

# The association between coronary atherosclerotic burden and asymmetric dimethylarginine, carotis intima media thickness and endothelial function

## Koroner aterosklerozu yükü ile asimetric dimetilarjinin, karotis intima medya kalınlığı ve endotel fonksiyonu arasındaki ilişki

Fatma Can, M.D., Murat Ziyrek, M.D., Şükran Erdem, M.D., Murat Civan, M.D., Uzay Görmüş, M.D.,# Sinan Şahin, M.D.,\* Zeydin Acar, M.D.,\* Çavlan Çiftçi, M.D.

Department of Cardiology, Istanbul Bilim University Faculty of Medicine, Istanbul;

#Department of Biochemistry, Istanbul Bilim University Faculty of Medicine, Istanbul;

\*Department of Cardiology, Trabzon Kanuni Training and Research Hospital, Trabzon

### ABSTRACT

**Objectives:** Detection of extent and severity of atherosclerosis using easy, non-invasive methods is of great importance. Atherosclerotic burden may be evaluated with the Gensini scoring system (GSS). Carotis intima media thickness (CIMT), plasma asymmetric dimethyl arginine (ADMA) level, and endothelial dysfunction are well known surrogate markers of atherosclerosis. The aim of this study was to evaluate the relationship between atherosclerotic burden determined by the GSS, and ADMA, CIMT and endothelial function.

**Study design:** Consecutive patients who had undergone coronary angiography were evaluated. 50 patients with acute coronary syndrome (ACS), 50 patients with stable coronary artery disease (SCA), and 50 patients with normal coronary arteries (NCA) were included. All subjects' GSS, ADMA, CIMT and endothelial functions were evaluated and compared.

**Results:** GSS was higher in ACS than SCA (75.4 vs 54.9;  $p<0.001$ ). CIMT was higher in ACS and SCA in compared to NCA (0.98, 0.96, 0.78 mm respectively;  $p<0.001$ ). Endothelium derived vasodilatory response (EDVR) was decreased in ACS and SCA in compared to NCA ( $3.5\pm 2.1\%$ ,  $3.3\pm 1.8\%$ ,  $7.2\pm 3.5\%$  respectively;  $p<0.001$ ). Plasma ADMA concentration was higher in ACS and SCA in compared to NCA (0.928, 0.992, 0.475  $\mu\text{mol/l}$  respectively;  $p<0.001$ ). There was a weak positive correlation between GSS and plasma ADMA levels ( $r=0.293$ ;  $p=0.002$ ), an intermediate positive correlation between GSS and CIMT ( $r=0.508$ ;  $p<0.001$ ), and an intermediate negative correlations between GSS and EDVR ( $r=-0.662$ ;  $p<0.001$ ).

**Conclusion:** This study showed that CIMT, ADMA concentration and endothelial dysfunction were significantly associated with CAD. However, only the GSS was significantly different between ACS and SCA groups.

### ÖZET

**Amaç:** Aterosklerozun şiddetinin ve yaygınlığının basit ve invaziv olmayan yöntemlerle tespiti oldukça önemlidir. Ateroskleroz yükü Gensini skor sistemi (GSS) kullanılarak belirlenebilmektedir. Karotis intima medya kalınlığı (KİMK), plazma asimetric dimetilarjinin (ADMA) seviyesi ve endotel fonksiyon bozukluğu aterosklerozun iyi bilinen belirteçleridir. Bu çalışmanın amacı GSS ile tespit edilen ateroskleroz yükü ile ADMA, KİMK ve endotel fonksiyon bozukluğu arasındaki ilişkiyi incelemektir.

**Çalışma planı:** Koroner anjiyografi yapılmış olan ardışık hastalar değerlendirildi. Akut koroner sendromlu (AKS) 50 hasta, stabil koroner arter (SKA) hastalığı olan 50 ve koroner arterleri normal (NKA) 50 olgu çalışmaya alındı. Çalışmaya alınan tüm olguların GSS, ADMA, KİMK ve endotel fonksiyonları ölçüldü ve karşılaştırıldı.

**Bulgular:** GSS değerleri AKS grubunda SKA grubuna göre daha yüksekti (75.4 ve 54.9;  $p<0.001$ ). KİMK AKS ve SKA gruplarında NKA grubundan daha yüksekti (sırasıyla, 0.98, 0.96, 0.78 mm;  $p<0.001$ ). Endotel bağımlı vasodilatör yanıt (EBVY) AKS ve SKA gruplarında NKA grubundan daha düşüktü (sırasıyla,  $3.5\pm 2.1\%$ ,  $3.3\pm 1.8\%$ ,  $7.2\pm 3.5\%$ ;  $p<0.001$ ). AKS ve SKA gruplarındaki plazma ADMA konsantrasyonu NKA grubundakinden daha düşüktü (sırasıyla, 0.928, 0.992, 0.475  $\mu\text{mol/l}$ ;  $p<0.001$ ). GSS ile plazma ADMA konsantrasyonu arasında zayıf pozitif korelasyon ( $r=0.293$ ;  $p=0.002$ ), GSS ile KİMK arasında orta derecede pozitif korelasyon ( $r=0.508$ ;  $p<0.001$ ), GSS ile EBVY arasında orta derecede negatif korelasyon saptandı ( $r=-0.662$ ;  $p<0.001$ ).

**Sonuç:** Bu çalışmada, plazma ADMA konsantrasyonu, KİMK ve endotel fonksiyon bozukluğu ile koroner arter hastalığı arasındaki ilişki gösterilmiş olmasına rağmen AKS ve SKA grupları arasında yalnızca GSS açısından anlamlı farklılık saptanmıştır.

Received: January 17, 2014 Accepted: May 02, 2014

Correspondence: Dr. Murat Ziyrek. Numune Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü, Maraş Caddesi, Merkez, Trabzon.

Tel: +90 462 - 229 70 70 e-mail: muziyrek@yahoo.com

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Coronary artery disease (CAD) is a common disease and has a serious impact on human health in the western world.<sup>[1,2]</sup> It will soon be the preeminent killer in the developing world as well,<sup>[3]</sup> which is why early detection of the extent and severity of CAD by easily applicable and cost-effective methods is of great importance.

Nitric oxide (NO) is an important cellular signaling molecule synthesized by the endothelium from the amino acid L-arginine by a family of NO synthase (NOS) enzymes. Asymmetric dimethyl arginine (ADMA) is an endogenous inhibitor of all major isoforms of NOS.<sup>[4,5]</sup> Elevated ADMA level decreases the availability of NO. Plasma ADMA level increases in various clinical settings, including atherosclerosis, hypertension, renal failure, liver failure, and impaired glucose tolerance.<sup>[6-9]</sup> Increased ADMA level is also an independent risk factor for progression of atherosclerosis and total mortality in CAD patients.<sup>[10,11]</sup> Carotid intima-media thickness (CIMT) and endothelial dysfunction are well-studied and known surrogate markers of atherosclerosis.<sup>[12,13]</sup>

Coronary angiography is the gold standard diagnostic technique for CAD and could also be used to determine the atherosclerotic burden, extent and severity of CAD with the help of various systems. The Gensini score (GSS) is one of the most popular coronary scoring systems used in clinical practice.

As we thought that the extent and severity of CAD is closely related to cardiovascular mortality, the aim of this study was to investigate the relationship between the atherosclerotic burden determined by the GSS and ADMA, CIMT and endothelial dysfunction.

## PATIENTS AND METHODS

### Study population

Consecutive patients who had undergone coronary angiography with a prediagnosis of CAD between 15/05/2011-30/09/2011 after admission to the cardiology outpatient clinic or emergency service were evaluated. Exclusion criteria were as follows: 1- having any type of malignancy, 2- having any type of infection, 3- having any type of inflammatory disease, 4- hepatic failure, 5- renal failure, 6- recent cerebrovascular disease, 7- using any type of thiazolidinedione group oral antidiabetics or corticosteroids, 8- hypothyroidism or hyperthyroidism, 9- Severe chronic obstructive

pulmonary disease, 10- class 4 congestive heart failure. After application of the exclusion criteria, 50 patients (33 male, 17 female) with stable coronary artery disease (SCA), 50 patients (39 male, 11 female) with acute coronary syndrome (ACS), 50 patients (31 male, 19 female) with normal coronary arteries

(NCA) were enrolled in the study. Coronary arteries having no atherosclerotic plaques were defined as NCA. Patients diagnosed with unstable angina pectoris, ST segment elevated MI during the previous 7 days and non ST segment elevated MI were included in the ACS group. Patients with CAD who were being followed for stable symptoms without evidence of any changes in symptoms for a long period of time were included in the SCAD group.

### Study protocol

This study was designed as a prospective case-controlled study. Basic demographic data of the enrolled patients included age, gender, body mass index (BMI), waist circumference, waist/hip ratio, presence of diabetes mellitus, and the presence of traditional major cardiovascular risk factors (age, sex, hypertension, dyslipidemia, family history of premature cardiovascular disease (CVD), and current smoking). Afterwards, venous blood samples were taken, ultrasonographic examinations done, and angiographic evaluation of all patients performed.

The study protocol was approved by the local ethics committee, and all patients provided written informed consent.

### Biochemical analysis

Venous blood samples of all patients were taken after 8-12 hours of fasting. Serum samples for ADMA analysis were stored at -800 C until analysis. Total

#### Abbreviations:

ACS	Acute coronary syndrome
ADMA	Asymmetric dimethyl arginine
BAD	Baseline arterial diameter
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CIMT	Carotid intima-media thickness
EDVR	Endothelium-derived vasodilatory response
FMD	Flow mediated dilatation
GSS	Gensini score
HDL	High density lipoprotein
LDL	Low density lipoprotein
NCA	Normal coronary arteries
NDVR	Nitroglycerine-derived vasodilatory response
NMD	Nitroglycerine, mediated dilatation
NO	Nitric oxide
NOS	NO synthase
SCA	Stable coronary artery
TC	Total cholesterol
TG	Triglyceride
VLDL	Very low density lipoprotein

cholesterol (TC), low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), triglyceride (TG), fasting blood glucose, blood urea nitrogen (BUN), creatinine, complete blood count (CBC), aspartate amino transferase (AST), alanine amino transferase (ALT), gamma glutamyl transferase (GGT), fasting insulin, C peptide and HbA1C levels were analysed on Roche Hitachi Cobas 6000 system (Roche Diagnostics, GmbH, Mannheim, Germany) by enzymatic methods. Measurements of plasma ADMA levels were done by a commercial ELISA reagent set (Immundiagnostik AG, Stubenwald-Allee 8a,D 64625 Bensheim).

### Ultrasonographic measurements

#### Measurement of carotis intima media thickness

CIMT measurements were performed on the subjects lying in supine position with the head in neutral position. Carotid duplex scanning was performed via high-resolution ultrasonography (Vivid 3 or Vivid I, GE Medical Systems, Milwaukee, WI, USA), using 8 MHz linear array transducers. The carotid arteries were scanned in longitudinal projection. Intima media is defined as the distance between the beginning of the tunica intima (far wall) and the beginning of the tunica adventitia. Intima media thickness measurements on the far wall of the common carotid artery were performed bilaterally according to the Mannheim-Consensus-protocol.<sup>[14]</sup> For reproducible measurements, a high-quality image acquisition was used along a minimum length of 10 mm of an arterial segment. The mean CIMT was calculated by three consecutive examinations.

#### Measurement of endothelial function

Subjects were evaluated after an overnight fast, without smoking, drinking alcohol/coffee, or taking vasoactive drugs or antioxidant vitamins 12 hours prior to testing. Subjects were examined in the supine position after 15 minutes of resting in a dark and quiet room with a temperature of 20-25 °C. Endothelium-dependent dilatation of the brachial artery was measured non-invasively by high resolution ultrasonography (General Electric Vivid 3 and Vivid-I), using an 8 MHz linear array transducer. The left arm was immobilized in the extended position to allow consistent access to the brachial artery for imaging. Baseline arterial diameter (BAD) was recorded twice at intervals of 1 minute. Following baseline establishment, a blood

pressure cuff was placed over the ipsilateral upper arm just above the transducer and inflated for 5 minutes at 50 mm Hg greater than systolic blood pressure. The cuff was then deflated suddenly and blood flow velocity measured immediately (hyperemic blood flow) as well as at 60, 75, 90, and 120 seconds later. Maximum brachial artery diameter observed during this time period was used to calculate flow mediated dilatation (FMD). The endothelium-derived vasodilatory response (EDVR) was calculated as follows:

$$\text{EDVR} = [(\text{FMD}-\text{BAD})/\text{BAD}] \times 100.^{[15]}$$

After 10 minutes of rest, endothelium-independent dilatation of brachial artery was measured using nitroglycerine. 4 minutes after sublingual administration of 400 µg glycerol trinitrate nitroglycerine, mediated dilatation (NMD) was measured. Nitroglycerine-derived vasodilatory response (NDVR) was calculated as follows:

$$\text{NDVR} = [(\text{NMD}-\text{BAD})/\text{BAD}] \times 100.^{[15]}$$

### Angiographic evaluation

Angiographic evaluations were done by two experienced cardiologists. The extent and severity of CAD were assessed by the GSS.<sup>[16]</sup> The GSS was calculated by multiplying the severity coefficient assigned to each coronary stenosis according to the degree of luminal narrowing (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively) by the coefficient identified, based on the functional importance of the myocardial area supplied by that segment as follows: Left main coronary artery, 5; proximal segment of left anterior descending coronary artery, 2.5; mid segment of left anterior descending coronary artery, 1.5; apical segment of left anterior descending coronary artery, 1; first diagonal branch, 1; second diagonal branch, 0.5; proximal segment of circumflex artery, 2.5 (if right coronary artery dominance existed 3.5); distal segment of circumflex artery, 1 (if dominant, 2); obtuse marginal branch, 1; posterolateral branch, 0.5; proximal segment of right coronary artery, 1; mid segment of right coronary artery, 1; distal segment of right coronary artery, 1; and posterior descending artery, 1.

### Statistical analysis

In this study, data were expressed as mean±SD for continuous variables, counts and percentages for categorical variables. "Paired Student t" test was used

for comparing continuous variables. The “Oneway Anova” test was used for comparison of categorical variables. Correlations of continuous variables were evaluated using the “Pearson” correlation analysis. Values between 0-0.3 indicated weak, 0.3-0.7 indicated intermediate, 0.7-1.0 indicated strong correlation. A p value <0.05 was considered statistically significant. Statistical analyses were conducted with a commercially available software package (SPSS version 16.0, SPSS, Chichago, IL).

## RESULTS

### Comparison of demographical, clinical and biochemical data

150 patients were enrolled in the study. Clinical and demographical characteristics of ACS, SCA and NCA groups are given in Table 1. The mean age value was significantly higher in the SCA than in the ACS and NCA groups ( $p<0.001$ ). Frequency of most of the

major cardiovascular risk factors (DM, HT, smoking, family history) were significantly higher in the ACS group than in the SCA and NCA groups ( $p=0.03$ ,  $<0.001$ ,  $<0.001$ ,  $0.04$  respectively). Moreover, frequencies of previous MI and CABG were significantly higher in ACS group than in the SCA group ( $p=0.01$ ,  $0.02$  respectively). However, previous PCI % was significantly higher in the SCA group ( $p<0.001$ ). Biochemical parameters of all 3 groups are given in Table 2. TC, LDL, fasting blood glucose, BUN, creatinine, HbA1C values were significantly higher in the ACS and SCA groups than in the NCA group ( $p=0.03$ ,  $<0.001$ ,  $<0.001$ ,  $<0.001$ ,  $<0.001$  respectively). On the other hand, VLDL, HDL, TG, fasting insulin levels were not significantly different in all 3 groups ( $p=0.42$ ,  $0.15$ ,  $0.41$   $0.08$  respectively).

### Relation between GSS, CIMT and endothelial dysfunction

GSS was 75.4 in the ACS group and 54.9 in the SCA

**Table 1. Demographic and clinical characteristics of ACS, SCA and NCA groups**

	ACS			SCA			NCA			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			59.14±3.6			65.43±2.8			54.61±3.4	<0.001
Male/Female	39-78	11-22		32-64	18-36		31-62	19-38		0.16
Mean Height (cm)			171.14±17.2			175.76±14.6			172.22±15.7	0.14
Mean Weight (kg)			79.37±3.6			81.49±2.1			79.26±2.7	0.91
Mean waist circumference (cm)			102.90±31.1			111.29±20.4			105.06±21.8	0.67
Mean waist / Hip ratio	0.89			0.93			0.91			0.59
Mean BMI (kg/m <sup>2</sup> )			28.19±1.4			29.66±0.8			27.73±2.3	0.64
Mean hypertension	46	91.8		35	71.4		23	44.9		<0.001
Mean DM	21	40.8		18	36.7		8	16.3		0.03
Family history	16	30.6		13	26.5		12	24.5		0.04
Smoking	31	61.2		16	32.7		17	34.7		<0.001
HL	33	65.3		38	77.6		17	34.7		<0.001
Alcohol	8	16.3		3	6.1		11	22.4		0.06
Previous CABG	8	16.0		5	9.6		0	0.0		0.02
Previous PCI	9	18.0		11	21.2		0	0.0		<0.001
Previous MI	18	36.0		9	19.2		0	0.0		0.01
Mean Systolic BP (mmHg)			127.60±24.5			127.79±21.6			122.40±22.7	0.21
Mean Diastolic BP (mmHg)			76.10±11.1			75.67±12.5			77.40±13.8	0.69

ACS: Acute coronary syndrome; SCA: Stable coronary artery; NCA: Normal coronary arteries; SD: Standard deviation; BMI: Body mass index; DM: Diabetes mellitus; HL: Hyperlipidemia; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; BP: Blood pressure.

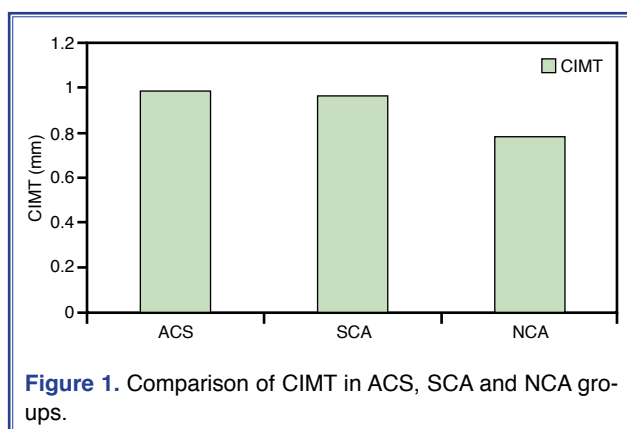


**Table 2.** Comparison of biochemical parameters between ACS, SCA and NCA groups

	ACS	SCA	NCA	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
Total cholesterol (mg/dl)	198.8±40.36	185.48±46.05	176.98±37.88	<b>0.03</b>
Low density lipoprotein (mg/dl)	125.10±31.15	112.96±36.53	103.28±27.96	<b>0.001</b>
Very low density lipoprotein (mg/dl)	30.76±25.32	25.11±18.11	29.10±22.48	0.42
High density lipoprotein (mg/dl)	41.16±13.86	45.21±13.78	46.44±15.01	0.15
Triglyceride (mg/dl)	180.06±132.18	155.17±123.75	149.18±112.53	0.41
Fasting glucose (mg/dl)	123.02±40.37	122.83±54.38	89.06±20.82	<b>0.001</b>
Fasting insulin (microunit/ml)	11.63±8.09	16.16±26.75	8.70±7.09	<b>0.08</b>
C peptide (nanogram/ml)	3.29±1.54	2.76±1.20	2.55±1.61	<b>0.03</b>
Blood urea nitrogen (mg/dl)	19.22±8.27	17.60±6.45	13.56±4.04	<b>0.001</b>
Creatinine (mg/dl)	0.88±0.22	0.86±0.22	0.75±0.16	<b>0.001</b>
Aspartate amino transferase (mg/dl)	45.66±56.05	23.50±10.24	23.08±11.20	<b>0.001</b>
Alanine aminotransferase (mg/dl)	27.74±15.73	23.69±18.99	25.72±22.64	0.57
Gama glutamyl transferase (mg/dl)	34.47±25.73	27.76±41.30	24.10±20.41	0.24
Hematocrit (%)	41.63±5.21	39.51±4.26	42.25±5.17	<b>0.01</b>
Hemoglobin (g/dl)	13.72±1.58	13.18±1.52	13.94±1.62	<b>0.05</b>
HbA1C (mg/dl)	6.10±1.38	6.05±1.49	5.23±0.41	<b>0.001</b>

ACS: Acute coronary syndrome; SCA: Stable coronary artery; NCA: Normal coronary arteries; SD: Standard deviation.

group. The difference between the two groups was statistically significant ( $p<0.001$ ). CIMT was 0.98 mm in the ACS group, 0.96 mm in the SCA group and 0.78 mm in the NCA group. The difference between the ACS and NCA groups was statistically significant ( $p<0.001$ ). Furthermore, there was a statistically significant difference between the SCA and NCA groups. However, the difference between the ACS and SCA groups was not statistically significant ( $p=0.22$ ) (Figure 1).

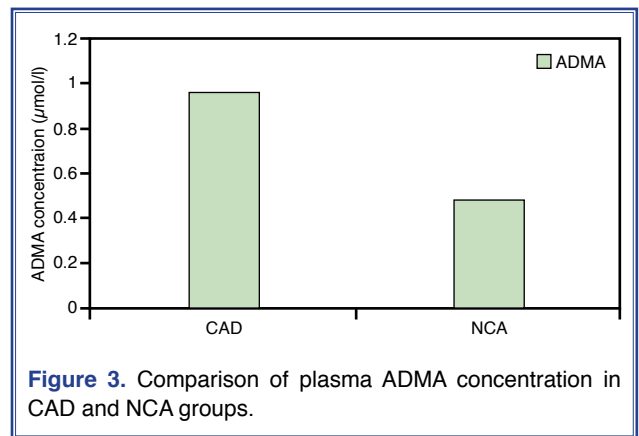
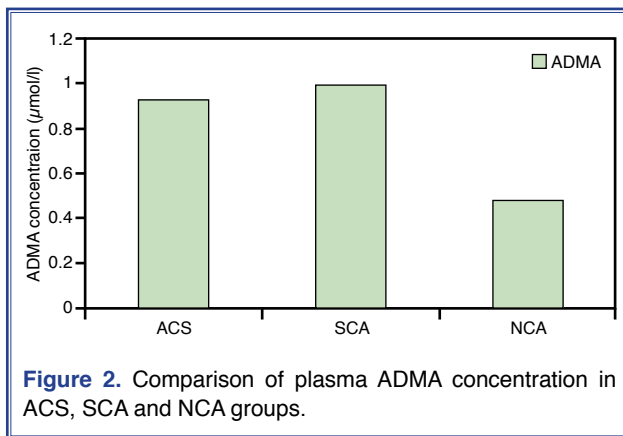


**Figure 1.** Comparison of CIMT in ACS, SCA and NCA groups.

EDVR was  $3.5\pm 2.1\%$  in the ACS group,  $3.3\pm 1.8\%$  in the SCA group and  $7.2\pm 3.5\%$  in the NCA group. EDVR significantly decreased in the ACS and SCA groups compared to the NCA group ( $p<0.001$ ). However, the difference between the ACS and SCA groups was not statistically significant ( $p=0.33$ ). On the other hand, NDVR was  $4.2\pm 1.7\%$  in the ACS group,  $4.5\pm 2.3\%$  in the SCA group and  $8.2\pm 3.7\%$  in the NCA group, indicating that NDVR was also significantly decreased in the ACS and SCA groups compared to the NCA group ( $p<0.001$ ). However, the difference between the ACS and SCA groups was not statistically significant ( $p=0.43$ ).

### Biochemical parameters

Mean plasma ADMA concentration was  $0.928\ \mu\text{mol/l}$  in the ACS group,  $0.992\ \mu\text{mol/l}$  in the SCA group and  $0.475\ \mu\text{mol/l}$  in the NCA group, being significantly increased in the ACS and SCA groups compared to the NCA group ( $p<0.001$ ) (Figure 2). When the ACS and SCA groups were joined together to form the CAD group, mean plasma ADMA concentration was  $0.960\ \mu\text{mol/l}$  and significantly higher than that of the NCA group ( $p=0.018$ ) (Figure 3). On the other hand,



the difference between the ACS and SCA groups was not statistically significant ( $p=0.31$ ).

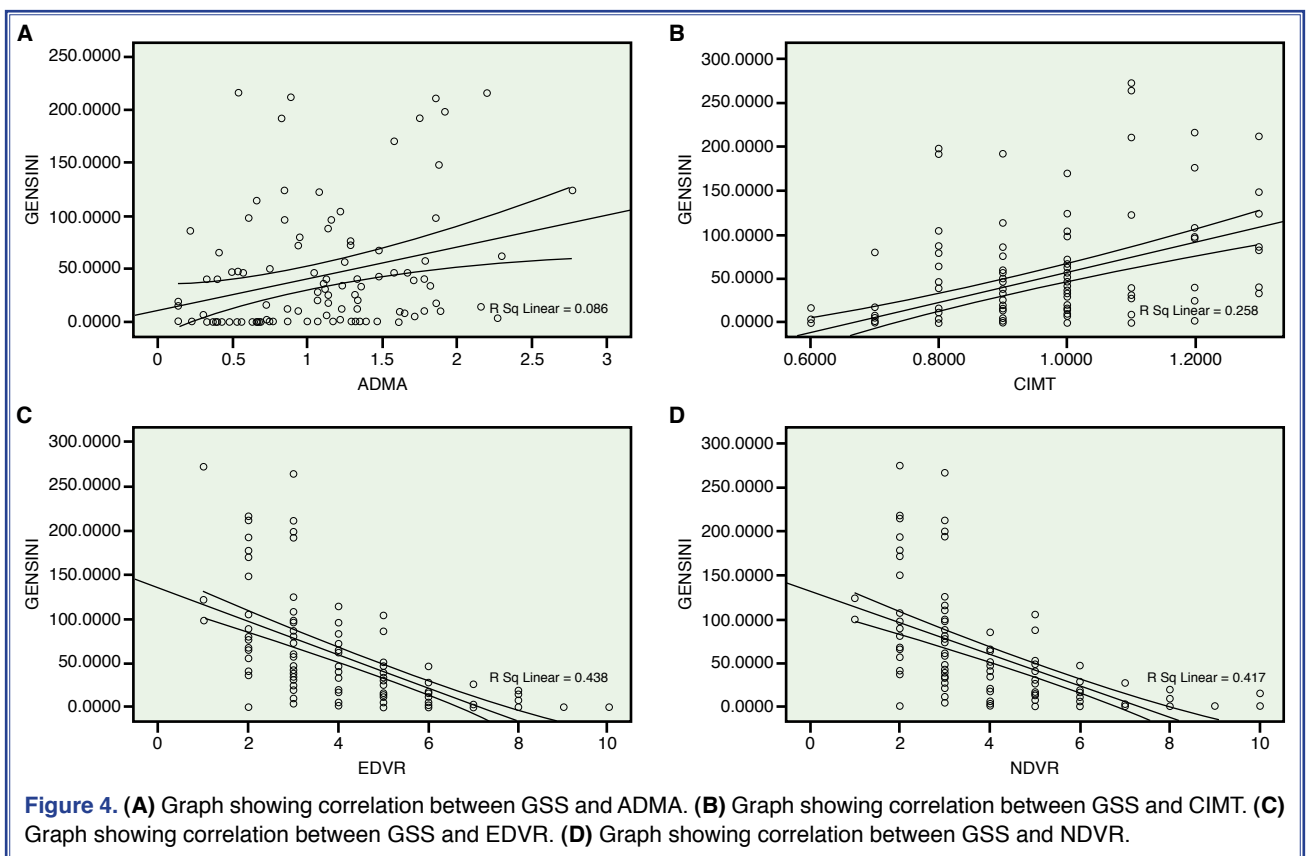
### Correlation analysis

Correlation analysis showed a weak positive correlation between GSS and plasma ADMA levels ( $r=0.293$ ;  $p=0.002$ , Figure 4a). There was an intermediate positive correlation between GSS and CIMT ( $r=0.508$ ;  $p<0.001$  Figure 4b). There were intermediate negative correlations between GSS and EDVR ( $r=-0.662$ ;

$p<0.001$ , Figure 4c) and NDVR ( $r=-0.646$ ;  $p<0.001$  Figure 4d).

### DISCUSSION

The main findings of our study were as follows: 1. GSS was significantly higher in the ACS group than in the SCA group; 2. GSS was significantly positively correlated with CIMT and ADMA levels, and negatively correlated with EDVR and NDVR; 3. ADMA



and CIMT were significantly higher in the SCA and ACS groups than NCA group. However, there was no significant difference between the ACS and SCA groups. 4. Endothelial function was significantly better in the NCA group than in the SCA and ACS groups. Difference between the ACS and SCA groups was not statistically significant.

It is known that atherosclerotic burden in CAD is independently associated with increased mortality.<sup>[17]</sup> Coronary scoring systems quantify severity of the coronary stenosis. There are various systems (Leaman score,<sup>[18]</sup> Gensini score,<sup>[19]</sup> American College of Cardiology/American Heart Association (ACC/AHA) score,<sup>[20]</sup> Bogaty score<sup>[21]</sup> etc.) which have been established to assess atherosclerotic burden, extent of atherosclerosis and also to provide prognostic information.<sup>[22,23]</sup> GSS was absolutely high in both the SCA and the ACS patients. There have been studies done showing the relationship between various parameters like serum uric acid level, N-Terminal pro-Brain natriuretic peptide level and GSS in ACS patients.<sup>[24,25]</sup> However, there is hardly any literature available comparing GSS between ACS and SCA patients. In this study, we showed that GSS was significantly higher in the ACS group than in the SCA group. Inflammation and oxidative stress play key roles in atherosclerotic plaque rupture and subsequent thrombus formation that constitute the principal mechanism of total vessel occlusion and ACS. Although historical data report that the majority of MI occur at locations of noncritical luminal stenosis,<sup>[26,27]</sup> recent studies suggest that atherosclerotic plaques causing hemodynamically significant coronary stenosis are more likely to cause MI.<sup>[28-30]</sup> This data could explain the high atherosclerotic burden in both SCA and ACS groups. As we all know, ACS is the result of total or nearly total coronary occlusions. Although SCA patients could also have high atherosclerotic burden, luminal stenosis severity differs between SCA and ACS groups. The most effective variable of GSS is luminal stenosis severity. As a result GSS, could be expected to be higher in ACS patients. To the best of our knowledge, the present study is the first to demonstrate significantly higher GSS in ACS patients compared to SCA patients.

It is known that plasma ADMA level is strongly associated with atherosclerosis. Lu et al. showed that plasma ADMA level was useful in predicting the pres-

ence of significant CAD, and suggested that plasma ADMA level may be a novel marker for CAD.<sup>[31]</sup> Song et al. also suggested that plasma ADMA levels were significantly correlated with the severity of coronary atherosclerosis.<sup>[32]</sup> Wilson et al. showed that ADMA levels correlate with disease severity and major adverse cardiovascular events in atherosclerotic peripheral arterial disease.<sup>[33]</sup> Kruszelnicka et al. showed that ADMA was not only associated with diffuse atherosclerosis in non-diabetic men, but also that an independent relationship between ADMA and coronary atherosclerotic burden may contribute to the well-recognized prognostic effect of ADMA in CAD.<sup>[34]</sup> Intima media thickness is a well-studied parameter which could be measured from various arteries. Femoral artery intima media thickness is known to be correlated with GSS.<sup>[35]</sup> Sillesen et al. showed that carotid plaque burden and CIMT is a measure of subclinical atherosclerosis.<sup>[36]</sup> Korkmaz et al. showed that higher atherosclerotic burden detected with syntax score is correlated with increased CIMT.<sup>[37]</sup> Furthermore, Sarikaya et al. postulated that mean CIMT was positively correlated with GSS.<sup>[38]</sup> Although CIMT measurements are increasingly being used, there are still no accepted standards on their use in various research areas. Hence, choices in the design and analysis of a CIMT study are generally based on experience and expert opinion rather than on solid evidence.<sup>[39]</sup> Nevertheless, the majority of the published data revealed a relationship between coronary atherosclerosis and CIMT.<sup>[40]</sup> A modest relation between CIMT and atherosclerosis most likely reflects variability in atherosclerosis development between different vascular beds rather than limitations of CIMT measurements.<sup>[40]</sup> Our results were well-correlated with the previous data. On the other hand, neither CIMT nor plasma ADMA level were significantly different between SCA and ACS groups. This could be because of the similar atherosclerotic burden in both groups, as previously mentioned. To our knowledge, this is the first study comparing plasma ADMA level and CIMT between SCA and ACS groups.

Endothelial dysfunction is the key element for atherosclerosis, and can be seen in the first stage of the atherosclerotic process. Manganaro et al. confirmed that FMD was reduced in patients with CAD and this reduction was related to the extent of the disease.<sup>[41]</sup> Kopeć et al. suggested that endothelial function may influence the progression of atherosclerosis.<sup>[42]</sup> Kalay

et al. showed that there was a relationship between FMD, CIMT and GSS in ACS patients.<sup>[43]</sup> In our study, we also detected significant correlation between GSS and endothelial function calculated with EDVR and NDVR.

## Conclusion

This study concluded that CIMT, ADMA concentration and endothelial dysfunction were significantly associated with CAD and correlated with atherosclerotic burden. However, only GSS was significantly different between SCA and ACS groups. Consequently, we suggest GSS may prove to be a useful parameter to distinguish between SCA and ACS patients. Additional research is definitely needed to further elucidate the clinical implications of these findings.

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

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**Key words:** Acute coronary syndrome; asymmetric dimethylarginine; carotid intima-media thickness; coronary artery disease; endothelium.

**Anahtar sözcükler:** Akut koroner sendrom; asimetric dimetil arjinin; korotis intima media kalınlığı; koroner arter hastalığı; endotel.