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Original Article

Correlation research on ADMA plasma levels and left ventricular function of peritoneal dialysis patients

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Abstract: Asymmetric dimethylarginine (ADMA) has been involved in the development mechanism of cardiovascular disease (CVD) in patients with chronic kidney disease. The aim of this study is to investigate the relationship between the plasma ADMA levels and echocardiography, and understand the relationship between ADMA and left ventricular function. All of the patients were divided into three groups, including End-stage renal disease patients on CAPD, Conservative treatment in patients with ESRD and Control group. All the cases in the outpatient clinic or hospital at the next morning were collected fasting venous blood 2 ml. All cases were detected by American GE company Vivid7 Colour Doppler Ultrasonic Echocardiograph to detected left ventricular end-diastolic dimension (LVEDD), Left atrial diameter (LAD), Left ventricular posterior wall thickness in diastole (LVPWT), Interventricular septum thickness in diastole (IVST), left ventricular ejection fraction (LVEF). There were significant differences among all of the three groups for the GFR, urine albumin, SGA, Hb, iPTH and ALB levels. There was statistically significant difference for serum ADMA levels among three groups ($F = 34.047$, $P = 0.000$). CAPD patient plasma ADMA levels were negatively correlated with LVEF, and positively correlated with LVMI, LVM, LVEDD, LAD. Conservative treatment group had higher proportion of average artery, left ventricular hypertrophy and left ventricular mass index. The peritoneal dialysis fluid ADMA levels of CAPD patients with peritoneal were positively correlated with LVEF ($r = 0.367$, $P = 0.046$), negatively correlated with LVMI. In conclusion, ADMA may be involved in change of left ventricular structure, function, and remodeling process through a complex network.

Keywords: Asymmetric dimethylarginine, cardiovascular disease, left ventricular function, peritoneal dialysis

Introduction

Asymmetric dimethylarginine (ADMA), as a new type of uremic toxins, is more and more cause the attention of people to be involved in the development mechanism of CVD in patients with chronic kidney disease. Some scholars put forward elevated ADMA as an important factor to predict cardiovascular events in dialysis patients [1-3].

This study examined plasma ADMA levels of ESRD patients with CAPD and conservative treatment, and the peritoneal dialysis fluid ADMA of ESRD patients on CAPD. To investigate the relationship between the plasma ADMA levels and echocardiography, and understand the relationship between ADMA and left ventricular function. Evaluation the influence of CAPD on plasma ADMA levels and therapeutic value in improving cardiac function.

Materials and methods

Specimen source and grouping

End-stage renal disease patients on CAPD: Select the hospital inpatient and outpatient follow-up of Affiliated Hospital of Inner Mongolia Medical College 30 cases of CAPD patients, the time of peritoneal dialysis is more than three months, 19 cases of male, 11 females, the average age (58.57 ± 13.95) years. The primary disease: chronic glomerulonephritis (20 cases), hypertensive nephropathy (3 cases), Diabetic Nephropathy (4 cases), Drug-induced renal impairment (2 cases), Henoch-Schonlein purpura nephritis (1 case), Guangzhou Baxter peritoneal dialysis fluid should be used in this group of patients, dose is 6-10 L/d.

Conservative treatment in patients with ESRD: Select the same period in our hospital and out-

Table 1. General clinical data of three groups

Items	CAPD group (n = 30)	Conservative treatment group (n = 30)	Control group (n = 30)	*P*
Age (years)	58.57 ± 13.95	51.53 ± 18.02	51.00 ± 14.40	0.116
Gender (M/F)	19/11	20/10	15/15	0.378
GFR (ml/min*1.73 m^2)	6.39 ± 2.31$^{\Delta}$	5.64 ± 1.79	89.22 ± 6.33*	
urine albumin (ml/24 h)	800.5 ± 210.4	950.6 ± 180.8	1800.5 ± 360.8*	
SGA	B	B	A	
Hb (g/L)	91.93 ± 18.80$^{\Delta}$	87.70 ± 10.07	136.60 ± 10.08*	
iPTH (pg/ml)	369.37 ± 166.94$^{\Delta}$	387.34 ± 268.75	32.77 ± 9.54*	
ALB (g/L)	32.77 ± 7.38$^{\Delta}$	35.69 ± 6.61	47.08 ± 5.35*	
Hypertension (yes/no)	10/20	8/22	-	0.573

$^{\Delta}$Compared with conservative treatment group $P > 0.05$, *Compared with control group $P < 0.05$.

Table 2. Plasma ADMA levels in three groups ($\bar{X} \pm S$)

Group	Cases (n)	ADMA (mmol/L)	F	*P*
CAPD group	30	0.125 ± 0.076	34.047	0.000
Conservative-treatment group	30	0.214 ± 0.121		
Control group	30	0.035 ± 0.291		

patient follow-up of 30 patients with conservative treatment, 20 cases of male, 10 females, the average age is 51.53 ± 18.02 years. The primary disease: chronic glomerulonephritis (17 cases), hypertensive nephropathy (5 cases), Diabetic Nephropathy (3 cases), Drug-induced renal impairment (2 cases), Henoch-Schonlein purpura nephritis (1 case), obstructive nephropathy (2 cases).

To calculate the above two groups of selected patients GFR, urine output, SGA assessment, determine its average haemoglobin concentration, parathyroid hormone levels, albumin and compare.

Control group: Select the same period in our hospital examination 30 healthy people, 15 cases of male, 15 females. The average age is (51.00 ± 14.40) years old.

Exclusion criteria

During the observation period with severe infection, malignant tumor, Hematological Diseases, active lupus, rheumatic heart disease, Congenital Heart Disease, corpulmonale, hyperthyroid heart disease, being treated for hormone or immunosuppressive agents.

Detection of ADMA

ADMA levels of plasma and peritoneal dialysis fluid were tested by enzyme-linked immunoblot assay (ELISA): ADMA Enzyme-linked Immunosorbent Assay kit (USCN LIFE).

Echocardiography

All cases were detected by American GE company Vivid7 Colour Doppler Ultrasonic Echocardiograph to detected left ventricular end-diastolic dimension (LVEDD), Left atrial diameter (LAD), Left ventricular posterior wall thickness in diastole (LVPWT), Interventricular septum thickness in diastole (IVST), left ventricular ejection fraction (LVEF). All measurements were repeated 3 times in different scanning averaged, Left ventricular mass index (LVMI) and left ventricle mass (LVM) were calculated according to the Devereux formula. International recommendation for left ventricular hypertrophy: male > 135 g/m^2, 10 females > 110 g/m^2.

The formula:

LVM (g) = 1.04 × [(IVST + LVPWT + LVDd) 3-LVDd3]-13.6

BSA (m^2) = 0.0061 × Length (cm) + 0.0124 × weigh (kg)-0.0099

LVMI (g/m^2) = LVM/BSA

Biochemical index, including blood routine, Biochemistry were detected by Automatic Biochemical Analyzer of Affiliated Hospital of Inner Mongolia Medical College, calculate Glomerular filtration rate using MDRD.

Specimens taking

All the cases in the outpatient clinic or hospital at the next morning were collected fasting

Table 3. Correlation analysis between CAPD patient plasma ADMA levels and echocardiograph indexes

Indexes	r	*P*
IVST	0.273	0.145
LVPWT	0.186	0.325
LVEDD	0.384	0.036
LAD	0.636	0.000
LVM	0.483	0.007
LVMI	0.470	0.009
LVEF	-0.562	0.001

venous blood 2 ml, adding EDTA anticoagulant tube, shaken up, specimens what were collected within 30 minutes were centrifuged at 1000 × g for 15 minutes, the supernatant can be detected, or was placed or stored at -80°C to 20°C, return out of 5 ml of peritoneal fluid for Peritoneal dialysis patients in the morning, specimens were centrifuged at 1000 × g for 15 minutes, the supernatant can be detected, or was placed or stored at -80°C to 20°C.

Statistical method

All statistical analysis were performed with SPSS13.0, Normal measurement data described by mean ± standard deviation ($\bar{X}$ ± S), Non-normally distributed data described by as median (interquartile range), Groups were compared using t-test, Analysis of variance, Rank sum test, Correlation analysis methods using Pearson and Spearman. P < 0.05 was considered statistically significant.

Results

General clinical data in three groups

The age, gender, residual renal function and urine albumin, hemoglobin and parathyroid hormone in End-stage renal disease patients on CAPD group, conservative treatment group and control group were detected. The statistical analysis showed that there were not significant differences between CAPD treatment and conservative treatment group for the age, gender and hypertension (**Table 1**, P > 0.05). However, there were significant differences among all of the three groups for the GFR, urine albumin, SGA, Hb, iPTH and ALB levels (**Table 1**, P < 0.05).

Plasma ADMA levels in three groups

The plasma ADMA levels of CAPD group is (0.125 ± 0.076) μmol/L, the conservative treatment group is (0.214 ± 0.121) μmol/L, the control group is (0.035 ± 0.291) μmol/L (**Table 2**). There was statistically significant difference between three groups (F = 34.047, P = 0.000). Pairwise comparisons between three groups were statistically significant difference (P = 0.000). Conservative treatment patients had the highest level of plasma ADMA compared with other two groups, normal group had the lowest levels.

The relationship between plasma ADMA levels and echocardiography

CAPD patients plasma ADMA levels were negatively correlated with LVEF (r = -0.562, P = 0.001), and were positively correlated with LVMI, LVM, LVEDD, LAD (**Table 3**, *P* < 0.05). The results indicated that ADMA may play an important role in left ventricular remodeling (**Table 3**).

Comparison of echocardiograph indexes and mean arterial pressure between CAPD group and conservative treatment group

Compared CAPD treatment group and the conservative treatment group of 30 patients with cardiac ultrasound and mean arterial pressure: CAPD treatment group with LVH is 8 case (29.6%), LVMI (113.25-41.45) g/m^2, LVEF (63.57 + 6.69)%, MABP (110.85-13.19) mmHg, conservative treatment group with LVH is 19 case (70.4%), LVMI (154.17 ± 47.43) g/m^2, LVEF (63.03 ± 8.15)%, MABP (120.97 ± 16.75) mmHg. Compared with CAPD treatment group, Conservative treatment group had higher proportion of average artery, left ventricular hypertrophy and left ventricular mass index (**Table 4**).

Correlation analysis between CAPD patient peritoneal dialysis fluid ADMA levels and echocardiograph indexes

The level of peritoneal dialysis fluid ADMA is (0.146 ± 0.077) μmol/L. The peritoneal dialysis fluid ADMA levels of CAPD patients with peritoneal were positively correlated with LVEF (r = 0.367, P = 0.046), negatively correlated with LVMI (r = -0.369, P = 0.045), was no correlation with LVEDD, LVM, LAD. **Table 5** show that ADMA may play an important role in left ventricular

Table 4. Comparison of echocardiograph indexes and mean arterial pressure between CAPD group and conservative treatment group

Items	CAPD group	conservative treatment group	*P*
cases	30	30	
LVH%	8 (29.6%)	19 (70.4%)*	0.04
LVMI (g/m^2)	113.25 ± 41.45	154.17 ± 47.43*	0.01
LVEF (%)	63.57 ± 6.69	63.03 ± 8.15	0.783
MABP (mmHg)	110.85 ± 13.19	120.97 ± 16.75*	0.012

*Compared with CAPD group $P < 0.05$.

Table 5. Correlation analysis between CAPD patient peritoneal dialysis fluid ADMA levels and echocardiograph indexes

indexes	r	*P*
LVEDD	0.051	0.790
LAD	0.129	0.497
LVM	-0.056	0.767
LVMI	-0.369	0.045
LVEF	0.367	0.046

remodeling. It can be inferred that peritoneal dialysis can remove plasma ADMA and it is a protective measure for cardiac function.

Discussion

The plasma ADMA levels is important prognostic factors of total mortality and cardiovascular disease for ESRD patients, and is important risk factor for kidney disease with cardiovascular disease [4, 5].

ADMA, low molecular weight (< 202 daltons), is a kind of small molecule toxins. Theoretically, using the dialysis to remove ADMA may be a good choice in patients with ESRD. Study confirms that although hemodialysis can reduce plasma ADMA levels, but plasma ADMA levels will appear rebound shortly after dialysis [6], This may be due to ADMA combined with larger molecular weight proteins results in the decrease of ADMA clearance, so the blood dialysis does not seem to be a good method for removal of ADM [7, 8]. Peritoneal dialysis in the effects of ADMA there is no unified the results reported.

This experimental research is obtained by plasma ADMA levels between three groups: Conservative treatment patients had the highest level of plasma ADMA compared with other two groups, normal group had the lowest levels. This proves that with the decline in renal function, which can lead to the accumulation of plasma ADMA. This study found that CAPD patients plasma ADMA levels were negatively correlated with LVEF ($r = -0.562$, $P = 0.001$), and were positively correlated with LVMI, LVM, LVEDD, LAD ($P < 0.05$). The results showed that ADMA may play an important role in left ventricular remodeling. The plasma ADMA levels of CAPD patients with LVH were lower than conservative treatment patients with LVH ($P = 0.02$). While comparing CAPD treatment group and the conservative treatment group of 30 patients with cardiac ultrasound and mean arterial pressure: CAPD treatment group with LVH is 8 case (29.6%), LVMI (113.25-41.45) g/m^2, LVEF (63.57 + 6.69)%, MABP (110.85-13.19) mmHg, conservative treatment group with LVH is 19 case (70.4%), LVMI (154.17 ± 47.43) g/m^2, LVEF (63.03 ± 8.15)%, MABP (120.97 ± 16.75) mmHg. Compared with CAPD treatment group, Conservative treatment group had higher proportion of average artery, left ventricular hypertrophy and left ventricular mass index. The ADMA of the peritoneal dialysis fluid was (0.146 ± 0.077) μmol/L. The peritoneal dialysis fluid ADMA levels of CAPD patients with peritoneal were positively correlated with LVEF ($r = 0.367$, $P = 0.046$), and negatively correlated with LVMI ($r = -0.369$, $P = 0.045$). It is suggested that peritoneal dialysis can remove plasma ADMA and it is a protective measure for cardiac function. Possible mechanisms of peritoneal dialysis patients with lower plasma ADMA levels: 1. Peritoneal dialysis is relatively better protect residual renal function 2. Peritoneal dialysis directly removes ADMA. In this experiment, the ADMA of the peritoneal dialysis fluid was detected and it is positively correlated with LVEF, is negatively correlated with LVMI 3. ADMA is mainly cleared by DDAH, and activity of DDAH is affected by a variety of endogenous substances, such as homocysteine (Hcy), elevated homocysteine concentration inhibits the activity of DDAH. High levels of Hcy hyperlipidemia in patients with ESRD is Widespread [9-11]. Several studies have confirmed, both at home and abroad, blood Hcy level three times

higher than normal, high homocysteine levels may be a risk factor for cardiovascular disease [12]. Hcy promotes oxidative stress to reduce the activity of the DDAH, so that elevated levels of ADMA [13]. Liu et al. [14] research shows that PD treatment can remove Hcy in certain degree. It can be inferred peritoneal dialysis treatment can improve DDAH activity to reduce serum ADMA and Hcy levels. Studies have shown that [15, 16] the heavy water sodium retention and can obviously restrain activity of DDAH causing ADMA levels. As ultrafiltration function in patients with CAPD treatment is good, the phenomenon of water sodium retention is a significant reduction in dialysis patients. The resulting DDAH activity improvement, increase the degradation of ADMA metabolism.

ADMA, as a novel uremic toxins, through a complex network in the body may be involved in change of left ventricular structure, function, and remodeling process. How and by what mechanisms involved in promoting the development and progression of left ventricular hypertrophy, still need further study. Whether we can detect the plasma ADMA levels, to evaluate the occurrence of cardiovascular disease and treatment effect, also need to further expand the sample research. At present, due to the different detection method of ADMA makes various plasma ADMA levels reported in literatures at home and at abroad. So it is necessary to standardize and unified test method and the unified standard, make it possible to predict cardiovascular disease, as clinical routine testing project.

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Disclosure of conflict of interest

None.

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