TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2018) 48: 1041-1047
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doi:10.3906/sag-1804-98

Serum ADMA, endothelial dysfunction, and atherosclerosis in hypervolemic hemodialysis patients

İbrahim DOĞAN[1,*], Barış ESER[1], Sultan ÖZKURT[2], Özlem YAYAR[3], Bülent ÖZGÜR[4], Hüseyin KAYADİBİ[5], Tolga DOĞAN[6], Ahmet MUŞMUL[7], Mehmet SOYDAN[2]

[1]Department of Nephrology, Faculty of Medicine, Hitit University, Çorum, Turkey
[2]Department of Nephrology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey
[3]Department of Nephrology, Çanakkale State Hospital, Çanakkale, Turkey
[4]Department of Nephrology, Eskişehir State Hospital, Eskişehir, Turkey
[5]Department of Biochemistry, Faculty of Science, Hitit University, Çorum, Turkey
[6]Department of Cardiology, Faculty of Medicine, Hitit University, Çorum, Turkey
[7]Department of Biostatistics, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

Received: 15.04.2018 • **Accepted/Published Online:** 26.07.2018 • **Final Version:** 31.10.2018

Background/aim: Asymmetric dimethyl arginine (ADMA) is a strong predictor of cardiovascular disease and mortality in patients under hemodialysis treatment. We aimed to investigate the relationship among volume status, endothelial dysfunction, and ADMA in hemodialysis patients.

Materials and methods: A total of 120 patients with a history of hemodialysis treatment were included. ADMA and CRP were measured. Echocardiographic evaluation and carotid artery intima–media thickness (CIMT) measurements were performed. Patients were divided into two groups according to clinical evaluation, ultrafiltration rate, vena cava inferior diameter (VCI), and cardiothoracic index (CTI); the two groups were hypervolemic and normovolemic.

Results: The hypervolemic group included 61 patients while the normovolemic group included 59 patients. CIMT was higher in the hypervolemic group, but this result was not statistically significant (0.95 mm versus 0.85 mm, $P = 0.232$). There was a statistically significant difference between the hypervolemic and normovolemic groups in terms of ADMA ($P < 0.001$) (0.69 ± 0.57 μmol/L and 0.41 ± 0.04 μmol/L, respectively). Positive correlations were observed between serum ADMA, VCI, CTI, CRP, CIMT, and cardiac mass ($P < 0.001$, $P = 0.016$, $P < 0.001$, $P = 0.006$, $P = 0.022$, respectively), and negative correlations were observed between ADMA and ejection fraction and albumin ($P = 0.024$, $P = 0.024$, respectively). In multiple linear regression analysis, ADMA was independently associated with age, systolic blood pressure, CTI, and volume status.

Conclusion: ADMA may be a potential determinant of hypervolemia as well as atherosclerosis in patients under hemodialysis treatment.

Key words: Asymmetric dimethyl arginine, atherosclerosis, endothelial dysfunction, hemodialysis, hypervolemia

1. Introduction

Atherosclerotic disease is the most important cause of mortality in end-stage renal disease (ESRD) (1). Along with the presence of traditional risk factors like hypertension (HT), diabetes mellitus (DM), dyslipidemia, and advanced age, novel risk factors such as endothelial dysfunction (ED), hyperphosphatemia, increased oxidative stress, and inflammation are highly prevalent and may play a more important role for the pathogenesis of vascular disease in patients with ESRD (2). Hypervolemia is also an important risk factor for cardiovascular (CV) disease in dialysis patients. Detection of dry weight in clinical practice is necessary to avoid excess volume. However, it is very difficult to determine dry weight. Many methods such as clinical evaluation, measurement of total body fluid, echocardiographic measurement of left atrium diameter and vena cava inferior diameter (VCI), atrial natriuretic peptide and b-type natriuretic peptide assessment, bioimpedance measurement, and relative plasma volume monitoring were used to detect excess fluid (3). Interdialytic excessive weight gain in patients under hemodialysis (HD) treatment is considered a sign of hypervolemia (1,4). Saran et al. reported that UF rate indexed for postdialysis weight >10 mL/h/kg was associated with a higher risk of

* Correspondence: dr.ibrahimdogan@hotmail.com

mortality among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS) (5). Tetsuka et al. reported a strong correlation between VCI diameter and the amount of body fluid in patients under HD treatment. In that study, VCI diameter and body weights of patients decreased after ultrafiltration (6). In addition, during expiration, VCI diameter correlates highly with blood volume during ultrafiltration (7).

Long-term hypervolemic conditions may lead to coronary ischemia due to cardiac dilation, left ventricular hypertrophy (LVH), HT, and decreased coronary reserve. In uremic patients, LVH is initially a useful response that develops as an adaptation to volume overload. However, over time, coronary perfusion reserve is reduced and left ventricular diastolic function is disturbed. This disturbed diastolic dysfunction leads to an increase in left ventricular mass (8).

The endothelium is affected by many molecules in the pathogenesis of ED. Nitric oxide (NO) is the most important of these molecules. Decreased NO level has a critical effect on the endothelial damage process. Asymmetric dimethyl arginine (ADMA), an endogenous and competitive inhibitor of endothelial nitric oxide synthase, is hydrolyzed by the enzyme of dimethyl arginine dimethyl amine hydrolase and is partly discarded through the renal route, resulting in accumulation in renal diseases (9). ADMA, one of the important mediators of accelerated atherosclerosis in CKD, is shown to be a strong predictor of CV disease and mortality in patients with ESRD (9). Increased ADMA level was associated with enlarged atrial volume in the Framingham heart study (8).

We did not find in the literature a study that investigated the association of ADMA with acute hypervolemia in dialysis patients, which is clearly shown to be related to the cardiac effects of chronic hypervolemia. In this study, we aimed to examine the relationship between serum ADMA levels and volume status, CIMT, and cardiac parameters in patients under HD treatment.

2. Materials and methods

This study was carried out in the Eskişehir Osmangazi University Medical Faculty Hospital in 2009 and 2010. The study protocol was in conformity with the ethical guidelines of our institutions (13.02.2008, No. 79), and informed consent was obtained from each participant.

A total of 120 patients with a history of HD treatment for at least 6 months were included in this study. Patients were treated 3 times weekly for 4 h with standard bicarbonate dialysis (138 mmol/L sodium, 35 mmol/L HCO_3, 1.5 mmol/L potassium, 1.25 mmol/L calcium). None of the patients had significant residual renal function. Duration of HD treatment, smoking habits, comorbid illnesses, and patients' medications were recorded.

The causes of ESRD were as follows: diabetic nephropathy in 39 patients, hypertensive nephrosclerosis in 32 patients, chronic glomerulonephritis in 18 patients, postrenal obstruction in 11 patients, polycystic kidney disease in 5 patients, amyloidosis in 4 patients, chronic pyelonephritis in 3 patients, and renovascular disease in 2 patients. The etiology of 6 patients was unknown.

Patients with an average Kt/V value of less than 1.2 within the last 6 months and those having an active infection, malignancy, coronary artery disease (CAD), cerebrovascular disease, decompensated liver or heart disease, history of surgery, burns, or trauma within the last month were excluded from the study.

2.1. Protocol procedures

All of the blood samples for the laboratory tests were taken before hemodialysis. Blood sampling was performed after an overnight fast between 0800 and 1300 hours. The samples were centrifuged at 3000 × *g* for 5 min, and then serum was used to analyze the laboratory parameters (sodium [Na], potassium [K], calcium [Ca], phosphorus, glucose, blood urea nitrogen [BUN], creatinine [Cr], uric acid, total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], triglyceride [TG], albumin, total protein, parathormone [PTH], ferritin, C reactive protein [CRP]). Plasma samples for ADMA measurement were stored at –80 °C until the analysis time.

Serum ADMA levels were measured with the enzyme-linked immunosorbent assay (ELISA) method by using an Immunodiagnostic human ADMA kit (Cat. No.: REF K7814 Immunodiagnostic AG, Bensheim, Germany).

The average values of the 12 measurements, which were taken predialytically from both arms in the previous 3 weeks, were accepted as the mean arterial blood pressure. Body mass index (BMI) was calculated according to the formula of weight (kg)/height (m^2).

2.2. Cardiac assessment

Transthoracic echocardiograms were performed using an Acuson Sequoia C256 device (Siemens AG, Munich, Germany) with a 3.5-MHz transducer. The subjects were examined while they were in the left lateral decubitus position. Echocardiographic measurements of the cardiac dimensions were performed according to the guidelines set by the American Society of Echocardiography (10). Basic measurements included left ventricular (LV) mass, LV mass index, and left ventricular ejection fraction (LVEF). Ejection fraction was higher than 35% in all included patients. Left ventricular mass was calculated by the Devereux formula (left ventricular mass = 0.8 × [1.04 (interventricular septum thickness + left ventricle end – diastolic diameter + posterior wall thickness)^3 – (left ventricle end – diastolic diameter)^3] + 0.6) and body surface area was calculated by the Mosteller formula

(body surface area = [body height (cm) × body weight (kg)/3600]$^{1/2}$). Left ventricular mass index was calculated dividing the left ventricle mass by body surface area.

Vena cava inferior diameters were measured during the expiratory phase. The postdialysis period was selected for echocardiography since this period allows efficient volume state control, due to the association with the least intravascular volume.

2.3. Carotid artery intima–media thickness (CIMT)

The carotid artery intima–media thickness (CIMT) was measured with the same device (Toshiba SSA-240 Ultrasound [Toshiba, Tokyo, Japan]) for all participants using the 7.5-MHz linear array transducer. The measurement was performed bilaterally through a 1-cm proximal bifurcation of the two main carotid arteries while the patient was in a supine position with the head in slight extension. Three measurements were obtained when the intima layer was seen in the anterior and posterior walls, and the arithmetical mean of these three random measurements was used. The presence of atherosclerotic plaque was recorded.

2.4. Study protocol

Cardiothoracic index (CTI) was calculated for all patients by an experienced radiologist. Patients with an ultrafiltration requirement during hemodialysis of over 10 mL/kg per hour according to the weight after dialysis were considered to be hypervolemic if one or more of the following characteristics were present: CTI value above 0.48, signs of hypervolemia in echocardiography (IVC diameter >1.8 cm), or presence of hypervolemia signs in physical examination. High jugular venous pressure, S3 gallop, inspiratory crackles, interstitial edema at chest radiograph, pulmonary venous congestion, and perihilar fullness were considered to be signs of hypervolemia in the physical examination. Patients without evidence of hypervolemia and patients with an ultrafiltration requirement during hemodialysis of less than 10 mL/kg per hour according to the weight after dialysis constituted the normovolemic group.

2.5. Statistical analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Normality distribution of the variables was analyzed using the Shapiro–Wilk test. The variables distributed normally are presented as mean ± standard deviation, whereas the variables not distributed normally are presented as median (25th–75th interquartile range). For normally distributed variables, comparisons between the two independent groups were performed using Student's t-test. For the variables not distributed normally, comparison of the two independent groups was performed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. The relationship between the variables was evaluated with Spearman or Pearson correlation analysis, as appropriate. The independent effect of each variable was assessed by using multivariate linear regression analysis to predict the ADMA. All of the reported P-values were 2-tailed, and those less than 0.05 were considered to be statistically significant.

3. Results

One hundred twenty patients (49 females; mean age: 58 ±1 years) with a HD history for at least 6 months were included in this study. Patients were divided into two groups, hypervolemic and normovolemic. The hypervolemic group included 61 patients (26 females) and the normovolemic group included 59 patients (23 females). Age, dialysis vintage, sex distribution, smoking habits, BMI, Kt/V, and diastolic and systolic blood pressure measurements were similar in the two groups. There was no statistically significant difference between the groups in terms of drugs used or comorbid diseases. The hypervolemia criteria, VCI and CTI, were significantly higher in the hypervolemic group than in the normovolemic group (P < 0.001) (Table 1).

There was no significant difference between the normovolemic group and the hypervolemic group according to Hb, Hct, Na, K, Ca × P, PTH, albumin, uric acid, total cholesterol, LDL-C, HDL-C, TG, or ferritin. In the normovolemic and hypervolemic groups, EF was 66.9 ±1.4% and 63.4 ±1.4%, respectively, but this difference was not statistically significant (P = 0.067). There was no statistically significant difference between the groups in terms of CRP (in the hypervolemic group, CRP was 6.8 [1.9–20.5] mg/dL, and in the normovolemic group, CRP was 5.0 [1.8–16.0] mg/dL, P = 0.631), cardiac mass (in the hypervolemic group, cardiac mass was 178 [152–222] g, and in the normovolemic group, it was 167 [138–203] g, P = 0.610), and mass index (in the hypervolemic group, mass index was 105 [82–125] g/m^2, and in the normovolemic group, it was 100 [84–120] g/m^2, P = 0.692). In the hypervolemic group, CIMT was 0.95 mm (0.72–1.12), and in the normovolemic group, it was 0.85 mm (0.65–1.05), P = 0.232). Thus, CIMT was higher in the hypervolemic group, but this result was not statistically significant. There was a statistically significant difference between the two groups in terms of ADMA (P <0.001); in the hypervolemic group ADMA was 0.69 ±0.57 μmol/L, in the normovolemic group, it was 0.41 ±0.04 μmol/L (Table 2; Figure).

There were positive correlations between serum ADMA and Ca × P, PTH, CRP, CIMT, cardiac mass, VCI, and CTI in the total cohort (P = 0.009, P = 0.021, P <0.001, P = 0.006, P = 0.022, P <0.001, P = 0.016, respectively). There were negative correlations between ADMA and EF

Table 1. Demographic data of hypervolemic and normovolemic patients.

	Normovolemic patients (n = 59)	Hypervolemic patients (n = 61)	P
Age (years)	57 ± 2	59 ± 2	0.475
Dialysis duration (months)	36 (20–50)	36 (19–63)	0.349
Sex (female/male)	23/36	26/35	0.685
Smoking (Y/N)	20/39	18/43	0.749
BMI (kg/m^2)	24.8 ± 0.6	24.9 ± 0.7	0.894
DBP (mmHg)	73 (70–80)	76 (70–80)	0.344
SBP (mmHg)	120 ± 2	122 ± 2	0.625
Kt/V	1.42 ± 0.03	1.49 ± 0.04	0.349
CTI	43.2 ± 0.5	50.6 ± 0.8	<0.001
VCI (cm)	1.42 ± 0.21	2.03 ± 0.18	<0.001
EPO (Y/N)	47/12	51/10	0.577
Calcitriol (Y/N)	9/50	18/43	0.062
ACE inhibitor (Y/N)	0/59	1/60	-
Beta blockers (Y/N)	9/50	5/56	0.229
Calcium channel blockers (Y/N)	4/55	4/57	0.961
Statin (Y/N)	8/51	3/58	0.101
HT (Y/N)	50/9	46/18	0.085
PAD (Y/N)	14/45	15/46	0.912
CAD (Y/N)	28/31	31/30	0.713
CPD (Y/N)	10/49	12/49	0.700
CVD (Y/N)	6/53	6/55	0.951
DM (Y/N)	23/36	26/35	0.685

BMI: Body mass index; Y: yes; N: no; CTI: cardiothoracic index; EPO: erythropoietin; HT: hypertension; PAD: peripheral artery disease; CAD: coronary artery disease; CPD: chronic pulmonary disease; CVD: cerebrovascular disease; DM: diabetes mellitus; DBP: diastolic blood pressure; SBP: systolic blood pressure.

and albumin (P = 0.024, P = 0.024, respectively) (Table 3), but there was no significant correlation between ADMA and mass index (P= 0.063).

As a result of multiple linear regression analysis, ADMA was independently associated with systolic BP, CTI, volume status, and age (P = 0.005, P <0.001, P = 0.003, P = 0.05, respectively) (Table 4).

4. Discussion

In our study, serum ADMA levels were significantly higher in hypervolemic patients under HD treatment and serum

Table 2. Comparison of hypervolemic and normovolemic patients.

	Normovolemic patients (n = 59)	Hypervolemic patients (n = 61)	P
Hb (g/dL)	11.3 ± 0.2	11.4 ± 0.2	0.835
Hct (%)	34.5 ± 0.5	35.0 ± 0.5	0.486
Na (mEq/L)	138 (135–139)	138 (135–139)	0.994
K (mEq/L)	4.2 (3.7–4.9)	4.4 (3.8–4.9)	0.332
Ca × P	59.3 ± 2.1	56.1 ± 2.4	0.310
Uric acid (mg/dL)	4.8 ± 0.2	4.5 ± 0.3	0.408
Ferritin (ng/mL)	708 ± 36	720 ± 38	0.805
Albumin (g/dL)	3.9 (3.8–4.0)	3.9 (3.7–4.1)	0.671
PTH (pg/mL)	249 (99–438)	240 (119–550)	0.500
HCO_3 (mmol/L)	22 ± 0.3	23 ± 0.3	0.536
Total cholesterol (mg/dL)	162 ± 6	166 ± 5	0.665
LDL-C (mg/dL)	83 ± 4	85 ± 4	0.803
Triglyceride (mg/dL)	162 (132–230)	159 (132–216)	0.838
HDL-C (mg/dL)	38 ± 1	41 ± 2	0.149
ADMA (μmol/L)	0.41 ± 0.04	0.69 ± 0.57	<0.001
CRP (mg/dL)	5.0 (1.8–16.0)	6.8 (1.9–20.5)	0.631
CIMT (mm)	0.85 (0.65–1.05)	0.95 (0.72–1.12)	0.232
EF (%)	66.9 ± 1.4	63.4 ± 1.4	0.067
Cardiac mass (g)	167 (138–203)	178 (152–222)	0.610
Mass index	100 (84–120)	105 (82–125)	0.692

BMI: Body mass index; CIMT: carotid artery intima–media thickness; CRP: C reactive protein; EF: ejection fraction.

Table 3. Correlation analysis between ADMA and other parameters in dialysis patients.

	r	P
CRP	0.303	<0.001
CIMT	0.230	0.006
Ca × P	0.218	0.009
PTH	0.193	0.021
Albumin	–0.188	0.024
EF	–0.190	0.024
Cardiac mass	0.217	0.022
Mass index	0.166	0.063
VCI	0.348	<0.001
CTI	0.201	0.016

Table 4. Prediction of ADMA by use of multiple linear regression analysis.

Variables	Multiple linear regression analysis		
	B (95% Cl)	T	P
Age	–0.005 (–0.010 to 0.001)	–1.987	0.050
CRP	0.001 (–0.001 to 0.004)	0.423	0.673
CIMT	0.021 (–0.209 to 0.251)	0.179	0.859
Volume	0.230 (0.083 to 0.378)	3.103	0.003
CTI	–0.030 (–0.045 to –0.014)	–3.862	<0.001
VCI	0.087 (–0.300 to 0.474)	0.446	0.657
Systolic BP	–0.007 (–0.012 to –0.002)	–2.903	0.005
Mass index	0.001 (–0.001 to 0.004)	1.260	0.211

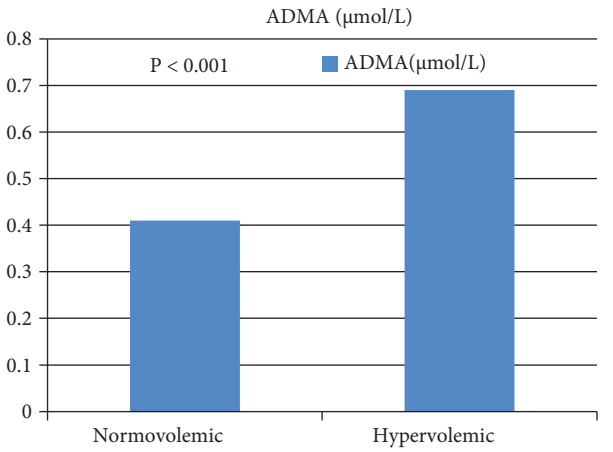

Figure. ADMA levels of hypervolemic and normovolemic patients.

ADMA levels were associated with LV mass, inflammation, malnutrition, and markers of atherosclerosis.

Hypervolemia is one of the most frequently studied subjects in ESRD patients, but the effect of hypervolemia on serum ADMA levels in patients under HD treatment who have the clinical findings of hypervolemia has not been studied before.

LVH, the most important predictor of mortality, is seen in about 75% of patients who initiate dialysis therapy (11). LVH etiology in ESRD is multifactorial. HT, anemia, hyperparathyroidism, volume overload, inflammation, and hyperhomocysteinemia may be involved in its etiology (12). This situation is strongly associated with all-cause mortality (13). Control of the hypervolemia results in the increased effectiveness of HD therapy, control of the hypertension, and improvement in the life quality of patients (14). It has been suggested that ADMA may cause LVH by causing HT (15). Ozkahya et al. found a significant reduction in LV mass and improvement in heart size in patients with reduced blood pressure by intensive ultrafiltration. Reduction in volume load is as important as decrease in blood pressure (16). Increased ultrafiltration, even in patients with peritoneal dialysis without findings of hypervolemia, resulted in a reduction in VCI size, better blood pressure control, and reduced left ventricular diameter (17).

In the study of Ozturk et al., serum ADMA levels were correlated with ultrafiltration volume and echocardiographic findings of hypervolemia in clinically nonhypervolemic patients under peritoneal dialysis treatment. In this study, ADMA was higher in hypertensive patients, males, and ASA users, and the relationship between HT and ADMA observed in univariate regression analysis was lost in multivariate regression analysis. In the same study, 13 of 14 patients using ASA were hypertensive, and findings like increased left atrial diameter and increased ultrafiltration volume were more frequent in hypertensive patients. In this study, in which hypertensive and normotensive patients were similar in terms of sex and BMI, the cause for the disappearance of the relationship between HT and ADMA in the multivariate regression analysis was thought to be due to the use of ASA and the effect of volumetric parameters. In addition, in this study, serum ADMA level was increased in ischemic heart disease, but it was not statistically significant (18). Therefore, according to this study, it is possible to say that ADMA may be affected by the atherosclerotic process and hypervolemia.

In our study, serum ADMA levels were higher in patients with clinical findings of acute hypervolemia than in normovolemic patients, although the patient groups were similar in terms of age, sex, BMI, smoking, HT, DM, drug use, and cardiovascular and cerebrovascular disease.

In addition, CIMT, cardiac mass, and office blood pressure were similar, while ADMA was only elevated in hypervolemic patients. Similarly, in multiple linear regression analysis, independent association of ADMA with hypervolemia suggested that ADMA may be elevated as a sign of hypervolemia.

Since high serum ADMA levels are associated with endothelial dysfunction leading to the onset and acceleration of atherosclerosis, it is considered to be an unconventional risk factor for cardiovascular disease (19). Serum ADMA levels were found to be associated with CIMT (20,21) and left ventricular hypertrophy (22) in both the general population and patients with ESRD. In the study of Zoccali et al., serum ADMA levels were associated with LVH in patients with preserved EF who

were normotensive and had the target dry weight (22). The cardiac and arterial systems create an integrated unit that responds consistently to hemodynamic stimuli as well as the endothelium, which plays an important role in the regulation of cardiovascular remodeling. London et al. showed parallel progression of cardiac and arterial remodeling in uremic patients (23). Atherosclerosis is a complex multifactorial process in which the endothelial dysfunction is believed to be the first stage. The decrease in NO synthesis is associated with increased blood pressure through vasoconstriction and endothelial dysfunction. ADMA has also been associated with uremic cardiomyopathy (24).

In our study, the association of LV mass and CIMT with ADMA suggests that ADMA may be indicative of vascular and structural pathologic findings in the development of cardiovascular adverse events.

Malnutrition, inflammation, and atherosclerosis (MIA) have been identified in uremic patients. Inflammation contributes to the development of endothelial dysfunction, atherosclerosis, and vascular calcification through the secretion of acute phase proteins and cytokines. Inflammation is also accompanied by malnutrition and hypoalbuminemia. In the study of Allawi et al., carotid atherosclerosis was shown to have a significant association with inflammation (high serum CRP) and malnutrition (low serum albumin) in patients under hemodialysis treatment (25). In our study, ADMA, known to be associated with ED and atherosclerosis, is associated with MIA markers (low albumin, high CRP, high CIMT).

In the inotropic state, NO production is increased by the human myocardium and contributes to the modulation of LV function (26,27). In our study, in findings similar to those of Zoccali et al., we found that the ADMA and ejection fractions were inversely related; this was thought to reflect the interaction of NO with the functional role on cardiac inotropism (21).

Our study has some limitations. All of the patients were from the same region. The number of patients was relatively small. Quantitative methods such as bioimpedance method and the inferior vena cava collapsing index could have been used for the detection of hypervolemic patients.

In conclusion, we found that serum ADMA level was an independent determinant of hypervolemia in HD patients with symptoms of hypervolemia, and ADMA was associated with cardiac mass, inflammation, malnutrition, and atherosclerosis markers (CIMT). These results suggest that ADMA may be a potential determinant of hypervolemia as well as atherosclerosis in patients under hemodialysis treatment.

A new uremic toxin, ADMA, seems to cause ED and appears to be involved in left ventricular structure, function, and remodeling. In addition, ADMA is elevated in hypervolemic patients independently of other factors, but it is not yet clear whether a high level of ADMA is a cause or a result.

References

1. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van WD, Bunnapradist S, Horwich TB, Fonarow GC. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. Circulation 2009; 119: 671-679.
2. Muntner, JH, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the Atherosclerosis Risk in Communities study. J Am Soc Nephrol 2005; 16: 529-538.
3. Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. Hypertension 2010; 56: 512-517.
4. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. Kidney Int 2002; 62: 1784-1790.
5. Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, Kimata N, Gillespie BW, Combe C, Bommer J et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int 2006; 69: 1222–1228.
6. Tetsuka T, Ando Y, Ono S, Asano Y. Change in inferior vena caval diameter detected by ultrasonography during and after hemodialysis. ASAIO J 1995; 41: 105-110.
7. Yashiro M, Kamata T, Yamadori N, Tomita M, Muso E. Evaluation of markers to estimate volume status in hemodialysis patients: atrial natriuretic peptide, inferior vena cava diameter, blood volume changes and filtration coefficients of microvasculature. Ther Apher Dial 2007; 11: 131-137.
8. Lieb W, Benndorf RA, Benjamin EJ, Sullivan LM, Maas R, Xanthakis V, Schwedhelm E, Aragam J, Schulze F, Böger RH et al. Plasma asymmetric dimethylarginine, L-arginine, and left ventricular structure and function in a community-based sample. Atherosclerosis 2009; 204: 282-287.
9. Shafi T, Hostetter TH, Meyer TW, Hwang S, Hai X, Melamed ML, Banerjee T, Coresh J, Powe NR. Serum asymmetric and symmetric dimethylarginine and morbidity and mortality in hemodialysis patients. Am J Kidney Dis 2017; 70: 48-58.
10. Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072-1083.
11. Shin SJ, Kim HW, Chung S, Chung HW, Lee SJ, Kim YS, Bang BK, Chang YS, Park CW. Late referral to a nephrologist increases the risk of uremia related cardiac hypertrophy in patients on hemodialysis. Nephron Clin Pract 2007; 107: 139-146.

12. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol 2009; 4: 79-91.

13. Agarwal R. Interdialytic hypertension: an update. Adv Chronic Kidney Dis 2011; 18: 11-16.

14. London GM, Marchais SJ, Guerin AP, Metivier F, Pannier B. Cardiac hypertrophy and arterial alteration in end-stage renal disease. Hemodynamic factors. Kidney Int 1993; 43: 42-49.

15. Zoccali C, Bode-Boger S, Mallamaci F, Benedetto F, Tripepi G, Malatino L, Cataliotti A, Bellanuova I, Fermo I, Frolich J et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. Lancet 2001; 358: 2113-2117.

16. Ozkahya M, Ok E, Cirit M, Aydin S, Akcicek F, Basci A, Dorhout Mees EJ. Regression of left ventricular hypertrophy in hemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. Nephrol Dial Transplant 1998; 13: 1489-1493.

17. de Castro Júnior JR, Fernandes N, Lacet TB, Maia FS, Bonato GR, Nogueira C, Barberato SH, de Paula RB. Total body water reduction in subjects with chronic kidney disease on peritoneal dialysis is associated with a better hypertension control. J Bras Nefrol 2014; 36:482-489.

18. Ozturk S, Karadag S, Yegen M, Gursu M, Uzun S, Aydin Z, Gurdal A, Koldas M, Kumbasar B, Kazancioglu R. The relationship of plasma ADMA levels with cardiac functions and metabolic parameters in peritoneal dialysis patients. Clin Exp Nephrol 2013; 17: 431-436.

19. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimburger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol 2008; 3: 505-5221.

20. Furuki K, Adachi H, Matsuoka H, Enomoto M, Satoh A, Hino A, Hirai Y, Imaizumi T. Plasma levels of asymmetric dimethylarginine (ADMA) are related to intima–media thickness of the carotid artery: an epidemiological study. Atherosclerosis 2007; 191: 206-210.

21. Zoccali C, Benedetto FA, Renkemaas, 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.

22. Zoccali C, Mallamaci F, Maas R. Left ventricular hypertrophy cardiac remodeling and asymmetric dimethylarginine (ADMA) in hemodialysis patients. Kidney Int 2002; 62: 339-345.

23. London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F. Cardiac and arterial interactions in end-stage renal disease. Kidney Int 1996; 50: 600-608.

24. Avci E, Coskun S, Cakir E, Kurt Y, Ozgur Akgul E, Bilgi C. Relations between concentrations of asymmetric dimethylarginine and neopterin as potential risk factors for cardiovascular diseases in haemodialysis-treated patients. Ren Fail 2008; 30: 784-790.

25. Allawi AAD. Malnutrition, inflammation, and atherosclerosis (MIA syndrome) in patients with end-stage renal disease on maintenance hemodialysis (a single centre experience). Diabetes Metab Syndr 2017; 17: 302-308.

26. Kuhlencordt PJ, Gyurko R, Han F, Scherrer-Crosbie M, Aretz TH, Hajjar R, Picard MH, Huang PL. Accelerated atherosclerosis, aortic aneurysm formation, and ischemic heart disease in apolipoprotein E/endothelial nitric oxide synthase double-knock-out mice. Circulation 2001; 104:448-454.

27. Hattler BG, Oddis CV, Zeevi A, Luss H, Shah N, Geller DA, Billiar TR, Simmons RL, Finkel MS. Regulation of constitutive nitric oxide synthase activity by the human heart. Am J Cardiol 1995; 76: 957-959.