Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: www.tandfonline.com/journals/irnf20

The Relationship among Asymmetric Dimethylarginine (ADMA) Levels, Residual Renal Function, and Left Ventricular Hypertrophy in Continuous Ambulatory Peritoneal Dialysis Patients

Fatma Ayerden Ebinç, Yasemin Erten, Haksun Ebinç, Hatice Paşaoğlu, Canan Demirtaş, Gülten Taçoy, Rüya Mutluay, Eyüp Koç, Ulver Derici, Kadriye Altok Reis, Musa Bali, Turgay Arınsoy & Şükrü Sindel

To cite this article: Fatma Ayerden Ebinç, Yasemin Erten, Haksun Ebinç, Hatice Paşaoğlu, Canan Demirtaş, Gülten Taçoy, Rüya Mutluay, Eyüp Koç, Ulver Derici, Kadriye Altok Reis, Musa Bali, Turgay Arınsoy & Şükrü Sindel (2008) The Relationship among Asymmetric Dimethylarginine (ADMA) Levels, Residual Renal Function, and Left Ventricular Hypertrophy in Continuous Ambulatory Peritoneal Dialysis Patients, Renal Failure, 30:4, 401-406, DOI: 10.1080/08860220801964285

To link to this article: https://doi.org/10.1080/08860220801964285

Published online: 07 Jul 2009.

Renal Failure, 30:401–406, 2008

ISSN: 0886-022X print / 1525-6049 online
DOI: 10.1080/08860220801964285

informa
healthcare

CLINICAL STUDY

The Relationship among Asymmetric Dimethylarginine (ADMA) Levels, Residual Renal Function, and Left Ventricular Hypertrophy in Continuous Ambulatory Peritoneal Dialysis Patients

Fatma Ayerden Ebinç and Yasemin Erten
Gazi University, Faculty of Medicine Department of Nephrology, Ankara, Turkey

Haksun Ebinç
Kırıkkale University, Faculty of Medicine Department of Cardiology, Kırıkkale, Turkey

Hatice Paşaoğlu and Canan Demirtaş
Gazi University, Faculty of Medicine, Department of Biochemistry, Ankara, Turkey

Gülten Taçoy
Gazi University, Faculty of Medicine Department of Cardiology, Ankara, Turkey

Rüya Mutluay, Eyüp Koç, Ulver Derici, Kadriye Altok Reis, Musa Bali, Turgay Arınsoy, and Şükrü Sindel
Gazi University, Faculty of Medicine, Department of Nephrology, Ankara, Turkey

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of endothelial-based nitric oxide synthase. Its level is increased by end stage renal disease. However, most studies showing an increase in ADMA in dialysis patients have focused on hemodialysis. Results with peritoneal dialysis patients have been more inconclusive. Recent studies suggest that ADMA may be a new cardiovascular risk factor. The aim of the present study was to evaluate the relationship between ADMA levels, residual renal function, and left ventricular hypertrophy in peritoneal dialysis patients. Serum ADMA measurements and echocardiographic evaluations were performed in 54 peritoneal dialysis patients and 26 healthy volunteers. Residual renal function was measured in peritoneal dialysis patients by urea clearance from a urine collection. Thirty-two of the 54 peritoneal dialysis patients had residual renal function. ADMA levels of the peritoneal dialysis group were found to be significantly higher than those of healthy individuals (p = 0.03). Within the peritoneal dialysis group, ADMA levels of patients with residual renal function were significantly lower than those without residual renal function (p = 0.01), though they were still higher than the ADMA levels of the control group (p = 0.04). Serum levels of ADMA were positively correlated with left ventricular mass index (r = 0.29, p = 0.01) and negatively correlated with early mitral inflow velocity (Em) (r = –0.28, p = 0.01), Em/Late mitral inflow velocity (Am) (r = –0,32, p = 0.00), and isovolumetric relaxation time (r = –0.30, p = 0.01). In conclusion, increased ADMA levels seem to be associated with left ventricular hypertrophy in peritoneal dialysis patients, and residual renal function may lead to a reduction of serum ADMA levels.

Keywords CAPD, ADMA, residual renal function, left ventricular hypertrophy

INTRODUCTION

It is well known that cardiovascular disease is the most important cause of mortality in end stage renal disease (ESRD) patients, and the mortality risk is increased more than 100 times when compared to the general population.[1] Defining the cardiovascular risk factors in these patients is

Address correspondence to Fatma Ayerden Ebinç MD, Gazi University, Faculty of Medicine, Department of Nephrology, 06510 Besevler, Ankara, Turkey; Fax: +90312 2129006; E-mail: fayerdenebin@yahoo.com

critical to the prevention of cardiovascular events.[2] Recent studies suggest that Asymmetric dimethylarginine (ADMA) may be a new cardiovascular risk factor in both normal subjects and ESRD patients.[3–5]

ADMA is an endogenous inhibitor of endothelial-based nitric oxide synthase.[4] Nitric oxide (NO) is not only an endothelial-based strong vasodilator, but it also prevents incidents that can trigger the development of atherosclerosis, such as leukocyte adhesion, platelet aggregation, and vascular smooth muscle cell proliferation.[5] NO also controls vascular regeneration through angiogenesis, thus protecting against the development of atherosclerosis.[5] It also protects against the development of left ventricular hypertrophy (LVH). Previous studies reported that NO controls the growth of the myocardium and is influential in the development of cardiac remodeling, which in turn has an antiproliferative effect on the myocardium.[6] As a peripheral vasodilator, it additionally reduces both afterload and preload. This hemodynamic effect of NO helps the prevention of LVH.[6] ADMA eliminates these positive effects by suppressing NO synthesis.[4] As a result, NO inhibition by ADMA may lead to cardiovascular events, including the development of atherosclerosis and LVH.

As ADMA is partially eliminated through urine, kidney failure causes its level to increase.[4] This increase is suggested to be related to an increase in cardiovascular risk commonly seen in dialysis patients.[4,5,7,8] This hypothesis was supported by Zoccali et al, who demonstrated a relationship between LVH and ADMA in hemodialysis patients.[9]

It has been postulated that cardiovascular mortality in dialysis patients decreases in the presence of residual renal function (RRF).[10] To the best of our knowledge, there is no study evaluating the relationship between ADMA level, RRF, and cardiovascular disease in ESRD patients.

In the present study, we aimed to evaluate the relationship between ADMA levels, RRF, and LVH in peritoneal dialysis patients.

MATERIAL AND METHODS

Fifty-four continuous peritoneal dialysis outpatients at Gazi University School of Medicine Clinic of Nephrology who had been receiving dialysis for at least six months were admitted to the study, along with 26 healthy volunteers in the control group. Subjects diagnosed with valve disease, atherosclerotic heart disease, or cardiovascular disease were excluded from the study, as were those with uncontrolled blood pressure, hypervolemia or a disease causing active inflammation. Kidney failure was due to amyloidosis in two subjects, polycystic kidneys in four, diabetes mellitus in five, glomerulonephritis in nine, and nephrolithiasis in four. The etiology was unknown in 30 of 54 patients. Of the patients, 8 had diabetes mellitus, and 39 had hypertension. Our patients were performing their CAPD treatment using lactate containing standard dialysis solution for four or five exchanges. The patients had been on peritoneal dialysis for 55.5 ± 49 months on average. Prior to the study, all patients were informed and their consent was taken. The study was approved by the Ethical Committee on Studies Involving Human Beings at Gazi University, Faculty of Medicine. The blood pressures of all subjects were calculated as the average values of eight measurements that were taken during a period of one month. Body mass index (BMI) was calculated as BM = kg/m^2). Blood samples were drawn after a 12-hour fasting, and serum glucose, albumin, high sensitive C-reactive protein (hsCRP), blood urea nitrogen (BUN), creatinine, calcium (Ca), phosphate ($P0_4$), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin, and intact parathormone (iPTH) measurements were made using standard methods in the routine biochemistry laboratory.

Serum samples separated for ADMA measurement were stored at −70°C for a short period of time, and the tests were performed by ELISA (enzyme-linked immunosorbent assay) method using immunodiagnostic AG kits (Stubenwald-Allee 8a D-64625 Bensheim, lot number K7812-070115). The dialysis adequacy of the patients was assessed by using the Kt/V formulation:

$$eKt/V = spKt/V - (0.6) \times (K/V) + 0.03.$$

In CAPD patients who had urine, 24-hours urine was collected, and residual renal function was calculated by urea clearance method.[11] Urea clearance was calculated with the following formula:

$$\text{Urea clearance (KRU) (mL/min)} = (U \times V)/1440 \times P$$

where U = urinary urea concentration (mmol/L), V = volume of the 24 hour urine collection (ml), and P = plasma urea concentration (mmol/L).

Echocardiography

All subjects in the study evaluated with 2D, M-Mode, pulse wave Doppler, and tissue doppler echocardiography using GE Vivid 7 dimension echocardiography machine. Echocardiographic evaluations were performed at left lateral decubitus position with standard techniques. 2D long-axis views were used to obtain linear measurements of left ventricular cavity. Left ventricular mass (LVM)

was estimated by using the anatomically validated formula of Devereux et al.[12]:

$$LVM = 0.8\ (1.04\ (IVST + LVID + LPWT)^3 - LVID^3) + 0.6$$

where IVST = interventricular septal thickness, LVID = left ventricular internal dimension, and LPWT = left posterior wall thickness. Left ventricular mass index (LVMI) was calculated by the following formula[12]:

$$LVM/height^{2,7}[12]$$

Mitral inflow velocities were obtained by pulse wave Doppler in the apical four-chamber view with the sample volume placed at the tips of the mitral valve leaflets. The ratio of early diastolic to late diastolic mitral inflow velocities was measured. Color tissue Doppler imaging was performed from the apical four-chamber view, and the images were digitized. Myocardial velocity profiles of the lateral mitral annulus were obtained by placing a 6 mm-sample volume at the junction of the mitral annulus and lateral myocardial wall. Early, late diastolic velocities, systolic velocities, and IVRT were measured from two consecutive cardiac cycles and averaged. The ratios of early to late diastolic mitral annular velocities were calculated.

Statistical Analysis

Data are shown as mean ± SD or as percentages. Comparisons between groups were performed by student's t test, chi-square test, or one-way analysis of variance (ANOVA), as appropriate. Univariate correlation was established by Pearson's correlation coefficient. To assess the influence of tested parameters on LVMI as the dependent variable, multiple regression analysis was performed. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS version 13). Significance was defined as a p value less than 0.05.

RESULTS

Thirty-two of the 54 peritoneal dialysis patients had RRF. Using the urea clearance method, mean RRF was 5.94 ± 5.07 mL/min in these patients. Their average ultrafiltration was 1123.17 ± 419.83, urine amount was 739.77 ± 506.54 milliliters, and the average Kt/V of patients was 1.55 ± 0.44.

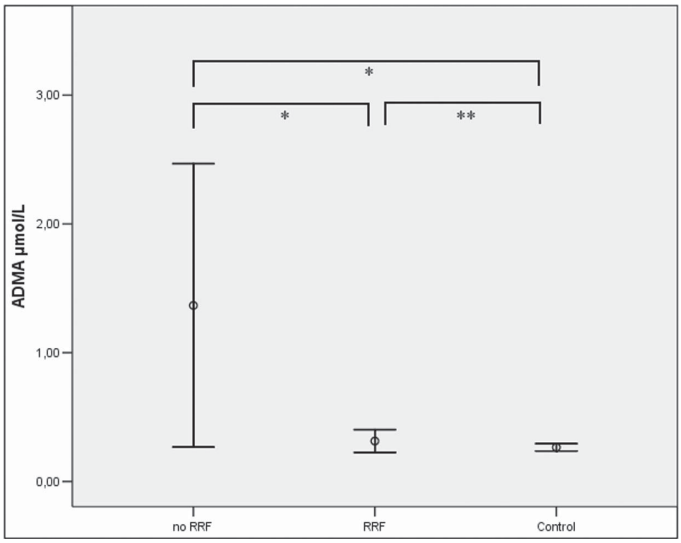
The anthropometric, demographic, and biochemical parameters comparing the control group and the peritoneal dialysis patients are given in Table 1. ADMA levels of the peritoneal dialysis group were found to be significantly higher than those of healthy individuals (p = 0.03; see Table 1). Within the peritoneal dialysis group, ADMA levels of patients with RRF were significantly lower than those without residual renal function (0.32 ± 0.24 μmol/L and 1.36 ± 2.48 μmol/L respectively; p = 0.014); however, they were still higher than the ADMA levels of the control group (0.25 ± 0.05 μmol/L, p = 0.04; see Figure 1). Among the peritoneal dialysis patients, those with residual renal function included 26 hypertensive patients, whereas those without residual renal function included 13 hypertensive patients. In the assessment done with the χ^2 test, no significant difference existed between groups with respect to the presence of hypertension (p = 0.07). When compared, there was no significant difference for the duration of dialysis, Kt/V levels, fasting blood glucose, hemoglobin, iPTH, Ca, $P0_4$, albumin, hsCRP, and ferritin levels between patients with and without RRF. Mean systolic/diastolic blood pressures were found in the RRF group, 122.58 ± 8.83/73.06 ± 10.85, and without the RRF group, 122.50 ± 9.85/71.36 ± 10.59. Difference between these groups was not significant.

Table 1
Comparison of selected characteristics between CAPD patients and control subjects

	CAPD patients (n = 54)	Control subjects (n = 26)
Gender (M/F)	29/25	12/14
Age (year)	45.4 ± 14.3	46.7 ± 10.7
BMI (kg/m^2)	24.48 ± 4.24	25.60 ± 3.88
Systolic BP (mmHg)	122.54 ± 9.18	121.71 ± 8.71
Diastolic BP (mmHg)	72.35 ± 10.67	70.76 ± 8.90
Hemoglobin (g/dL)	11.50 ± 1.82†	14.50 ± 1.16†
Fasting blood glucose (mg/dL)	97.06 ± 23.41	91.31 ± 8.78
Blood urea nitrogen (mg/dL)	50.68 ± 12.67†	12.54 ± 2.89†
Creatinine (mg/dL)	8.95 ± 3.18†	0.95 ± 0.20†
Albumine (g/dL)	4.11 ± 0.47†	4.96 ± 0.30†
Calcium (mg/dL)	9.14 ± 0.69†	9.54 ± 0.44†
Phosphate (mg/dL)	5.00 ± 1.35†	3.39 ± 0.43†
T cholesterol (mg/dL)	184.14 ± 44.54	189.18 ± 29.83
LDL cholesterol (mg/dL)	106.92 ± 30.07	118.31 ± 24.73
Triglycerides (mg/dL)	153.32 ± 72.08†	107.22 ± 34.73†
hsCRP (mg/dL)	0.87 ± 2.15	0.98 ± 3.27
iPTH (pg/mL)	358.26 ± 269.27	—
Duration of dialysis (month)	55.50 ± 49.91	—
ADMA (μmol/L)	0.74 ± 1.65	0.25 ± 0.05*

*p < 0.05, $^\dagger p$ < 0.001.

Abbreviations: hsCRP = high sensitive C-reactive protein, iPTH = intact parathormone.



*p = 0.01, **p = 0.04

Figure 1. Comparison of ADMA levels between CAPD patients with residual renal function and those without residual renal function or healthy subjects.

Echocardiographic Findings

A comparison of tissue Doppler echocardiographic parameters of the peritoneal dialysis and control groups is given in Table 2. Left ventricular mass index was higher in the peritoneal dialysis group compared to control subjects. Among the diastolic function parameters obtained through tissue Doppler echocardiography, the early mitral inflow velocity (Em) and Em/Late mitral inflow velocity (Am) levels were significantly lower in CAPD patients when compared to the control group ($p < 0.05$). The IVRT value was significantly prolonged in the patient group ($p < 0.05$; see Table 2). Left ventricular mass of the patients with RRF, without RRF, and the control group were 236.96 ± 72.76 (gr), 204.23 ± 68.43 (gr), and 164.76 ± 45.35 (gr), respectively. The LVMI of these groups were 63.36 ± 21.92 (gr/m^{2,7}), 54.59 ± 13.60 (gr/m^{2,7}), and 42.43 ± 11.33 (gr/m^{2,7}), respectively. The difference between the with-RRF and without-RRF groups was not significant. Additionally, the left atrial diameters of these groups were 34.42 ± 6.19 (mm), 33.42 ± 5.90 (mm), and 30.27 ± 6.45 (mm), respectively. The difference between groups was not statistically significant.

There was a significant negative correlation between ADMA and Em (r = –0.28, p=0.01), Em/Am (r = –0.32, p = 0.00), and IVRT (r = –0.30, p = 0.01), and a positive correlation with LVMI (r = 0.29, p = 0.01) in CAPD patients. When the LVMI was taken as the dependent variable and ADMA, BMI, age, and hCRP were taken as independent variables, linear regression analysis showed that statistical significance was only seen between BMI and left ventricular mass index (β = 0.294, p = 0.04).

Table 2
Comparison of echocardiographic parameters between CAPD patients and control subjects

Echocardiographic parameters	CAPD patients (n = 54)	Control subjects (n = 26)
Ejection fraction (%)	66.84 ± 6.80	62.33 ± 12.09
Fractional shortening (%)	37.32 ± 5.39	34.00 ± 7.51
Em (cm/sn)	9.27 ± 2.66*	11.47 ± 2.65*
Am (cm/sn)	10.62 ± 2.67	10.50 ± 1.84
Em/Am	0.92 ± 0.34*	1.14 ± 0.40*
IVRT (msn)	92.74 ± 24.6†	76.77 ± 13.83†
Systolic velocity (cm/sn)	8.02 ± 1.64	8.19 ± 1.74
LVMI (gr/m^{2,7})	59.74 ± 19.25†	42.43 ± 11.33†

*$p < 0.05$, $^{\dagger}p < 0.001$.

Abbreviations: Em = mitral annular early velocity, Am = mitral annular late velocity, IVRT = isovolumetric relaxation time, LVMI = left ventricular mass index.

DISCUSSION

In our study, we found ADMA levels to be significantly higher in peritoneal dialysis patients than the control group. Studies showing an increase in ADMA in dialysis patients have mostly focused on hemodialysis.[4] However, results of evaluating serum ADMA levels in

CAPD patients are inconclusive.[8,13,14] While some studies reported ADMA levels 2–6 greater in CAPD patients,[13,14] Kielstein et al. did not report any difference of ADMA levels in CAPD patients and healthy subjects.[8] Additionally, there are several reports suggesting increased cardiovascular risk in hemodialysis and CAPD patients with high serum levels of ADMA.[4,5,7,8] This increased risk is believed to be a result of the NO inhibition. In the blood vessel, NO relaxes vascular smooth muscle to increase blood flow and suppresses processes involved in vascular disease, including leukocyte adhesion, platelet aggregation and vascular smooth muscle cell proliferation. All of these factors have a role in the development of atherosclerosis. Consequently an endogenous NO synthase inhibitor such as ADMA should be associated with vascular disease.[4,5,15] Increased ADMA level is also suggested to be related to the development of endothelial dysfunction. Endothelial dysfunction refers to a disruption in the regulating role of endothelium in cardiovascular incidents, such as vascular dilatation, fibrinolysis, or smooth muscle cell proliferation.[16] The most important reason for endothelial dysfunction is a reduction in the amount of nitric oxide or its bioavailability.[16] The inhibitor effects of ADMA on NO synthesis may also lead to endothelial dysfunction, which may in turn cause an increase in cardiovascular events.[16]

Another risk factor increasing cardiovascular mortality in end stage renal disease patients is LVH.[17] The present study demonstrated a significant relationship between LVMI and ADMA level in CAPD patients. The relationship between ADMA and LVH may be due to hemodynamic load as a result of the decrease in NO synthesis, disruption in cardiac remodeling, and the development of endothelial dysfunction.[6] Pannier et al. postulated that endothelial dysfunction and the development of LVH are related in patients with advanced kidney failure.[18] Several experimental studies have also suggested a relationship between NO inhibition and LVH.[19]

Similar to study reported by Zoccali et al. in hemodialysis patients,[9] we found a positive relationship between LVMI and serum ADMA levels in CAPD patients. They also suggested that ADMA is an independent risk factor in left ventricular hypertrophy development in hemodialysis patients.[9] Although a significant relationship between ADMA and LVMI was demonstrated in the present study, linear regression analysis did not show ADMA as an independent risk factor for LVH. This may be due to the small number of patients in our study. A result of this study's negative correlation was found between ADMA levels and Em, Em/Am, and IVRT. This result suggests that elevated ADMA levels may negatively affect left ventricular diastolic functions in CAPD patients. Our study is the first study a relationship shown between ADMA and left ventricular diastolic dysfunction. Further large-scale, prospective studies are needed concerning this subject.

Another conclusion of the present study is that ADMA levels are lower in the presence of RRF. This may be due to the contribution of RRF to ADMA's renal elimination and metabolism.

Recently, it has been claimed that RRF has positive effects on cardiovascular events and LVH.[10] However, in our study, LVMI was higher in patients with RRF than in patients without RRF. This condition has been thought to be related to a higher rate of hypertension in patients with RRF.

RRF is generally accepted to have positive effects on the cardiovascular outcome.[10] These effects cannot be solely explained by the better volume control of patients with RRF. Low serum ADMA levels in the presence of RRF may also reduce cardiovascular events.

A major limitation of our study was the cross-sectional design. A prospective study with a large sample size may be more meaningful about this issue.

In conclusion, the present study has found serum ADMA levels of peritoneal dialysis patients to be significantly higher than healthy individuals. Increased ADMA level may have a negative effect on left ventricular structure. Therefore, observing ADMA levels may lead to an awareness of early cardiovascular risk increase in dialysis patients. Additionally, factors leading to a reduction in ADMA levels, such as RRF, may lead to a reduction of cardiovascular events. Larger scale studies are needed to support of this issue.

REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ.Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32(5 Suppl. 3):S112–S119.
2. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med*. 2003;115(4):291–297.
3. Zoccali C, Bode-Boger S, Mallamaci F, Benedetto F, Tripepi G, Malatino L, et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: A prospective study. *Lancet*. 2001; 358(9299): 2113–2117.
4. Kielstein JT, Bode-Boger SM, Frolich JC, Haller H, Boger RH. Relationship of asymmetric dimethylarginine to dialysis treatment and atherosclerotic disease. *Kidney Int Suppl*. 2001;78:S9–S13.
5. Kielstein JT, Fliser D. The past, presence and future of ADMA in nephrology. *Nephrol Ther*. 2007;3(2):47–54.
6. Simko F, Simko J. The potential role of nitric oxide in the hypertrophic growth of the left ventricle. *Physiol Res*. 2000;49(1):37–46.

7. Kielstein JT, Zoccali C. Asymmetric dimethylarginine: A cardiovascular risk factor and a uremic toxin coming of age? *Am J Kidney Dis*. 2005;46(2):186–202.
8. Kielstein JT, Boger RH, Bode-Boger SM, Schaffer J, Barbey M, Koch KM, Frolich JC. Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: relationship to treatment method and atherosclerotic disease. *J Am Soc Nephrol*. 1999;10(3):594–600.
9. Zoccali C, Mallamaci F, Maas R, Benedetto FA, Tripepi G, Malatino LS, et al. CREED Investigators. Left ventricular hypertrophy, cardiac remodeling and asymmetric dimethylarginine (ADMA) in hemodialysis patients. *Kidney Int.* 2002;62(1):339–345.
10. Wang AY, Lai KN. The importance of residual renal function in dialysis patients. *Kidney Int.* 2006;69(10):1726–1732.
11. McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K. Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. *Kidney Int.* 2002;61(1):256–265.
12. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roan RJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. *Journal of the American College of Cardiology*. 1992;20:1251–1260.
13. Anderstam B, Katzarski K, Bergstrom J. Serum levels of NG, NG-dimethyl-L-arginine, a potential endogenous nitric oxide inhibitor in dialysis patients. *J Am Soc Nephrol*. 1997;8(9):1437–1442.
14. Schmidt RJ, Domico J, Samsell LS, Yokota S, Tracy TS, Sorkin MI, et al. Indices of activity of the nitric oxide system in hemodialysis patients. *Am J Kidney Dis.* 1999;34(2):228–234.
15. 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(8):2449–2455.
16. Yilmaz MI, Saglam M, Caglar K, Cakir E, Sonmez A, Ozgurtas T, et al. The determinants of endothelial dysfunction in CKD: Oxidative stress and asymmetric dimethylarginine. *Am J Kidney Dis.* 2006;47(1):42–50.
17. Erten Y, Tulmac M, Derici U, Pasaoglu H, Altok Reis K, Bali M, et al. An association between inflammatory state and left ventricular hypertrophy in hemodialysis patients. *Ren Fail.* 2005;27(5):581–589.
18. Pannier B, Guerin AP, Marchais SJ, Metivier F, Safar ME, London GM. Postischemic vasodilation, endothelial activation, and cardiovascular remodeling in end-stage renal disease. *Kidney Int.* 2000;57(3):1091–1099.
19. Sladek T, Gerova M, Znojil V, Devat L. Morphometric characteristics of cardiac hypertrophy induced by long-term inhibition of NO synthase. *Physiol Res.* 1996;45(4):335–338.