dl)			179.4±43.8			197.1±58.6	0.25
LDL-cholesterol (mg/dl)			113.2±37.8			120.6±45.6	0.56
HDL-cholesterol (mg/dl)			34 (29-42)			40.5 (36.7-45.2)	0.21
Triglyceride (mg/dl)			145±73.2			182±110	0.16
Hemoglobin (g/dl)			13.9±1.8			13.6±1.8	0.67
ACEI	57	71.3		6	60		0.46
ARB	5	6.3		1	10		0.41
Thiazide	20	25		1	10		0.29
Statin	35	43.8		4	40		0.82
Mehran risk score			5 (5-7)			8 (5.75-10)	0.01
ADMA (ng/ml)			91.5 (65.2-122.1)			210.6 (115.6-217.2)	0.01

A value of p<0.05 was considered statistically significant. CIN: Contrast-induced nephropathy; SD: Standard deviation; BMI: Body mass index; LVEF: Left ventricular ejection fraction; CrCl: Creatinine clearance; CA dose: Contrast agent dose; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

The ROC curves of serum ADMA level for predicting CIN are shown in Figure 2. In this study, a serum ADMA level of >124.7 ng/ml had 80% sensitivity and 76% specificity in predicting the development of CIN. In addition, we found a statistically significant correlation between the levels of SCr change and serum ADMA levels, but this correlation was low to moderate (p=0.001, r=0.35) (Fig. 3).

Table 2. Effect of asymmetrical dimethylarginine (ADMA), Mehran risk score and diabetes mellitus on the development of contrast-induced nephropathy in multivariate logistic regression analyses

Variables	OR	95% CI	*p*
ADMA	1.030	1.011-1.050	0.002
Mehran risk score	1.565	1.102-2.223	0.012
Diabetes mellitus	9.422	1.441-61.598	0.019

The OR was mutually adjusted for each of the presented variables. OR: Odds ratio; CI: Confidence interval.

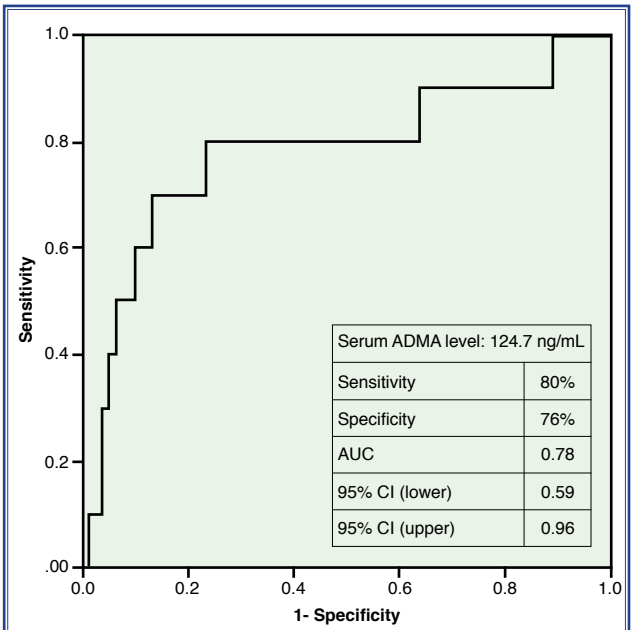

Figure 2. The receiver operating characteristic curve of serum ADMA level for predicting CIN.

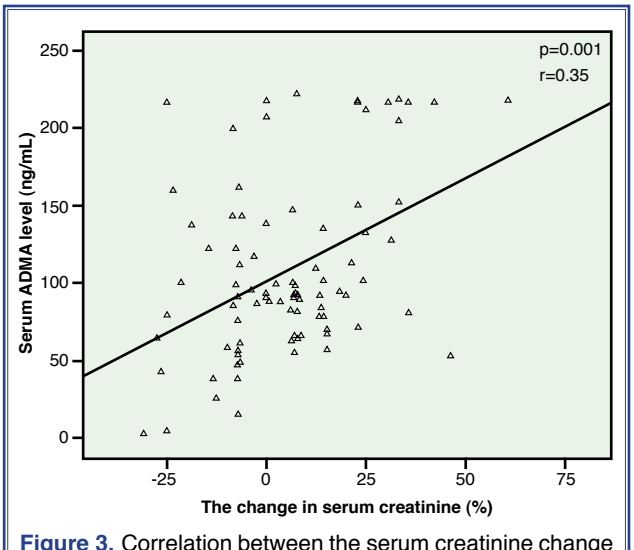

Figure 3. Correlation between the serum creatinine change (%) and serum asymmetric dimethylarginine (ADMA) level.

DISCUSSION

Contrast-induced nephropathy is the third most common cause of hospital-acquired renal failure.[14] Because of the high mortality and morbidity rates attributed to CIN, many studies have been designed to disclose how clinicians can best predict the patients at risk for CIN. More accurate prediction of CIN facilitates taking preventive measures earlier and monitoring renal function tests more closely. To date, many individual risk factors have been reported and several risk prediction models have been developed based on these factors.[1,3,14]

Advanced age, basal renal dysfunction, DM, anemia, hypertension, hemodynamic instability, high contrast volume, and heart failure are well-known risk factors for CIN. These risk factors have been proven by many studies and have been included in risk-scoring schemes.[1,3,6-8,14] In addition, many studies have shown that the risk for CIN was higher in patients with more severe and extensive cardiovascular disease.[1,7,8,15] In other words, CIN was more likely to occur in patients with more extensive atherosclerotic burden and endothelial dysfunction.

Although little is known about the underlying cellular mechanisms in the pathophysiology of CIN, decrease in NO production and increase in oxidative stress have been suggested in many studies as some of the underlying mechanisms leading to vasoconstriction, direct renal tubular damage and CIN.[16-18] Thus, in the literature, many agents have been studied for their potential to prevent the negative effects of radiocontrast on renal function based on these mechanisms. For instance, N-acetylcysteine (NAC), the most commonly used agent for CIN prophylaxis, has been evaluated by numerous studies due to its antioxidative properties.[19,20] In addition, the value of statins in the prevention of CIN has been evaluated by many authors, since statins increase NO bioavailability, improve endothelial function and have antioxidative properties.[21,22] It should be highlighted that many promising results have been achieved with those agents that exert antioxidative and anti-inflammatory effects, increase NO bioavailability and improve endothelial function.[20,21,23]

It is well known that secretion of NO is one of the main functions of the endothelium. NO, a potent vasodilator, is synthesized by NOS, and its synthesis reduces in the presence of endothelial dysfunction.[24] ADMA, an endogenous competitive inhibitor of NOS, impairs endothelial function, thus leading to atherosclerosis and atherosclerosis-related diseases.[25-27] Increased plasma ADMA levels have been shown in patients with coronary artery disease,[26] peripheral arterial disease,[28] DM,[29] hypertension,[30] stroke,[31] hyperhomocysteinemia,[32] and end-stage renal disease,[33] all of which have already been proven to be

related to endothelial dysfunction. Furthermore, several studies have reported that ADMA induces oxidative stress.[12,34] In this context, the study conducted by Mihout et al.[35] is especially noteworthy because they demonstrated clearly increased renal oxidative stress in rats exposed to exogenous ADMA. They showed elevated superoxide anion (O2-) levels in ADMA-administered rats. Besides increasing endothelial dysfunction and oxidative stress, ADMA could be involved in the progression of renal injury. In a study reported by Fliser et al.,[36] ADMA was found to predict the progression of chronic kidney disease. In that study, the renal functions of the patients with higher ADMA levels deteriorated faster than those with lower ADMA. Likewise, Lajer et al.[37] demonstrated that elevated ADMA levels predicted the deterioration of glomerular filtration rate during an 11.3-year follow-up period in type 1 diabetic patients. The effect of ADMA on renal injury can be summarized as induction of glomerular fibrosis, increased renal concentration of TGF-a1 and collagen type 1, as well as increased renal oxidative stress.[35]

Accurate risk stratification for CIN is extremely important to determine the evidence-based prophylactic measures. To date, for prediction of CIN, many risk scoring schemes have been published. However, no scheme used any marker for this purpose. Based on the above-mentioned data about the pathogenesis of CIN and the effect of ADMA on endothelial function, oxidative status and renal damage, we aimed to understand whether ADMA could be used as a marker in the prediction of CIN. The main result of our study is that ADMA is an independent risk marker for the development of CIN. This study is unique because no study to date has demonstrated any relationship between serum ADMA level and CIN. It is noteworthy that only a few studies have evaluated biomarkers in CIN prediction. Osthoff et al.[38] showed that mannose-binding lectin is an inverse predictor of CIN. Another study conducted by McCullough et al.[39] demonstrated that baseline neutrophil gelatinase-associated lipocalin (NGAL) is an independent predictor of changes in the post-contrast NGAL. Although many risk prediction schemes for CIN are available, clinicians lack risk prediction biomarkers. We believe that in order to indentify high- risk patients earlier and more accurately, new studies that will bring novel biomarkers into clinical practice are necessary. In our study, we found higher serum ADMA level in the CIN(+) group compared to that of the CIN(-) group. We also demonstrated that a serum ADMA level of >124.7 ng/ml had 80% sensitivity and 76% specificity in predicting the development of CIN. Despite the small patient population of our study, we suggest that ADMA deserves further examination as a potential marker in the prediction of CIN. The Mehran risk-scoring method is the most frequently used scheme in CIN prediction. It is important to note that the CIN ratio (11%) of the present study was concordant with the study of Mehran et al., suggesting a CIN risk of 7.5% and 14% for risk scores of 1-6 and 6-10, respectively. Furthermore, in our study, DM was found to be an independent risk factor for CIN as well as the Mehran risk score, as suggested in previous studies.[1,3,5]

Study limitations

The major limitation of the present study is the enrollment of a limited number of patients. Larger studies are necessary to confirm our findings. In addition, Mehran risk scores of most patients in our study were below 10. Therefore, our study did not reveal the value of ADMA in CIN prediction in high-risk patients. In addition, we defined CIN as an increase ≥0.5 mg/dl and/or ≥25% in SCr concentration at day 2 of the procedure. However, SCr level may increase up to 1-2 weeks after contrast exposure.[1,23] Therefore, some patients with CIN may be overlooked. Lastly, ADMA concentrations were assessed by ELISA method in our study. However, high-performance liquid chromatography (HPLC) assay is suggested as a robust method to measure ADMA level with high accuracy.

In conclusion, our study demonstrates that serum ADMA level is an independent predictor for the development of CIN. Large, prospective, multicenter studies will be required to understand more clearly the future role of ADMA as a risk prediction marker of CIN.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Angina pectoris; asymmetric dimethylarginine; contrast media/adverse effects; coronary angiography; creatinine/blood.

Anahtar sözcükler: Anjina pektoris; asimetrik dimetilarjinin; kontrast madde/yan etki; koroner anjiyografi; kreatinin/kan.