Association Between Asymmetric Dimethylarginine and the Severity of Coronary Artery Disease in Patients with Chronic Kidney Disease

Kronik Böbrek Yetmezliği Hastalarında Koroner Arter Hastalığı Ciddiyeti ile "Asymmetrical Dimethylarginine" Arasındaki İlişki

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ABSTRACT

OBJECTIVE: Cardiovascular diseases are the most common cause of death in patients with end-stage renal disease. Asymmetrical dimethylarginine (ADMA) is increased in conditions associated with increased risk of atherosclerosis. We aimed to examine the association between severity of coronary stenosis and the ADMA levels in a group of chronic kidney disease (CKD) stage 1 to 3.

MATERIAL and METHODS: Eighty-eight (88) consecutive patients with decreased renal function (glomerular filtration rate (GFR) between 90 and 30 ml/min), undergoing cardiac catheterization for proven or clinically suspected coronary artery disease were enrolled at the study. Serum levels of creatinine, ADMA, nitric oxide (NO), calcium, phosphate, total cholesterol, HDL and LDL fractions, triglycerides were determined using measurement techniques. The Gensini scoring system was used for the detection of the severity of coronary atherosclerosis.

RESULTS: The mean serum values were 81.48 ± 13.8 micromol/l for ADMA and 3.7 ± 1.7 mmol/L for NO. The mean Gensini score in the study group was 30.4 ± 40.1. All patients were classified into tertiles of Gensini score level. Patients in the highest tertile had statistically significantly lower GFR values. The ADMA values increased statistically significantly in the third tertile compared with the first tertile. The Gensini score values significantly correlated in univariate analysis with the GFR, ADMA and presence of hypertension. In a multivariate regression model, ADMA was the only statistically significant independent predictor of Gensini score.

CONCLUSION: ADMA appears to be one of the strongest risk markers for atherosclerosis in patients with mild and moderate CKD.

KEY WORDS: Asymmetrical dimethylarginine, Chronic kidney disease, Coronary artery disease, Gensini score

ÖZ

AMAÇ: Son dönem böbrek yetmezliği hastalarında en genel ölüm sebebi kardiyovasküler hastalıklardır. Asymmetrical dimethylarginine (ADMA) aterosklerozis riskinin artması ile ilişkili durumlarda artmaktadır. Bu çalışmada amaç, kronik böbrek yetmezliği evre 1-3 grubunda, koroner arter darlığı ciddiyeti ile ADMA düzeyleri arasındaki ilişkiyi saptamaktır.

GEREÇ ve YÖNTEMLER: Böbrek işlevleri azalmış, klinik koroner arter hastalığı kuşkusu veya kanıtlanmış koroner arter hastalığı ile koroner anjiyografi yapılan 88 hasta çalışmaya alındı. Serum kreatinin, ADMA, nitrik oksit (NO), kalsiyum, fosfat, total kolesterol, HDL, LDL fraksiyonları ve trigliserid düzeyleri ölçüldü. Koroner aterosklerozis ciddiyetini belirlemek için Gensini skorlama sistemi kullanıldı.

BULGULAR: Ortalama serum düzeyleri ADMA için 81.48±13.8 micromol/l, NO için 3.7±1.7 milimol/L ölçüldü. Bu çalışmada ortalama Gensini skoru olarak 30.4±40.1. saptandı. Tüm hastalar Gensini skoruna göre üç gruba ayrıldı. En yüksek gruptaki hastaların glomerüler filtrasyon hızı (GFR) düzeyleri istatiksel olarak anlamlı derecede düşük saptandı. İlk grupla karşılaştırıldığında üçüncü grupta ADMA düzeyleri anlamlı olarak yüksekti. Tek değişkenli analizde Gensini skoru değerlerinin, ADMA düzeyleri, GFR ve hipertansiyon mevcudiyeti ile uyumlu olduğu saptandı. Çok değişkenli regresyon modelinde, yalnızca ADMA düzeyi Gensini skoru için bağımsız bir belirleyici etken olduğu saptandı.

SONUÇ: Hafif-orta dereceli kronik böbrek yetmezliği hastalarında, ADMA düzeyleri ateroskleroz için güçlü bir belirteç olarak görülmektedir.

ANAHTAR SÖZCÜKLER: Asymmetrical dimethylarginine, Kronik böbrek yetmezliği, Koroner arter hastalığı, Gensini skoru

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INTRODUCTION

Patients with renal functional impairment have increased risk of cardiovascular disease and mortality. The prevalence of traditional cardiovascular risk factors is very high in chronic kidney disease (CKD) and non-traditional risk factors such as inflammation and oxidative stress are observed frequently in CKD, causing atherosclerosis (1,2).

Nitric oxide is the most important molecule as it regulates the functions of the endothelium and represents the health of endothelial function. Endothelial dysfunction due to the reduced bioavailability of nitric oxide (NO) is involved in the course of atherosclerotic cardiovascular disease. NO is synthesized from L-arginine via the action of NO synthase (3). Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of endothelial nitric oxide synthase. ADMA may contribute to endothelial dysfunction. ADMA is produced in human cell during proteolysis of methylated nuclear proteins and is mainly metabolized by dimethylarginine dimethylaminohydrolase (4). ADMA is increased in conditions associated with an increased risk of atherosclerosis, such as hypertension, hyperhomocysteinemia, impaired renal function, hypercholesterolemia, insulin resistance and diabetes mellitus (5-11). ADMA may participate actively in development of atherogenesis in patients with end-stage renal disease. Additionally, the plasma level of ADMA is a strong predictor of progression of renal dysfunction in patients with chronic kidney disease (12).

The multicentric CARDİAC study showed that manifestations of cardiovascular diseases were concomitant with high plasma concentrations of ADMA. ADMA may be a new marker for cardiovascular disease (13).

Deterioration of kidney function is accompanied by mineral metabolism disturbances (increased phosphorus and parathyroid hormone) that have been linked to the increased cardiovascular morbidity and mortality seen in these patients, possibly via coronary calcification (14).

In the present study, we aimed to examine the association between mineral metabolism levels (Ca, P, CaxP), ADMA, nitric oxide (NO) and the severity of coronary artery disease in a group of chronic kidney disease (CKD) patients (GFR between 90 and 30 ml/min/1.73m^2).

METHODS

A total of 212 consecutive patients undergoing cardiac catheterization for proven or clinically suspected coronary artery disease were collected for the study between November 2008 and March 2009. Eighty-eight (88) patients were included in the study. Exclusion criteria included the following: calculated GFR > 90 ml/min/1.73 m^2 or GFR < 30 ml/min/1.73 m^2, patients with severe congestive heart failure (NYHA class III - IV), myocardial infarction, valvular heart disease, presence of coronary artery by-pass graft surgery history, hepatic dysfunction, diabetes mellitus, the use of calcium supplements or vitamin D treatment. A total of 124 patients were excluded from the study: 42 patients had GFR≥ 90 ml/min/1.73 m^2, 3 patients had GFR ≤ 30 ml/min/1.73 m^2 and 20 patients were on dialysis; 11 patients had a positive history for coronary artery by-pass graft surgery; 9 patients had class IV congestive heart failure, and 48 patients were diagnosed with diabetes mellitus. The study was approved by the ethics committee.

All patients in the study underwent selective coronary artery angiography (Philips Allura Xper FD10) after appropriate patient preparation. Femoral artery cannulation was used for arterial access site and the Judkins system was applied for cannulation the left and right coronary arteries. All angiograms were evaluated by two experienced physicians blinded to the study. Angiograms with a stenotic lesion in all major epicardial coronary arteries including the left main, left anterior descending (LAD), left circumflex (LCx), and right coronary (RCA) arteries were evaluated and the severity of coronary artery disease was assessed by using the Gensini scoring system (15).

The glomerular filtration rate was used for the detection of renal functional status. This parameter might be calculated by different methods. Although collected 24-hour urine sample is widely used for the calculation (Cockcroft-Gault equation), we chose a simpler method, which does not contain 24-hour urine sampling in the present study: GFR (ml/min) = (140-age [years]) X body weight (kg)/ plasma creatinine X 72. For female patients, the obtained value was multiplied by 0.85.

Blood samples were collected on the morning of the procedure after a 12-hour fasting period, and then stored and analyzed by the laboratory. We collected blood samples before angiography to perform ADMA, nitric oxide and all other analyses (glucose, lipoprotein profile, uric acid, serum creatinine).

Serum concentrations of ADMA were measured by immunochemical quantification, the ELISA method (kit, ADMA® ELISA, DLD Diagnostika GmbH, Hamburg) (16).

Nitric oxide was measured by chemiluminescence with a Sievers Nitric Oxide Analyzer, model 280 (Boulder, Colorado). Blood samples were cen-trifuged at 2500 rpm for 20 minutes at 10 °C. The supernatant was removed and stored at -70 C. The nitric oxide assay was standardized by a calibration curve using known concentrations of nitrate (0.01 to 100 jLtmol/L) obtained from sodium nitrate. For each measurement, a 4 JLLL sample was placed in a reducing vessel with 5 mL of 0.1 mole vanadium III chloride per L, 1 mole of hydrochloric acid per L, and 100 JLLL of antifoaming agent (Sievers) at 90 °C. Each standard was analyzed three times, and each plasma sample was analyzed at least five times. The mean value was used for all subsequent analysis.

Statistical Analysis

Data were analyzed using the SSPS 15.0 for Windows software (SPSS® Inc. Chicago IL). All data are presented as mean ± standard deviation (SD) unless stated otherwise in the text. Continuous variables were checked for the normal distribution assumption using the Kolmogorov-Smirnov statistics and those that did not satisfy the criteria were log-transformed to attain normal distribution. The study group was divided into three subgroups based on the Gensini score tertiles. Correlations between two continuous variables were assessed using the t-test. The ANOVA test was used for multiple group comparisons of normally distributed variables. Chi square was used to test differences in frequency distributions. All potential (physiologically meaningful) determinants of the Gensini score were investigated in a univariate screening procedure, using the Pearson's coefficient of correlation test. Significant determinants identified from these analyses were studied in a multiple regression model using the F statistic. P<0.05 was considered as statistically significant for the final model. The Kruskal-Wallis test was applied to assess the distribution of continuous variables. A two-tailed p-value of < 0.05 was considered to be statistically significant.

Table I: Baseline demographic, laboratory and treatment data characteristics.

	Mean value
Age (years)	42.5 ± 11.9
Gender (male, %)	64%
GFR (ml/min/1.73m²)	73.9 ± 8.0
Total cholesterol (mg/dl)	192.3 ± 37
LDL cholesterol (mg/dl)	120.0 ± 34
HDL cholesterol (mg/dl)	40 ± 10
Triglyceride (mg/dl)	163 ± 90
Calcium (mg/dl)	9.1 ± 0.4
Phosphate (mg/dl)	3.3 ± 0.5
CaxP product (mg²/dl²)	30.3 ± 4.3
ADMA (μmol/l)	81.48 ± 13.8
NO (mmol/L)	3.7 ± 1.7
ACE inhibitor, %	24.0
ARB, %	17.3
Beta blocker, %	36.4
Calcium channel blockers, %	18.3
Diuretics, %	21.3
Statins, %	20.3
Smoking, %	28

ADMA, asymmetric dimethylarginine; **NO,** nitric oxide; **ACE,** angiotensin-converting enzyme inhibitors; **ARB,** angiotensin receptor blocker

RESULTS

A total of 88 patients that satisfied the selection criteria was included in the analysis. The mean age in the study group was 42.5 ± 11.9 years; 64 % were men, 61.3% were hypertensive, and 28.3% were smokers.

Baseline demographic and biological data of the entire study group are outlined in Table I. The mean serum lipid values, were 192 ± 37 mg/dl for total cholesterol, 120 ± 34 mg/dl for LDL cholesterol, 40 ± 10 mg/dl for HDL cholesterol, and 163 ± 90 mg/dl for triglycerides. The percentage of the study population with lipid abnormalities was 22.8% for hypercholesterolemia, 54% for high LDL cholesterol, 31% for low HDL cholesterol and 42% for hypertrigliceridemia.

The mean serum values were 81.48 ± 13.8 micromol/l for ADMA and 3.7 ± 1.7 mmol/L for NO. The mean Gensini score in the study group was 30.4 ± 40.1.

Gensini Score Subgroup Analysis

All patients were classified into tertiles of Gensini score level to evaluate whether the Gensini score was associated with the severity of decreased renal function in the study. The demographic, laboratory and treatment characteristics of the three groups are outlined in Table II. The mean age in three subgroups according to tertiles of Gensini score was similar but patients in the highest tertile were younger (41.2 ± 11.6 years vs 42.7 ± 12.4 years in the second tertile, 43.7 ± 11.7 years in the first tertile, p > 0.05)

Patients in the highest tertile had statistically significant lower GFR values (71.1 ± 10.9 ml/min/1.73 m² vs 77.7 ± 6.5 ml/min/1.73 m² in the first tertile and 73.0 ± 6.8 ml/min/1.73 m² in the second tertile; p for trend = 0.019)

No statistical significance was present between subgroups for measurement of total, – LDL,- HDL- cholesterols and triglyceride levels. Total cholesterol levels decreased in second and third tertile of patients possibly due to more aggressive statin treatment. The mean values of triglycerides were abnormal in all subgroups.

There was a statistically higher incidence of hypertension in the third tertile of the Gensini score (p for trend = 0.008). The use of angiotensin converting enzime inhibitors, beta-blockers and diuretics was also statistically significantly higher in the third tertile compared with the first tertile of the Gensini score (p for trend 0.018 and 0.01 and 0.019)

Across the Gensini tertiles, the ADMA values increased statistically significant in the third tertile compared with the first

Table II: Demographic, laboratory and treatment data in the three gensini score tertiles.

Gensini tertile	1st Tertile (n=30 patients)	2nd Tertile (n= 28 patients)	3rd Tertile (n= 30 patients)	P for trend
Age (years)	43.7 ± 11.7	42.7 ± 12.4	41.2 ± 11.6	NS
Gender (male; female)	12;18	20;8	25;5	
GFR (ml/min/1.73m^2)	77.7 ± 6.5	73.0 ± 6.8	71.1 ± 10.9	0.019
Creatinine (mg/dl)	0.76 ± 0.14	0.87 ± 0.2	0.97 ± 0.28	0.001
Total cholesterol (mg/dl)	195.4 ± 28.0	191.1 ± 34.1	192.1 ± 48.2	0.8
LDL cholesterol (mg/dl)	123.1 ± 31.5	114.5 ± 28.7	123.5 ± 42.1	0.6
HDL cholesterol (mg/dl)	40.6 ± 11.5	41.3 ± 9.6	39.2 ± 10.4	0.6
Triglyceride (mg/dl)	156.5 ± 103	173.6 ± 95	158.3 ± 75	0.7
Calcium (mg/dl)	9.1 ± 0.45	9.2 ± 0.45	9.1 ± 0.41	0.78
Phosphate (mg/dl)	3.1 ± 0.4	3.5 ± 0.6	3.2 ± 0.4	0.04
CaxP product (mg^2/dl^2)	28.3 ± 3.4	32.4 ± 6.2	30.2 ± 4.4	0.062
ADMA (μmol/l)	74.9 ± 10.11	79.6 ± 12.5	89.7 ± 14.3	0.001
NO (mmol/L)	3.7 ± 1.2	4.1 ± 2.1	3.2 ± 1.5	0.054
ACE inhibitor, %	10	21.4	40	0.018
ARB, %	26.1	7.1	20	0.1
Beta blocker, %	6.7	39.3	53.3	0.01
Calcium channel blockers,%	10	17.9	30	0.12
Diuretics, %	20	7.1	36.7	0.019
Statins, %	0	14.3	46.7	0.01
Hypertension, %	13	60.7	80	0.008
Smoking, %	30	25	30	0.8

GFR - glomerular filtration rate; **LDL** cholesterol - low density lipoprotein cholesterol; **HDL** cholesterol - high density lipoprotein cholesterol; **ACE** - angiotensin conversion enzyme; **ARB** - angiotensin receptor blockers; **ADMA**, asymmetrical dimethylarginine; **NO**, nitric oxide

tertile (89.7 ± 14.3 micromol/l vs 74.9 ± 10.11 micromol/l; p for trend = 0.0001) and NO values decreased significantly in the third tertile as compared to the patients in the first and second tertiles (3.2 ± 1.5 vs 3.7 ± 1.2 and 4.1 ± 2.1mmol/L; p for trend = 0.05).

The Gensini score values significantly correlated with the glomerular filtration rate (R = - 0.343, P 0 0.001); ADMA (R = 0.531, P = 0.000); and the presence of hypertension (R = 0.298, P = 0.005) but not with the NO values; the Ca, P, Ca×P, LDL cholesterol and smoking (Table III) in univariate analysis.

In a multivariate regression model, we introduced the metabolism parameters and the factors considered to influence coronary artery disease: the Ca, P, Ca×P product, NO, ADMA and GFR. In this step, ADMA (B= 0.340; p= 0.007) was the only statistically significant independent predictor of Gensini score (Table IV).

We adjusted for the presence of the traditional risk factors (hypertension, smoking, lipid profile and gender) and GFR. Even after these adjustments, the ADMA (B= 1.131; p= 0.001) and the presence of hypertension (B= 24.8; p= 0.01) remained statistically significantly predictors of the Gensini score but not with the total cholesterol (B= 0.05; p= 0.7), HDL cholesterol (B= 0.04; p= 0.9), triglyceride (B= -0.04; p= 0.5), gender (B=19.2; p= 0.08), and smoking (B= 10; p= 0.3).

DISCUSSION

Survival of patients with renal functional impairments is low because of increased risk of death from cardiovascular causes. Cardiovascular mortality in end-stage renal disease (ESRD) and

Table III: Correlations between the gensini score and the renal function, ADMA, NO, Hypertension, LDL cholesterol, smoking.

Gensini score	ADMA (μmol/l)	NO (mmol/l)	GFR (ml/min/1.73 m^2)	Calcium (mg/dl)	Phosphorus (mg/dl)	CaxP product (mg^2/dl^2)	Hypertension	LDL cholesterol (mg/dl)	Smoking
R^2	0.531 (**)	- 0.081	- 0.343 (**)	0.041	0.140	0.151	0.298 (**)	-0.013	0.059
P	0.000	0.451	0.001	0.742	0.245	0.21	0.005	0.91	0.586

GFR, glomerular filtration rate; **ADMA,** symmetrical dimethylarginine; **NO,** nitric oxide
** Correlation is significant at the 0.01 level (2-tailed)

predialysis CKD patients is increased and not entirely explained by traditional risk factors (17).

In this cross-sectional study of patients with CKD 1-3 not yet on dialysis, we report a significant association between elevated levels of ADMA and increased coronary artery lesions as objectively assessed by coronary angiography. Moreover, this association remained statistically significant after adjustment for established cardiovascular risk factors such as gender, lipid profile, smoking, hypertension and GFR. Besides, determinants of the mineral metabolism in CKD patients (serum Ca, P, Ca×P product) were not found to be statistically significant predictors of the Gensini score of coronary lesions in multivariate analysis.

Though the prevalence of traditional Framingham risk factors (such as hypertension, diabetes mellitus, dyslipidemia, smoking) is very high in patients with renal impairment, non-traditional risk factors such as inflammation and oxidative stress, which are observed frequently in renal failure causing atherosclerosis, have also been investigated (1,18). In our study, this was directly correlated to CAD severity in the general population as regards the presence of hypertension. The presence of hypertension remained a statistically significant predictor of the Gensini score in multivariate analysis.

Gradaus et al. have demonstrated that a more rapid progression of coronary stenosis in patients with ESRD is present compared to patients with normal renal function (19). In the Atherosclerosis Risk in Communities Study, subjects with a GFR of 15 to 59 ml/min/1.73 m^2 and 60 to 89 ml/min/1.73 m^2 had an increased adjusted risk of atherosclerotic CVD (HR = 1.38 [1.02, 1.87]; HR = 1.16 [1.00, 1.34] respectively) compared with subjects with GFR of 90 to 150 ml/min/1.73 m^2 (20).

The calculated GFR correlated with the Gensini score with univariate analysis in our study. GFR had emerged as an important predictor for the risk of severity for CAD in a previous study. However, the GFR did not reach statistical significance as an

Table IV: Multivariate regression analysis for the gensini score.

Model summary				
Model	**R**	**R Square**	**Adjusted R Square**	**Sig. (2-tailed)**
1	0.415 (a)	0.172	0.104	0.038

Multivariate analysis: ADMA, NO, GFR, phosphorus, CaxP product			
	Beta	**Sig (2 tailed)**	
(Constant)		0.342	
Phosphate (mg/dl)	-0.192	0.643	
CaxP product (mg^2/dl^2)	0.261	0.535	
ADMA (μmol/l)	0.340	0.007	
NO (mmol/l)	-0.092	0.466	
GFR(ml/min/1.73 m^2)	-0.139	0.257	

GFR - glomerular filtration rate; **ADMA,** asymmetrical dimethylarginine; **NO,** nitric oxide

independent predictor of CAD in adjusted multivariate analysis that includes the ADMA as a predictor of the Gensini score.

Coronary artery calcification correlates with the extent of coronary artery atherosclerosis, occurring more frequently in uremic patients. Strong relationships between increased serum phosphate, calcium-phosphate product, parathyroid hormone, and mortality from cardiovascular causes have recently been demonstrated. Clinical studies have shown that serum Ca and P are normal until GFR < 40 ml/min (21). Similarly, there were minimal abnormalities in serum Ca, P levels and the Ca×P product in our study. We also found no correlation between the Ca and P levels and Ca×P product and the Gensini score values on univariate analysis and they did not emerge as independent predictors of CAD on multivariate analysis.

NO is a cardiovascular protective substance because it causes vasodilation and leucocyte aggregation. NO inhibition by ADMA may therefore be relevant as a pro-atherogenic mechanism (12). Miyazaki et al. have demonstrated that intima-media thickness is strongly related to plasma ADMA in apparently healthy subjects, indicating that this substance is an early marker of atherosclerosis (22). The CARDIAC study showed that the ADMA may be a causal factor in the initiation and progression of ischemic vascular disease (13). ADMA predicts death, cardiovascular complications and progression of intimal lesions independently of other risk factors in ESDR patients (23). The association between ADMA and survival has been very recently confirmed in patients with CKD in the pre-dialysis phase (24,25).

In our study the ADMA level was slightly elevated in the first two tertiles of the Gensini score but increased significantly in patients in the third tertile. The association with the Gensini score was present in univariate analysis and maintained in multivariate analysis after adjustment for traditional risk factors, NO and GFR. The data suggests that the ADMA levels can reflect a possible independent role in CAD pathogenesis.

There are several limitations in our study: first, we believe that it is limited in the number of study population. Second, our study did not include diabetic patients and we cannot postulate that the only link would be through an insulin resistance mechanism.

In conclusion, ADMA in patients with mild to moderate CKD is an independent prognostic factor for coronary artery disease extent.

REFERENCES

1. Stenvinkel P, Alvestrand P: Inflammation in end-stage renal disease: Sources, consequences and therapy. Seminar Dial 2002; 15: 330-338
2. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM: The elephant of uremia: Oxidative stress as a unifying concept of cardiovascular disease in uremia. Kidney Int 2002; 62: 1524-1538
3. Ueda S, Yamagishi S, Matsumoto Y, Fukami K, Okuda S: Asymmetric dimethylarginine (ADMA) is a novel emerging risk factor for cardiovascular disease and the development of renal injury in chronic kidney disease. Clin Exp Nephrol 2007; 11: 115-121
4. Zoccali C, Kielstein JT: Asymmetric dimethylarginine: A new player in the pathogenesis of renal disease? Curr Opin Nephrol Hypertens 2006; 15: 314-320
5. Vallance P, Leone A, Calver A, Collier J, Moncada S: Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 1992; 339: 572-575
6. Boger RH, Bode-Boger SM, Szuba A, Tsao PS, Chan JR, Tangphao O, Blaschke TF, Cooke JP: Asymmetric dimethylarginine (ADMA): A novel risk factor for endothelial dysfunction: Its role in hypercholesterolemia. Circulation 1998; 98: 1842-1847
7. Lundman P, Eriksson MJ, Stuhlinger M, Cooke JP, Hamsten A, Tornvall P: Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine. J Am Coll Cardiol 2001; 38: 111-116
8. Stuhlinger MC, Abbasi F, Chu JW, Lamendola C, McLaughlin TL, Cooke JP, Reaven GM, Tsao PS: Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. JAMA 2002; 287: 1420-1426
9. Abbasi F, Asagmi T, Cooke JP, Lamendola C, McLaughlin T, Reaven GM, Stuehlinger M, Tsao PS: Plasma concentrations of asymmetric dimethylarginine are increased in patients with type 2 diabetes mellitus. Am J Cardiol 2001; 88: 1201-1203
10. Stuhlinger MC, Stanger O: Asymmetric dimethyl-L-arginine (ADMA): A possible link between homocyst(e)ine and endothelial dysfunction. Curr Drug Metab 2005; 6: 3-14
11. Surdacki A, Nowicki M, Sandmann J, Tsikas D, Boeger RH, Bode-Boeger SM, Kruszelnicka-Kwiatkowska O, Kokot F, Dubiel JS, Froelich JC: Reduced urinary excretion of nitric oxide metabolites and increased plasma levels of asymmetric dimethylarginine in men with essential hypertension. J Cardiovasc Pharmacol 1999; 33: 652-658
12. Zoccali C: Asymmetric dimethylarginine (ADMA): A cardiovascular and renal risk factor on the move. Journal of Hypertension 2006; 24: 611-619
13. Müggea A, Hanefeld C, Böger RH, CARDIAC study investigators: Plasma concentration of asymmetric dimethylarginine and the risk of coronary heart disease: Rationale and design of the multicenter CARDIAC study. Atherosclerosis Supplement 4 2003; 29-32

14. Ganesh SK, Stack AG, Levin N, Hulbert-Shearon T, Port FK: Association of elevated serum PO4, Ca-PO4 product and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12: 2131-2138
15. Gensini GG: A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983; 51: 606
16. Schulze F, Wesemann R, Schwedhelm E, Sydow K, Albsmeier J, Cooke JP, Böger RH: Determination of asymmetric dimethylarginine (ADMA) using a novel ELISA assay. Clin Chem Lab Med 2004; 42: 1377
17. Cay S, Metin F, Korkmaz S: Association of renal functional impairment and the severity of coronary artery disease. Anadolu Kardiyol Derg 2007; 7: 44-48
18. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM: The elephant of uremia: Oxidative stress as a unifying concept of cardiovascular disease in uremia. Kidney Int 2002; 62**:** 1524-1538
19. Gradaus F, Ivens K, Peters AJ, Heering P, Schoebel FC, Grabense B, Strauer BE: Angiographic progression of coronary artery disease in patients with end-stage renal disease. Nephrol Dial Transplant 2001; 16: 1198-1202
20. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J: Change in Estimated GFR Associates with Coronary Heart Disease and Mortality. J Am Soc Nephrol 2009; 20: 2617-2624
21. Ganesh SK, Stack AG, Levin N, Hulbert-Shearon T, Port FK: Association of elevated serum PO4, Ca-PO4 product and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12: 2131-2138
22. Miyazaki H, Matsuoka H, Cooke JP, Usui M, Ueda S, Okuda S, Imaizumi T: Endogenous nitric oxide synthase inhibitor: A novel marker of atherosclerosis. Circulation 1999; 99: 1141-1146
23. Zoccali C, Benedetto FA, Maas R, Mallamaci F, Tripepi G, Malatino LS, Böger R, CREED Investigators: Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. J Am Soc Nephrol 2002; 13: 490-496
24. Ravani P, Tripepi G, Malberti F, Testa S, Mallamaci F, Zoccali C: Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: A competing risks modeling approach. J Am Soc Nephrol 2005; 16: 2449-2455
25. Yilmaz MI, Eyileten T, Yenicesu M: Kronik böbrek hastalığında yeni bir oyuncu: Asimetrik dimetilarginin (ADMA). Turk Neph Dial Transpl 2007; 16(3): 93-101