Could plasma asymmetric dimethylarginine level be a novel predictor beyond the classic predictors of stent restenosis?

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ABSTRACT

Objective: The aim of this study was to investigate the factors associated with coronary stent restenosis and if there is an association between plasma asymmetric dimethylarginine (ADMA) levels and stent restenosis.

Methods: Ninety-one patients, who had a history of coronary bare metal stent implantation due to any cause in the last one year period, were admitted to this observational cross-sectional study. Coronary angiography was performed to all patients and quantitative angiography was used to determine the presence of stent restenosis. Laboratory parameters and angiographic features that contribute to stent restenosis were evaluated. Plasma ADMA levels were measured by using high performance liquid chromatography. Logistic regression analysis was used to determine the independent factors of stent restenosis.

Results: Angiographic restenosis was found in 35 patients (38.5%). Stent diameter (p=0.038) and left ventricular ejection fraction (p=0.023) were lower and stent implantation history due to acute coronary syndrome (p=0.029), plasma ADMA level ($5.0\pm1.8x10^{-4}$ mmol/L vs. $3.9\pm1.0x10^{-4}$ mmol/L, p=0.001), C-reactive protein concentration (p=0.016), white blood cell count (p=0.044) and stent length (p=0.005) were higher in patients with restenosis. Plasma ADMA level (β=0.536; OR: 1.710; CI: 1.022-2.861; p=0.041), C-reactive protein concentration (β=0.062; OR: 1.064; CI: 1.003-1.129; p=0.041), stent diameter (β=-3.047; OR: 0.048; CI: 0.007-0.313; p=0.002) and length (β=0.165; OR: 1.179; CI: 1.036-1.343; p=0.013) were found to be the independent predictors of stent restenosis in logistic regression analysis.

Conclusion: We conclude that plasma ADMA levels may be used as a novel marker for stent restenosis beyond the classic stent restenosis markers. *(Anadolu Kardiyol Derg 2014; 14: 491-7)*

Key words: stent, restenosis, plasma asymmetric dimethylarginine

Introduction

In recent years, stents are widely used for the treatment of coronary artery disease. During the wide spread usage of coronary stent implantation, stent restenosis was found to be the major problem related to this intervention. Neointimal hyperplasia composed of vascular smooth muscle cells and the matrix is the mainstay of stent restenosis (1). Nitric oxide (NO) was converted from L-arginine by nitric oxide synthase (NOS) and released from intact endothelium (2, 3). Nitric oxide inhibits vascular smooth muscle cell proliferation and prevents neointimal hyperplasia. Thanyasiri et al. (4) showed that endothelium-dependent coronary artery dilatation was reduced in subjects with restenosis after percutaneous coronary intervention. It has also been shown that the NO prevents the development of restenosis after percutaneous transluminal coronary angioplasty (PTCA) by inhibiting the formation of mitogenic substances resulted from injured endothelial tissue and the adhesion of leukocyte and thrombocytes (5, 6). Asymmetric dimethylarginine (ADMA) is a potent competitive inhibitor of NOS and occurs during protein degradation of arginine residues (7, 8). As a result of NOS inhibition by ADMA, NO formation and therefore its protective effects against the stent restenosis diminishes.

Many factors contribute to stent restenosis. Stent diameter and length were well known predictors for stent restenosis but there is not enough knowledge about ADMA and its role on stent restenosis. In recent years few studies reveal a link between ADMA and stent restenosis due to its role on NO formation (9-11). Derkacz et al. (9) concluded that pre-procedural elevated plasma ADMA levels increases the risk of restenosis in patients

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who underwent coronary angioplasty and stenting with bare metal stents. Khalifa et al. (10) found that the patients who developed stent restenosis had an increase in ADMA levels following coronary stenting. Arı et al. (11) found that the plasma levels of ADMA obtained before the procedure predict the development of restenosis and major adverse cardiac events in patients who underwent elective percutaneous transluminal coronary angioplasty and bare metal stent procedures. All of these studies attempted to evaluate the predictive value of ADMA on stent restenosis but more data is still needed in this regard. The aim of this study was to investigate the factors associated with coronary stent restenosis and also decide to evaluate the association between ADMA levels and stent restenosis on the patients with coronary stent and who need a diagnostic coronary angiography due to symptoms or high risk positive stress tests or laboratory parameters.

Methods

This study was designed as an observational cross-sectional study and has been approved by the Başkent University Ethical Committee. The patients who were admitted to our emergency service or outpatient clinics with a history of coronary bare metal stent implantation in the last one year period were evaluated for the study participation. Exclusion criteria were defined as chronic renal failure, chronic liver disease, cerebrovascular event in the last year, severe peripheral arterial disease, uncontrolled diabetes mellitus (HbA1c >%7), uncontrolled hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg regardless of hypertension status or preexisting antihypertensive medication use) (12), clinical hyperthyroidism, erectile dysfunction and pulmonary hypertension (mean pulmonary arterial pressure >30 mm Hg). Patients with drug eluting stents (DES) were also excluded because DES have different mechanisms of restenosis and might be seen after a long time period (delayed restenosis). Ninety-one patients with recurrent angina pectoris under optimal medication or high risk positive stress tests or acute coronary syndrome were enrolled to the study. All patients were informed about the study protocol and written informed consent was obtained.

The demographic characteristics, cardiovascular risk factors and the medication history of the patients were recorded and all underwent an extensive physical examination. Patients with two consecutive fasting serum glucose measurements > 126 mg/dL (13) or those on oral antidiabetic drug and/or insulin were diagnosed as diabetic. Hypertensive patients with the systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg on physical examination under drug therapy were diagnosed as controlled hypertensive. Hyperlipidemia was defined as LDL cholesterol >100 mg/dL, HDL cholesterol <40 mg/dL or triglyceride >150 mg/dL or usage of lipid lowering drug therapy (14). Body mass index (BMI) was calculated by division of weight to height's square (kg/m^2) and patients with BMI >30 kg/m^2 were diagnosed as obese (15).

Serum levels of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, glucose, creatinine, C-reactive protein and hemogram were determined by using commercial tests (Belliver Industrial Estate, Plymouth, UK) after 8 hours of fasting period.

Percutaneous coronary intervention views and reports of the patients were analyzed cautiously by one experienced cardiologist and the factors (predilatation, stent diameter, stent length, oversizing, undersizing, residue stenosis) that might contribute to stent restenosis were noted.

Electrocardiography and echocardiography were performed to all patients. Especially left ventricle ejection fraction, left ventricle hypertrophy and pulmonary blood pressures were calculated cautiously by one experienced echocardiographer.

After these steps, an elective coronary angiography was assessed for the patients. Blood samples (10 mL) were collected into the ethylenediaminetetraacetic acid containing tubes from femoral arterial sheath before coronary angiography was performed. Whole blood samples were centrifuged immediately in biochemistry laboratory at 3000 g for 10 minutes. Each plasma samples were put into two Eppendorf tubes (Labor Teknik, İstanbul, Turkey) by using a plastic pipe and stored in a deep freezer at -80 degree (Celsius) until analysis. One of the plasma samples was analyzed in biochemistry laboratory and the other sample was stored in the freezer for the backup.

Coronary angiographic examination was performed after local anesthesia by employing the modified Seldinger technique through the femoral artery. All coronary arteries were visualized at right and left anterior oblique projections with caudal and cranial angulations and left lateral projection (Philips, Artis zee, Munich, Germany). Left ventriculography was also performed at right and left anterior oblique projections. Iohexol was used in coronary angiography and left ventriculography as the contrast agent. Coronary angiography views were assessed by two experienced cardiologists who had no knowledge about the patients' clinical demographics and laboratory parameters. The degree of coronary stenosis was determined at the projection which shows the stenosis more severe. Quantitative coronary angiography was used to determine the severity of stenosis and angiographic restenosis is defined as ≥50% luminal narrowing (16).

Plasma ADMA levels were analyzed by using high performance liquid chromatography (HPLC). The method includes reversed-phase HPLC analysis by using fluorescence detection (Shimadzu LC 10A fluorescent detector, Japan) in a high-performance liquid chromatography system (Shimadzu RF 10XL, Japan). The plasma concentrations of ADMA were measured by HPLC with precolumn derivatization with o-phthaldialdehyde (OPA) and 3-mercaptopropionic acid. Samples and standards were incubated with OPA reagent for exactly 30 s before injection into the HPLC system (17).

Statistical analysis

Statistical analyses were performed by using the statistical program for the social sciences (SPSS) version 15.0 (Chicago, IL,

USA). Data were submitted to a frequency distribution analysis by Kolmogorov-Smirnov's test. Values displaying normal distribution were expressed as the mean (standard deviation; SD) and values with skewed distribution were expressed as median (interquartile range). While comparing parametric variables 'Independent Samples T' test and in nonparametric variables 'Mann-Whitney U' test were used. Categorical variables were compared using chi-square tests, or if small expected cell frequencies, exact tests. To determine the independent factors of stent restenosis, "Logistic Regression Analysis" method was used for significant variables which were found in binary comparisons. The p values less than 0.05 were accepted as statistically significant.

Results

The patients who had a history of coronary stent implantation within one year (9.0±1.7 months) and planned to undergo an elective coronary angiography in our center were evaluated for study participation. 91 patients, 72 (79.1%) men, 19 women (20.9%) and mean age 58.96±8.72 years were included in the study. 32 patients were diabetic (35.2%), 62 (68.1%) had hypertension and 77 (84.6%) had hyperlipidemia. Out of 91 patients, 35 had an established stent restenosis after coronary angiography. The time period after stent implantation to coronary angiography had a mean 8.7±1.8 months in patients with stent restenosis.

1. Clinical characteristics/ Laboratory parameters and stent restenosis:

When we compared the clinical characteristics of the patients, only the incidence of stent implantation due to acute coronary syndrome was significantly higher in the patients with restenosis than the patients without restenosis (77.1% vs. 55.4%; p=0.029, respectively). There were no association between age and plasma ADMA levels (p=0.524 for women and p=0.260 for men). There was no significant difference between two groups according to the usage of medications and also between plasma ADMA levels and the type of medication (all p values >0.05).

Among the laboratory parameters studied, patients with restenosis has significantly higher plasma ADMA levels than the patients without restenosis (5.1±1.8x10^{-4} mmol/L vs. 3.9±1.0x 10^{-4} mmol/L; p=0.001) (Fig. 1). Also serum C-reactive protein levels [6.0 (11.1) mg/L vs. 1.9 (3.0) mg/L; p=0.016] and white blood cell count (8.036±1.964×10^3/μL vs. 7.238±1.530×10^3/μL; p=0.044) were higher and left ventricle ejection fraction was lower (49.6±10.4% vs. 54.1±8.2%; p=0.023) in the patients with restenosis than the patients without restenosis. All the clinical characteristics and laboratory parameters of patients with and without stent restenosis were summarized in Table 1.

2. Relationship between plasma ADMA levels and clinical characteristics/Laboratory parameters:

There was no significant relationship between plasma ADMA levels and clinical characteristics. But plasma ADMA levels tended to be higher in diabetic patients (n=32) compared

Table 1. Clinical characteristics and laboratory parameters of patients with and without stent restenosis

Clinical characteristics	Restenosis (+) n=35	Restenosis (-) n=56	*P*
Age, years	57.5±7.2	59.8±9.5	0.139
Gender, male, (%)	30 (85.7)	42 (75.0)	0.169
Diabetes mellitus, (%)	13 (37.1)	19 (33.9)	0.463
Hypertension, (%)	22 (62.9)	40 (71.4)	0.266
Hyperlipidemia, (%)	31 (88.6)	46 (82.1)	0.304
Smoking, (%)	19 (54.3)	30 (53.6)	0.560
Alcohol consumption, (%)	1 (2.9)	4 (7.1)	0.359
Family history of CAD, (%)	16 (45.7)	27 (48.2)	0.494
History of PAD, (%)	2 (5.7)	0 (0.0)	0.145
Presentation with ACS before stent implantation, (%)	27 (77.1)	31 (55.4)	0.029
BMI > 30 kg/m^2, (%)	6 (17.1)	13 (23.2)	0.338
Medications			
Acetylsalicylic acid, (%)	32 (91.4)	48 (85.7)	0.416
Beta blockers, (%)	26 (74.2)	45 (80.3)	0.496
ACEI/ARB, (%)	25 (71.4)	39 (69.6)	0.856
Calcium canal blockers, (%)	9 (25.7)	17 (30.3)	0.633
Statins, (%)	27 (77.1)	45 (80.3)	0.714
Nitrates, (%)	14 (40.0)	22 (39.3)	0.946
Laboratory parameters			
Plasma ADMA, 10^{-4} mmol/L	5.1±1.8	3.9±1.0	0.001
Serum CRP, mg/L*	6.0 (11.1)	1.9 (3.0)	0.016
Serum glucose, mg/dL*	111.74 (38)	107.16 (17)	0.394
Serum HbA1c, %**	6.8±1.0	6.3±0.9	0.208
Serum creatinine, mg/dL*	1.00 (0.2)	0.93 (0.2)	0.06
Serum HDL cholesterol, mg/dL	40.1±11.0	43.3±8.5	0.139
Serum LDL cholesterol, mg/dL	101.2±25.3	91.6±25.8	0.088
Serum triglyceride, mg/dL	161.3±50.0	141.4±68.0	0.141
Serum AST, U/L	24±10	23±9	0.770
Serum ALT, U/L	28±17	24±11	0.217
Serum ALP, U/L	169±41	148±57	0.273
Serum GGT, U/L	35±20	26±13	0.078
Hemoglobin, g/dL	14.2±1.5	14.2±1.3	0.872
White blood cell, ×10^3/μL	8.036±1.964	7.238±1.530	0.044
Platelet, ×10^3/μL	242±54	241±86	0.982
Left ventricle EF, %	49.6±10.4	54.1±8.2	0.023

ACS - acute coronary syndrome; ADMA - asymmetric dimethylarginine; ALP - alkaline phosphatase; ALT - alanine aminotransferase; AST - aspartate aminotransferase; BMI - body mass index; BUN - blood urea nitrogen; CAD - coronary artery disease; CRP - C-reactive protein; EF - ejection fraction; GGT - gamma-glutamyl transferase; HDL - high density lipoprotein; LDL - low density lipoprotein; PAD - peripheral artery disease
Parametric; value given as mean±standard deviation
*Non-parametric; value given as median (interquartile range)
**Data for diabetic patients

Table 2. Properties of stent and stent implantation procedure in patients with and without stent restenosis

	Restenosis (+) n=35	Restenosis (-) n=56	*P*
Predilatation, %	24 (67.4)	26 (47.8)	0.025
Stent diameter, mm	2.81±0.33	3.00±0.39	0.018
Stent length, mm	16.05±5.14	14.27±4.13	0.047
Stent oversizing, %	2 (5.7)	4 (7.14)	0.366
Stent undersizing, %	3 (8.5)	4 (7.14)	0.404
Residual stenosis after PCI, %	1 (2.8)	3 (5.3)	0.260

PCI - percutaneous coronary intervention
Parametric; value given as mean±standard deviation

Table 3. Independent predictors of stent restenosis

	β	Odds ratio (OR)	*P*	Confidence interval (CI)
Plasma ADMA	0.536	1.710	0.041	1.022-2.861
CRP	0.062	1.064	0.041	1.003-1.129
EF	-0.064	0.938	0.065	0.877-1.004
Stent diameter	-3.047	0.048	0.002	0.007-0.313
Stent lenght	0.165	1.179	0.013	1.036-1.343

ADMA - asymmetric dimethylarginine; CRP - C-reactive protein; EF - ejection fraction
Binary logistic regression analysis was used and Odd's ratios and 95% confidence intervals were calculated for the risk factors of stent restenosis

to nondiabetics (p=0.068) (Fig. 2). Also in hyperlipidemic patients a tendency for higher plasma ADMA levels were observed compared to patients with normal lipid levels (p=0.053).

3. Stent /implantation procedure properties and stent restenosis:

When we consider the properties of stent and the implantation procedure, we found that the stent length (16.05±5.14 mm vs. 14.27±4.13 mm; p=0.047) was significantly higher and the stent diameter (2.81±0.33 mm vs. 3.00±0.39 mm; p=0.018) was significantly lower in patients with stent restenosis. Predilatation history before stent implantation (67.4% vs. 47.8%; p=0.025) was also significantly higher in the patients with stent restenosis. The other properties of stent and implantation procedure were not significantly different between the patients with or without stent restenosis (Table 2).

4. Independent predictors of stent restenosis

Logistic regression analysis was used to determine the independent predictors for the development of stent restenosis. The variables (plasma ADMA levels, CRP, white blood cell count, left ventricle ejection fraction, acute coronary syndrome clinic before stent implantation, stent diameter, stent length and predilatation before stent implantation) which were significantly ($p<0.05$) different in patients with or without stent restenosis were evaluated by using backward elimination method. Plasma ADMA levels (β=0.536; OR: 1.710; CI: 1.022-2.861; p=0.041), CRP (β=0.062; OR: 1.064; CI: 1.003-1.129; p=0.041), stent diameter (β=-3.047; OR: 0.048; CI: 0.007-0.313; p=0.002) and length (β=0.165; OR: 1.179; CI: 1.036-1.343; p=0.013) were found to be the independent predictors of stent restenosis in logistic regression analysis (Table 3).

Discussion

In our study we found higher plasma ADMA levels in patients with stent restenosis than without stent restenosis and stent diameter, stent length, CRP and ADMA were the independent predictor of stent restenosis. Our results indicate that plasma ADMA levels may be used to predict the development of stent restenosis.

Restenosis is the most important problem that limits the success of percutaneous coronary revascularization interventions in the long term. In 1980s, the high ratio of restenosis after balloon angioplasty declined to 20-30% with the usage of bare metal stents and to 8-15% with the drug eluting stents in 2000s (18, 19).

Very complex molecular and cellular mechanisms play role in stent restenosis. Different growth factors/receptors, cytokines, secondary messengers and proto-oncogenes mediate this process (20). Most important mechanism in the development of stent restenosis is neointimal hyperplasia. Since stent implantation inhibits elastic recoil and negative remodeling by its mechanical effect, stent restenosis develops mainly by neointimal hyperplasia (1, 21). The development rate of neointimal hyperplasia is higher in the first six months and continues in a lower rate for 3 years after stent implantation. Neointima basically contains proliferated smooth muscle cells and extracellular matrix (22, 23).

Nitric oxide is a potent vasodilator which converted from its precursor L-arginine by NOS and it released by intact endothelium. Behind the potent vasodilator effect, NO also protects the healthy vessels against atherosclerosis and restenosis. This effect achieved by inhibition of smooth muscle cells' migration and proliferation. Nitric oxide also inhibits leukocytes and platelets' adhesion, aggregation and reconstruction attend to thrombosis (2, 5, 24, 25).

After an injury on the vessel wall NO synthesis and its protecting effect against the restenosis decreases because of endothelial dysfunction. Lee et al. (26) showed that NO inhalation decreases neointimal hyperplasia by 50% after angioplasty in rat vessels. Do et al. (27) reported that intima-media ratio was 32-46% less with NO releasing stent implantation than bare metal stent on rabbit aorta. In a human study Suziki et al. (28) found that intramural L-arginine implementation after stent implantation decreases neointimal volume by 35% at the end of six months. As a result, all these studies show the effects of NO against the development of restenosis.

At 1992, ADMA was discovered as an endogenous inhibitor of NOS and was thought to have an effect on the dysfunction of L-arginine/nitric oxide pathway (29). Asymmetric dimethylarginine inhibits NO production and high levels of ADMA causes superoxide radicals' production instead of NO by endothelial NOS (30).

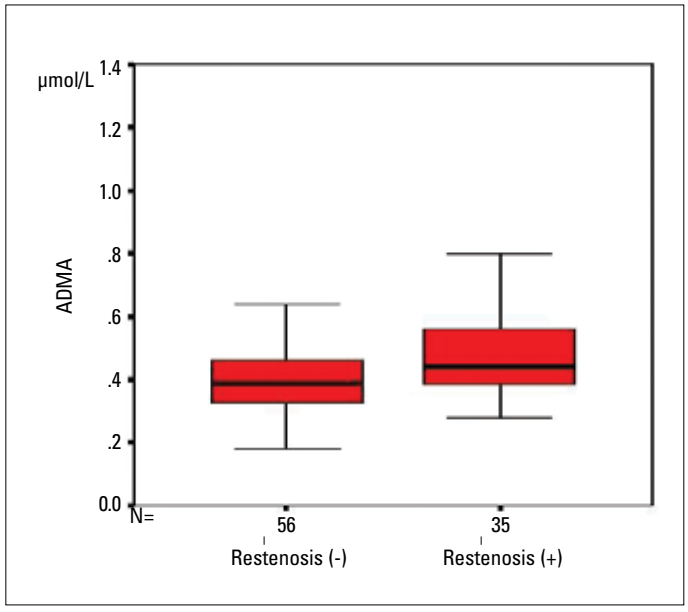

Figure 1. Plasma asymmetric dimethylarginine in restenotic and non-restenotic patients
ADMA - asymmetric dimethylarginine

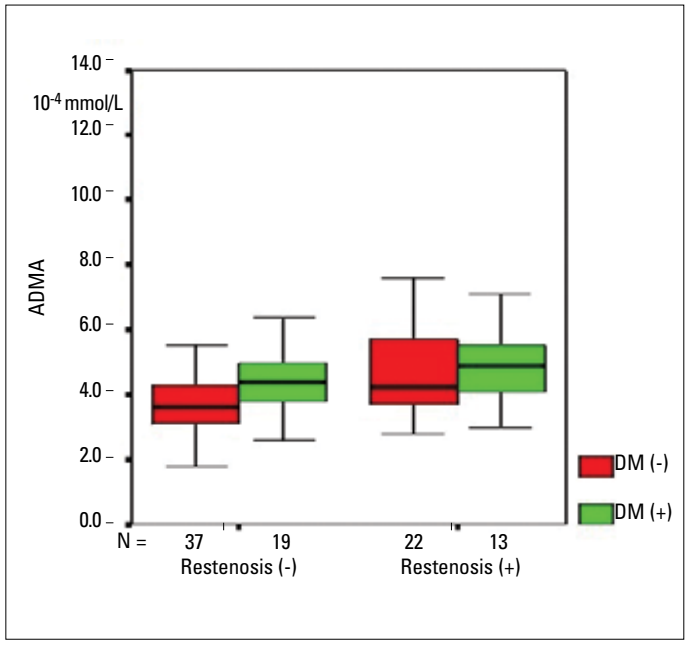

Figure 2. Plasma asymmetric dimethylarginine in diabetic and non-diabetic patients
ADMA - asymmetric dimethylarginine; DM - diabetes mellitus

In our study we want to search 'if there is any role of ADMA on stent restenosis beyond the classic stent restenosis markers'. We thought that if ADMA inhibits NO synthesis, also it decreases the inhibiting effects of NO on the development of stent restenosis. So we admitted the patients who had a history of stent implantation in the past year and had a clinical indication for coronary angiography to our study. We measured plasma ADMA levels in those patients and compared them with the clinical characteristics and the angiographic features.

When the clinical characteristics are considered, the key point for the development of restenosis is whether the patient's clinic at the time of stent implantation was acute coronary syndrome or not. Cutlip et al. (18) studied 6.186 patients (6.219 lesions) pooled from several recently completed coronary stent trials and unstable angina was marked as an independent predictor of stent restenosis. Similar to these findings we found significantly higher rates of stent restenosis in patients with acute coronary syndrome presentation at the time of stent implantation.

Controversial data are displayed in literature on the relationship between ADMA and diabetes mellitus. Most of the studies reported that plasma ADMA levels were higher in patients with type II diabetes mellitus but not higher in patients with type I diabetes mellitus (31). In our study, all diabetic patients had type II diabetes mellitus. Similar to literature we found a tendency for higher plasma ADMA levels in patients with diabetes mellitus compared to nondiabetic patients.

In literature there are many studies which support the presence of an inflammatory response against the stents after stent implantation. Almagor et al. (32) showed an inflammatory response with high CRP levels after stent implantation to patients who have stable angina pectoris. Xu et al. (33) also found that the CRP levels at both pre-percutaneous coronary intervention and follow-up were significantly correlated with stent restenosis. In our study, when we evaluated the laboratory parameters of the patients, we found significantly higher serum CRP levels and white blood cell count in the patients with restenosis. In a prospective study Kozinski et al. (34) highlighted that inflammatory response and elevated CRP levels were more prominent in the patients with stent restenosis and it is similar to our findings.

In a prospective study done by Derkacz et al. (9) it has been demonstrated that pre-procedural elevated plasma ADMA levels increased the risk of restenosis in patients who underwent coronary angioplasty and stenting with bare metal stents. In our study we did not analyzed the plasma ADMA levels before stenting. We analyzed the plasma ADMA levels at the time of control angiography and found higher plasma ADMA levels in patients with stent restenosis after restenosis developed. Khalifa et al. (10) found that the patients who developed stent restenosis had a 35% increase in ADMA levels following coronary stenting. This finding is similar to our study but they have enrolled 37 patients in that study. In our study we have enrolled 91 patients and this is statistically more powerful. Also Arı et al. (11) found that the plasma levels of ADMA obtained before the procedure predict the development of restenosis and major adverse cardiac events in patients who underwent elective percutaneous transluminal coronary angioplasty and bare metal stent procedures. The results of this study were also in parallel with our findings.

Study limitations

Coronary angiography was not routinely performed to every patient after stent implantation as control angiography. We per-

formed control angiography to patients presenting with recurrent angina pectoris under optimal medication or high risk positive stress tests or acute coronary syndrome. So the rate of stent restenosis was found to be higher in the present study than general population.

Measurement of NO and arginine levels might improve the results of this study but we were not able to measure these parameters.

Fractional flow reserve might be better to define the stent restenosis than quantitative angiography. But it was not feasible to every restenotic patient in our country.

Conclusion

We conclude that plasma ADMA levels can be used as a novel marker for stent restenosis beyond the classic stent restenosis markers. By reducing plasma ADMA levels or by increasing NO synthesis, the development of stent restenosis may be prevented. Nevertheless, large randomized and controlled trials are needed to further clarify the effect of ADMA on the development of stent restenosis.

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