Relationship of Serum Asymmetric Dimethylarginine Levels with Inflammation and Cardiac Functions in Autosomal Dominant Polycystic Kidney Disease

Otozomal Dominant Polikistik Böbrek Hastalığında Serum Asimetrik Dimetilarginin Düzeyi ile İnflamasyon ve Kardiyak Fonksiyonlar Arasındaki İlişki

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ABSTRACT

OBJECTIVE: Most deaths in autosomal dominant polycystic kidney disease (ADPKD) are attributable to cardiovascular disease (CVD). The relationship between serum asymmetric dimethylarginine (ADMA) and CVD has been investigated. We aimed to search the relationship between serum ADMA, atherosclerosis, inflammation and cardiac functions in ADPKD.

MATERIAL and METHODS: Fifty-seven ADPKD patients and 23 healthy control subjects were enrolled. Carotid artery intima-media thickness (CIMT) and echocardiographic measurements were performed. ADMA, inflammatory markers, Neutrophil Count/Lymphocyte Count (NLR), echocardiographic findings and CIMT values were compared between the groups. Correlation analyses were performed.

RESULTS: ADMA levels were lower in patients compared to controls [10106 ng/L (2010-60000) vs. 20161 ng/L (2902-60000), p=0.006]. CIMT was 0.67±0.03 mm in the patient group and 0.62±0.03 mm in the control group (p>0.05). In the patient group, left ventricular mass (LVM), left ventricular mass index (LVMI), left atrial diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) values were higher (p<0.001, p<0.001, p<0.05, p<0.01). NLR was 2.0 (0.96-13) in the patient group and 1.6 (0.81-6.06) in the control group (p<0.01). Serum ADMA levels were negatively correlated with CIMT and LAD (p<0.05, p<0.001).

CONCLUSION: Serum ADMA levels were found to be low in ADPKD patients. Additional studies are needed to determine the possible affect of ADMA on atherosclerosis and inflammation in early stage of ADPKD.

KEY WORDS: Asymmetric dimethylarginine, Atherosclerosis, Autosomal dominant polycystic kidney disease, Carotid artery intima-media thickness, Inflammation

ÖZ

AMAÇ: Otozomal Dominant Polikistik Böbrek Hastalığı (ODPBH)'nda en önemli mortalite nedeni kardiyovasküler (KV) hastalıklardır. Birçok çalışmada, serum asimetrik dimetilarjinin (ADMA) ile KV hastalıkların ilişkisi araştırılmıştır. Çalışmamızda erken evre ODPBH'da serum ADMA düzeyi ile inflamasyon ve atheroskleroz arasındaki ilişkiyi araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya ODPBH'lı 57 hasta ve 23 sağlıklı kontrol grubu alındı. Katılımcıların karotis arter intima-media kalınlığı (KIMK) ve ekokardiyografik (EKO) ölçümleri alındı. Gruplar arasında serum ADMA, inflamasyon belirteçleri, Nötrofil/Lenfosit oranı (NLO), EKO bulgular ve KİMK değerleri karşılaştırıldı. Korelasyon analizleri yapıldı.

BULGULAR: Serum ADMA düzeyi hasta grubunda kontrol grubuna göre daha düşük saptandı [10106 ng/L (2010-60000) vs 20161 ng/L (2902-60000), p=0,006]. KIMK hasta grubunda 0,67±0,03mm, kontrol grubunda ise 0,62±0,03mm olarak saptandı (p>0,05). Hasta grubunda, sol ventrikül kitlesi (p<0,001), sol ventrikül kitle indeksi (p<0,001), sol atriyum çapı (p=0,023) ve sol ventrikül diyastol

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sonu çap (p=0,009) anlamlı olarak daha yüksek bulundu. NLO hasta grubunda 2,0 (0,96-13), kontrol grubunda ise 1,6 (0,81-6,06) olarak saptandı (p<0,01). ADMA düzeyi KİMK ve sol atrium çapı ile negatif korole saptandı. (p<0,05, p<0,001)

SONUÇ: Çalışmamızda ODPBH'da serum ADMA düzeyi daha düşük saptandı. Erken evre ODPKBH'da ADMA'nın aterosklerozis ve inflamasyon üzerine etki mekanizmasını açıklayacak ilave çalışmalara ihtiyaç vardır.

ANAHTAR SÖZCÜKLER: Asimetrik dimetilarjinin, Ateroskleroz, İnflamasyon, Karotis arter intima-media kalınlığı, Otozomal dominant polikistik böbrek hastalığı

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease (1). Its prevalence is 1/600-1/1000 and constitutes 7-10% of the end-stage renal disease (ESRD) cases (2,3). The main cause of mortality and morbidity in ADPKD is cardiovascular disease (CVD). The causes of endothelial dysfunction (ED) in ADPKD is endothelium-dependent relaxation dysfunction and reduction in the nitric oxide synthetase (NOS) activity of the endotelium (4). Carotid intima media thickness (CIMT) has been found to be increased independent of the presence of hypertension in addition to ED in ADPKD patients with normal renal function (5). These findings suggest that atherosclerosis begins early in the course of the disease.

Nitric oxide (NO) is a strong anti atherogenic molecule that is synthesized by NOS and is a vasodilator and inhibitor of smooth muscle proliferation (6,7). ADMA is the endogenous inhibitor of NOS (8,9). High serum ADMA levels have been suggested to be an important predictor of acute coronary events in the general population (10) and of cardiovascular (CV) mortality in intensive care unit patients (11, 12). High ADMA levels have also been shown to be associated with concentric left ventricular hypertrophy and increased CIMT. High ADMA levels in chronic kidney disease (CKD) may be related to increased mortality and morbidity due to atherosclerosis (12-14).

In this study, we aimed to evaluate the association between inflammation, atherosclerosis, cardiac functions and serum ADMA levels in ADPKD.

MATERIALS and METHODS

This cross-sectional study was conducted at the Bursa Yuksek Ihtisas Training and Research Hospital, Clinic of Internal Medicine. It was approved by the local ethics committee and informed consent was obtained from the study participants.

ADPKD patients in the early stages and age-matched healthy volunteers were included in the study. Clinical and drug history was taken and physical examination was performed. Blood pressure measurements were noted as the average of 12 measurements from both arms in the last week. Body Mass Index (BMI) was calculated according to the formula; Weight/height^2 (kg/m^2). Patients having a history of active infections and malignancies, acute vascular event and surgery within the last 6 weeks, decompensated liver disease, New York Heart Association class 3 or 4 heart failure, recent burns or severe trauma were excluded. Co-morbidities of the patients are listed in Table I.

Blood samples were taken from all participants in the morning after 12 hours of fasting and complete blood count, biochemical parameters, parathyroid hormone (PTH), serum ferritin, and C- reactive protein (CRP) were studied. The ratio of the absolute neutrophil count to absolute lymphocyte count (NLR) was calculated. Serum samples for assessment of ADMA were centrifuged for five minutes with at 3000 rev/min and stored at - 80 ºC. The human ADMA ELISA Kit (Catalog No. CK- E11310, Eastbiopharm, Inc. Zhejiang, China) was used in serum ADMA assessment**.**

Echocardiography was performed by the same cardiologist with the Cardiovascular D - Vivid 4 ultrasound device with a 3.5 MHz transducer according to the standardisation of the working group of the American Society of Echocardiography. Standard images were obtained by M-mode and cross-sectional studies. The biplane Simpson's method and Teichols method were used in the assessment of the left ventricular function (15). The same radiologist measured CIMT with a Logic 5 Pro (GE Healthcare, Milwaukee, USA) Ultrasound using a 7.5 MHz linear transducer. CIMT was measured at approximately 1 cm proximal to both common carotid artery bifurcations from the anterior and posterior wall and the arithmetic mean of the 3 measurements was used.

Table I: Concomitant Co-morbid diseases in the patient group.

Co-Morbidity	HT	CAD	DM	PAD	COPD	CVE
N(%)	40 (70.2%)	8 (14%)	10 (17.5%)	2 (3.5%)	4 (7%)	2 (3.5%)

HT: Hypertension, **CAD:** Coronary artery disease, **OPD:** Chronic obstructive pulmonary disease, **DM:** Diabetes mellitus, **PAD:** Peripheral arterial disease, **CVE:** Cerebro-vascular event.

The SPSS for Windows 20.0 package program was used in the analysis. $p< 0.05$ was identified as significant.

RESULTS

A total of 57 ADPKD patients (31 females, mean age 45.68±14.32 years) and 23 healthy subjects (12 female, mean age 46.52 ± 6.28 years) were included in the study. There was no difference between the groups in terms of age, sex and body mass index (BMI) ($p>0.05$). There was statistically significant difference between the study and the control groups in terms of systolic blood pressure (SBP) and diastolic blood pressure (DBP) ($p<0.001$) (Table II). Albumin and glucose were statistically significantly higher in the patient group and the hemoglobin concentration was statistically significantly low ($p<0.05$) (Table II). In the patient group, NLR ($p<0.01$), blood urea nitrogen (BUN) ($p<0.05$) and PTH ($p<0.01$) were significantly higher than in the control group respectively (Table II). Calcium, phosphorus, uric acid, cholesterol, HDL, LDL, TG, CRP and ferritin levels were not different between the groups ($p>0.05$). ADMA levels were found to be significantly low in the patient group ($p<0.01$) (Table II). There was no significant difference between the groups in terms of CIMT ($p>0.05$).

Left Ventricular Mass (LVM), Left Ventricular Mass Index (LVMI), Left Atrial Diameter (LAD) and Left Ventricular End Diastolic Diameter (LVEDD) values were significantly increased in the patient group ($p<0.001$, $p<0.001$, $p<0.05$ and $p<0.01$ respectively) but the Left Ventricular End Systolic Diameter (LVESD) value was not different between the groups ($p>0.05$).

Correlation analysis was performed between ADMA and the inflammatory markers and cardiac parameters. Serum ADMA levels were negatively correlated with creatinine, total protein, PTH, CIMT and LAD ($p<0.05$, $p<0.05$, $p<0.01$, $p<0.05$ and $p<0.001$ respectively) and ADMA levels were positively correlated with CrCl ($p<0.05$). CIMT was positively correlated with age, BMI, SBP, glucose, BUN, creatinine, serum uric acid (SUA), triglyceride, PTH, LAD, LVM and LVMI ($p<0.001$, $p<0.001$, $p<0.05$, $p<0.05$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.05$, $p<0.05$, $p<0.01$, $p<0.001$, $p< 0.001$ respectively) and negatively correlated with albumin, high density lipoprotein (HDL) and CrCl ($p<0.05$, $p<0.001$ and $p<0.001$ respectively) (Table III).

DISCUSSION

In our study, serum ADMA levels were low in the patient group and were not correlated with inflammatory indicators. There was a weak negative correlation between CIMT and ADMA levels. No correlation was determined between ADMA and LVM.

In ADPKD, the glomerular filtration rate (GFR) decreases progressively and the presence of CRF is a risk factor for CVD (16). Besides classical risk factors, oxidative stress, ED and insulin resistance are accused in the pathogenesis of CVD in CRF (17).

NO is an important mediator in the regulation of endothelial function and plays a role in the pathogenesis of atherogenesis. It also inhibits monocyte adhesion, platelet aggregation and smooth muscle cell proliferation. A decrease in NO synthesis causes decreases in vascular dilatation and blood flow that promote atherosclerosis (18). ADMA is an important molecule in the NO pathway and elevated plasma ADMA levels have been associated with ED (19). In experimental studies, infusion of ADMA has caused elevation of blood pressure (19), decline in blood flow by vasoconstriction in mesenteric arterioles (20), and if used for a long time, coronary microvascular lesions (21). Systemic administration of ADMA also suppresses the production of NO, increases renal vascular resistance, and decreases renal plasma flow and urinary sodium excretion (22).

For the first time in 1974, enhanced atherosclerosis in dialysis patients was thought to be associated with prolonged maintenance hemodialysis (23). ADMA was found to be higher in HD patients with atherosclerosis than without atherosclerosis (12). In subsequent studies, higher plasma ADMA levels were detected in both hemodialysis patients (14, 24), and in the early stages of CKD compared to healthy subjects (24, 25).

In a few studies conducted in the early stages ADPKD, both serum ADMA levels and oxidative stress parameters were increased and found to be associated with ED (26-28). In another study, a negative correlation was detected between NO and ADMA after exercise in the early phase of normotensive ADPKD and this was thought to be related to ED (29). The ADMA levels were lower in the patient population compared to the control group in the current study. When these findings are evaluated with the findings in the literature, it is thought that studies including a higher number of patients are needed.

In the pathogenesis of hypertension that occurs in the early stages of ADPKD, activation of the renin angiotensin aldosterone system, vascular remodelling, NO deficiency and ED are thought to play a role. Subcutaneous vascular samples taken from ADPKD with normal GFR has shown decreased NO activity and ED (30). NOS type 1 and type 3 expressions were also found to be imbalanced and NOS activity was decreased in ADPKD (31,32).

The blood pressure was significantly higher in our study group compared to the control group and 70.2% of the patients had HT. LAD, LVEDD, LVM and LVMI were also higher in the patient group, possibly related to the higher blood pressure. In a study on subjects without CAD, the ADMA levels were found to be correlated with SBP (33). In another study in hypertensive patients, no correlation was detected between ADMA levels and central-brachial blood pressure but serum ADMA levels were correlated with CIMT and ED (34).

In a study by Kocaman et al. in ADPKD patients with preserved renal function, with and without HT, endothelial dependent vasodilatation was shown to be decreased and CIMT was found to be increased when compared with healthy controls (5).

Table II: Comparison of variables between the patient and control groups.

Variables	Patients (n= 57)	Controls (n= 23)	p
Gender (F/M)	31/26	12/11	0.857
Age (year)*	46±14	47±6	0.717
BMI (kg/m²)*	27.60± 4.80	26.4± 3.60	0.200
SBP (mm Hg)**	140 (90-200)	110 (80-130)	<0.001
DBP (mm Hg)**	80 (60-100)	70 (50-80)	<0.001
Hemoglobin (gr/dl)*	13.2±1.4	14.1±4.1	0.010
NLR**	2.0 (0.96-13)	1.6 (0.81-6.06)	0.002
Glucose (mg/dl)**	93 (64-182)	84 (65-107)	0,020
BUN (mg/dl)**	15.9 (8.4-60.8)	12.8 (6.4-45.5)	0.016
Creatinine (mg/dl)**	1.03 (0.67-2.88)	0.87 (0.59-1.26)	0,001
Total Protein (g/dl) (gr/dl)*	7.6±0.4	7.1±0.4	<0.001
Albumin (g/dl)*	4.4±0.3	4.2±0.2	0.017
Calcium (mg/dl)*	9.2±0.4	9.3±0.3	0.564
Phosphorus (mg/dl)**	3.2 (2.2-5.9)	3.4 (2.4-4.3)	0.466
Uric acid (mg/dl)**	5.0 (2.2-10.5)	4.9 (2.9-7.4)	0.236
LDL (mg/dl)*	123±39	121±25	0.861
Cholesterol (mg/dl)**	189 (114-291)	198 (128-247)	0.537
HDL (mg/dl)**	44 (25-80)	42 (28-71)	0.509
Triglycerides (mg/dl)**	123 (31-500)	94 (32-259)	0.496
PTH (pg/ml)**	79 (6-363)	47 (25-163)	0.003
CRP (mg/dl)**	3.2 (0.8-32.8)	3.3(3.1-14.6)	0.283
CrCl (ml/min/1,73m²)**	69 (21-122)	96 (68-148)	<0.001
Ferritin (ng/ml)**	45 (2.9-366)	42 (4.2-280)	0.718
ADMA (ng/l)**	10106 (2010- 60000)	20161 (2902-60000)	0.006
CIMT (mm)**	0.67±0.03	0.62±0.03	0.463
LVM (gr)*	215.5±55.8	157±38.5	<0.001
LVMI (gr/m²)*	115.8±25.1	89.8±21.5	<0.001
EF (%) **	65(50-87)	65(59-89)	0.228
LAD (cm)**	3.7(2.7-4.4)	3.4(2.7-3.7)	0.023
LVEDD (cm)**	4.9 (4.0-5,6)	4.6 (3.6-5.5)	0,009
LVESD (cm)*	2.75±0.39	2.63±0.39	0.208

ADMA: Asymmetric dimethyl-arginine, **NLR:** Neutrophil Count/Lymphocyte Count, **BMI:** Bady Mass Index, **BUN:** Blood Urea Nitrogen, **CIMT:** Carotid Intima-Media Thickness, **CrCl:** Creatinine Clearance, **CRP:** c-Reactive Protein, **DBP:** Diastolic Blood Pressure, **EF:** Ejection Fraction, **HDL:** High Density Lipoprotein, **LAD:** Left Atrial Diameter, **LDL:** Low Density Lipoprotein, **LVEDD:** Left Ventricular End-Diastolic Diameter, **LVESD:** Left Ventricular End-Systolic Diameter, **LVM:** Left Ventricular Mass, **LVMI:** Left Ventricular Mass Index, **PTH:** Parathyroid hormone, **SBP:** Systolic Blood Pressure.

*Parametric distributed variables are mean ±standard error, **Non-parametric distributed variables median (%25-75) were expressed as.

Table III: Correlation analysis with ADMA and CIMT.

	ADMA (ng/l)		CIMT (mm)	
	r	p	r	p
Age (year)	-0.127	0.346	0.743	<0.001
BMI (kg/m^2)	-0.172	0.201	0.507	<0.001
SBP (mm Hg)	-0.157	0.242	0.317	0.016
DBP (mm Hg)	-0.202	0.133	0.614	0.068
Hemoglobin (gr/dl)	0.056	0.619	-0.006	0.966
NLR	-0.182	0.106	0.362	0.006
BUN (mg/dl)	-0.207	0.066	0.572	<0.001
Creatinine (mg/dl)	-0.231	0.040	0.584	<0.001
Calcium (mg/dl)	-0.002	0.987	-0.059	0.664
Phosphorus (mg/dl)	0.159	0.238	-0.067	0.623
Uric Acid (mg/dl)	-0.084	0.461	0.633	<0.001
Albumin (g/dl)	-0.120	0.288	-0.313	0.018
Cholesterol (mg/dl)	-0.060	0.598	0.151	0.263
LDL (mg/dl)	-0.074	0.517	0.217	0.105
HDL (mg/dl)	0.071	0.532	-0.477	<0.001
Triglycerides (mg/dl)	-0.121	0.287	0.267	0.045
PTH (pg/ml)	-0.294	0.008	0.268	0.044
CRP (mg/dl)	-0.157	0.164	0.138	0.305
Crcl (ml/min/1.73m^2)	0.235	0.036	-0.488	<0.001
Ferritin (ng/ml)	0.117	0.303	0.087	0.521
CIMT (mm)	-0.261	0.020	1	1
EF (%)	-0.151	0.181	0.072	0.595
LAD (cm)	-0.385	<0.001	0.391	0.003
LVESD (cm)	-0.014	0.904	0.066	0.625
LVEDD (cm)	-0.146	0.197	0.249	0.062
LVM (gr)	-0.169	0.133	0.554	<0.001
LVMI (gr/m^2)	-0.048	0.670	0.463	<0.001

ADMA: Asymmetric dimethyl-arginine, **NLR:** Neutrophil Count/Lymphocyte Count, **BMI:** Bady Mass Index, **BUN:** Blood Urea Nitrogen, **CIMT:** Carotid Intima-Media Thickness, **CrCl:** Creatinine Clearance, **CRP:** c-Reactive Protein, **DBP:** Diastolic Blood Pressure, **EF:** Ejection Fraction, **HDL:** High Density Lipoprotein, **LDL:** Low Density Lipoprotein, **LAD:** Left Atrial Diameter, **LVEDD:** Left Ventricular End-Diastolic Diameter, **LVESD:** Left Ventricular End- Systolic Diameter, **LVM:** Left Ventricular Mass, **LVMI:** Left Ventricular Mass Index, **PTH:** Parathyroid hormone, **SBP:** Systolic Blood Pressure.

In our study, we did not observe a correlation between CIMT, serum ADMA levels and blood pressure. A positive correlation was detected between CIMT and SBP. In addition, a positive correlation was detected between age, BMI, uremic status, hyperparathyroidism and CIMT which are traditional risk factors.

Recently, NLR was found to be positively correlated with inflammation in various patient groups (35,36) and a positive correlation was detected between hsCRP, NLR and CIMT (36). However, in a prospective study on HD patients, plasma ADMA and CRP levels were associated with CIMT progression (37). In another study, as compared to healthy controls in ADPKD,

NLR and CIMT were found to be increased and a positive correlation was detected between NLR and CIMT (38). In our study, CRP levels were not different between groups but NLR was higher in the patient group. On correlation analysis, no correlation was detected between ADMA with NLR and CIMT with NLR. Well[designed prospective trials with higher patient numbers are therefore needed to understand the relation between inflammation, atherosclerosis and ED.

In the general population, the serum uric acid (SUA) level is an important risk factor for CVD (39,40). In various studies, SUA levels have been thought to be an important marker for ED and an early indicator of vascular injury in renal failure, HT and CVD (41, 42). In a study using endothelial cell cultures, SUA decreased NO synthesis (43) and was shown to contribute to ED by gaining a pro-oxidative property (44,45). In ADPKD, the SUA levels increased as a result of a decrease in GFR (46-48) and high SUA levels were related to early onset HT and renal disease progression (49). In another study on early ADPKD, higher DBP, CRP and serum ADMA levels were detected in the hyperuricemic group. In the entire cohort, serum ADMA levels were reported to correlate with SUA levels (50). In our study, SBP and DBP were higher in the study group but SUA levels were not different. ADMA and SUA were also not correlated. However, in the patient group, SUA levels were correlated with CIMT. Taken together with data from the literature, high SUA levels may be an important indicator of atherosclerosis. Clinically asymptomatic hyperuricemia treatment is not recommended (51). However, treatment of these patients had a positive effect on ED in a study (52). Prospective randomised controlled studies are therefore needed to understand the effect of hyperuricemia treatment on CVD and renal progression.

In conclusion, serum ADMA levels were lower than the control group in the early stage ADPKD group in our study. LVM and LVMI were significantly higher in the patient group. However, CIMT, as an atherosclerosis marker, was not different between groups so factors other than ADMA may be responsible for ED. In our study, NLR and SUA levels were positively correlated with CIMT and these inflammatory markers may be involved in the pathogenesis of ED. We can comment that there was no relation among ADMA levels, ED and atherosclerosis in our study but because of the cross-sectional nature, we can only reach conclusions regarding a numerical relationship and we should be cautious during our interpretation. More comprehensive and prospective studies are therefore needed to understand the pathways in the pathogenesis of the disease to provide potential therapeutic targets in slowing disease progression.

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