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Association between advanced oxidation protein products (AOPP) and vascular calcification in uremic patients

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Abstract. – OBJECTIVE: To investigate the correlation between serum advanced oxidation protein products (AOPP) and vascular calcification in uremic patients.

PATIENTS AND METHODS: The general data of included subjects were collected, and the serum AOPP, intact parathyroid hormone (iPTH), creatinine (Cre), Urea, calcium (Ca), phosphorus (P), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterin (LDL-C), hemoglobin (Hb) and albumin (ALB) were detected. Coronary artery computed tomography (CT) scan was performed and the coronary arterial calcification score (CACS) was calculated; the whole abdomen CT scan was performed and abdominal aortic calcification index (AACI) was calculated. SPSS l9.0 software was used for data analysis.

RESULTS: The coronary artery CT and detection of serum indexes showed that AOPP in positive coronary arterial calcification group was significantly increased compared with that in negative coronary arterial calcification group (59.14 ± 14.57 *vs*. 37.59 ± 5.31) μmol/L. The whole abdomen CT and detection of serum indexes showed that AOPP in positive abdominal aortic calcification group was significantly increased compared with that in negative abdominal aortic calcification group (60.32 ± 15.43 *vs*. 39.57 ± 6.25) μmol/L. AOPP in severe calcification group was significantly higher than negative group (70.72 ± 18.18 *vs*. 39.57 ± 6.25) μmol/L. There were no significant differences in AOPP between hypertension and non-hypertension groups, diabetic nephropathy, and non-diabetic nephropathy groups. Correlation analysis showed that AOPP of uremic patients had a significantly positive correlation with $\log_{l0}^{[CACS+1]}$ and had a significantly positive correlation with inferior AACI.

CONCLUSIONS: AOPP in positive coronary arterial calcification group and positive abdominal aortic calcification group was higher than that in negative group and AOPP in severe calcification group was significantly higher than that in negative group. AOPP of uremic patients has a significantly positive correlation with CACS and AACI.

Key Words:
Advanced Oxidation Protein Products (AOPP), Vascular calcification, Uremia.

Introduction

Chronic kidney disease (CKD) has become a global concern due to its high incidence rate, high mortality rate and high medical costs[1]. The cause of death of CKD is mainly the cardiovascular disease (CVD). Vascular calcification (VC) is a common pathological and physiological phenomenon in the occurrence and development of CKD. VC is a potent predictor of cardiovascular events and death in patients with end-stage renal disease, which is closely associated with cardiovascular events, such as myocardial infarction and sudden cardiac arrest[2,3].

There are few clinical studies on the correlation between VC and advanced oxidation protein products (AOPP)[4-8]. In addition, there is little research on whether serum AOPP level can be used as a predictive index of uremia VC. This study aimed to investigate the association between serum AOPP and VC in uremic patients and provide clues for clinical prevention and treatment of VC.

Patients and Methods

Patients

A total of 89 uremic patients admitted into Weifang People's Hospital from January 2015 to January 2017 were enrolled into this study. Exclusion criteria: (1) Patients who took drugs affecting folic acid metabolism (folic acid, B Vitamins) within 3 months; (2) Patients with

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apparent infection. Signed written informed consents were obtained from all participants before the study. Informed consent was confirmed according of the Ethical Committee of Weifang People's Hospital.

Methods

General data and serum indexes: age, gender, underlying disease, past medical history and medication history were recorded. After fasting for 8 h, fasting blood was drawn and the serum AOPP, intact parathyroid hormone (iPTH), creatinine (Cre), Urea, calcium (Ca), phosphorus (P), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterin (LDL-C), hemoglobin (Hb) and albumin (ALB) were detected.

Coronary arterial calcification score (CACS): CACS was calculated by the experienced radiologist in our hospital using the blind method. The scores of left main coronary artery (LM), left anterior descending branch (LAD), left circumflex artery (LCX) and right coronary artery (RCA) were calculated[9]. The sum of the four scores was the total CACS. According to the classification method of Rumberger, calcification was divided into the following four types: < 10 points: no calcification; 11-100 points: mild calcification; 101-400 points: moderate calcification; > 400 points: severe calcification. CACS larger than 10 points indicated the positive coronary arterial calcification, while CACS less than 10 points indicated the negative coronary arterial calcification.

Abdominal aortic calcification index (AACI): AACI was calculated semi-quantitatively by the experienced radiologist in our hospital using the blind method[10]. According to the classification method of Nitta, AACI was divided into the following three types: ≤ 10%: mild calcification; 11-30%: moderate calcification; > 30%: severe calcification.

Statistical Analysis

All statistics were performed using SPSS19.0 software (Version X; IBM, Armonk, NY, USA). The Student's *t*-test was performed for the comparison of mean value. One-way ANOVA test was used to analyze comparison between groups followed by LSD (Least Significant Difference). Percentage (%) was used to express the enumeration data and x^2 test was used for data analysis. Pearson analysis was used to evaluate the relationship between CACS, AACI and AOPP. $p < 0.05$ suggested that the difference was statistically significant.

Results

General Data

89 uremic patients admitted into Urology Department of our hospital from January 2015 to January 2017 were collected, and 5 patients were excluded due to incomplete data, so a total of 84 patients were qualified, including 50 males and 34 females with an average age of 56.98±17.04 years old. According to the primary disease, there were 31 cases of chronic glomerulonephritis, 26 cases of diabetic nephropathy, 13 cases of hypertensive renal damage, 5 cases of polycystic kidney, 5 cases of drug-induced nephropathy, 2 cases of obstructive nephropathy and 2 cases of lupus nephritis.

Comparisons of Serum Indexes Between Negative Coronary Arterial Calcification Group and Positive Coronary Arterial Calcification Group

60 patients received the coronary artery computed tomography (CT) and detection of serum indexes simultaneously, and the results showed that AOPP in positive coronary arterial calcification group was significantly increased compared with that in negative coronary arterial calcification group, and the difference was statistically significant ($p < 0.05$). The differences of blood Cre, blood urea nitrogen (BUN), Ca, P, Ca×P, TG, TC, LDL-C, ALB, hemoglobin (HB), fasting blood glucose (FBG) and iPTH between the two groups were not statistically significant ($p > 0.05$) (Table I).

Comparisons of AOPP Among Groups with Coronary Arterial Calcification in Different Degrees

60 uremic patients received the coronary artery CT and AOPP detection simultaneously. According to the classification criteria of coronary arterial calcification, patients were divided into negative group, mild group, moderate group and severe group. The statistical results showed that there were no statistically significant differences in AOPP among groups with coronary arterial calcification in different degrees ($p > 0.05$) (Table II).

Comparisons of Serum Indexes Between Negative Abdominal Aortic Calcification Group and Positive Abdominal Aortic Calcification Group

72 uremic patients received the whole abdomen CT and detection of serum indexes simul-

Table I. Comparison of serum indexes between negative and positive coronary arterial calcification group.

	Negative (n = 25)	Positive (n = 35)	*t*	*p*
Male/Female	8/17	25/10	–	0.071
Age (y)	54.51 ± 15.96	61.68 ± 14.07	1.224	0.083
Cre (μmol/L)	822.01 ± 472.86	714.53 ± 380.22	-0.925	0.337
BUN (mmol/L)	30.45 ± 14.69	27.78 ± 13.09	-0.513	0.435
Ca (mmol/L)	1.94 ± 0.23	2.06 ± 0.19	1.926	0.124
P (mmol/L)	2.11 ± 0.57	1.98 ± 0.69	-0.217	0.609
Ca*P (mg/dL)^2	46.75 ± 12.06	49.84 ± 16.37	0.542	0.572
TG (mmol/L)	1.39 ± 1.04	1.48 ± 0.94	0.414	0.628
TC (mmol/L)	3.98 ± 1.65	4.62 ± 1.57	1.459	0.201
LDL-C (mmol/L)	6.73 ± 6.04	3.28 ± 1.22	-0.784	0.386
ALB (mmol/L)	36.84 ± 5.06	35.94 ± 5.72	0.045	0.897
HB (g/L)	80.73 ± 24.15	88.18 ± 25.56	1.214	0.319
FBG (mmol/L)	5.02 ± 1.38	5.67 ± 1.60	1.148	0.314
iPTH (pg/ml)	298.11 ± 220.36	219.32 ± 218.71	-1.021	0.405
AOPP (μmol/L)	37.59 ± 5.31	59.14 ± 14.57	3.128	0.004

Abbreviation: Cre: creatinine, BUN: blood urea nitrogen, TG: triglycerides, TC: total cholesterol, HDL: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, ALB: albumin, HB: hemoglobin, FBG: fasting blood glucose, iPTH: immunoreactive parathyroid hormone, AOPP: advanced oxidation protein product.

taneously, and the results showed that AOPP in positive abdominal aortic calcification group was significantly increased compared with that in negative abdominal aortic calcification group ($p < 0.05$). The differences of gender ratio, age, blood Cre, BUN, Ca, P, Ca×P, TG, TC, LDL-C, ALB, HB, FBG and iPTH between the two groups were not statistically significant ($p > 0.05$) (Table III).

Comparisons of AOPP Among Groups with Abdominal Aortic Calcification in Different Degrees

72 uremic patients received the whole abdomen CT and AOPP detection simultaneously. According to the classification criteria of abdominal aortic calcification, patients were divided into negative group, mild group, moderate group and severe group. There were statistically significant differences in AOPP among the four groups ($p < 0.05$). AOPP in severe calcification group was significantly increased compared with that in negative group, and there were no statistically significant differences among the other groups (Table IV).

Comparison of Serum AOPP in Different Disease Groups

78 uremic patients received the AOPP detection. According to whether there is a history of hypertension, patients were divided into hypertension group and non-hypertension group. The results showed that there was no significant difference in AOPP between hypertension group and non-hypertension group ($p > 0.05$) (Table V). According to whether there is a history of diabetic nephropathy, 78 patients were divided into diabetic nephropathy group and non-diabetic nephropathy group. There was no significant difference in AOPP between diabetic nephropathy group and non-diabetic nephropathy group ($p > 0.05$) (Table V).

Correlation Analysis

60 uremic patients received coronary artery CT and AOPP detection simultaneously. CACS was logarithmically converted into $\log_{10}^{[CACS+1]}$, namely CACS 1, suggesting that AOPP is positively correlated with $\log_{10}^{[CACS+1]}$. 72 uremic patients received the whole abdomen CT and AOPP detection simultaneously, and correla-

Table II. Comparison of AOPP among groups with coronary arterial calcification in different degrees.

	Negative (n = 25)	Mild (n = 16)	Moderate (n = 13)	Severem (n = 6)	F	*p*
AOPP (umol/L)	37.59 ± 5.31	44.26 ± 10.32	54.17 ± 15.01	68.03 ± 16.19	2.118	0.134

Abbreviation: AOPP: advanced oxidation protein product.

Table III. Comparison of serum indexes between negative and positive abdominal aortic calcification group.

	Negative (n = 10)	Positive (n = 62)	t	p
Male/Female	4/6	40/22	–	0.614
Age (y)	54.04 ± 16.75	60.91 ± 12.58	1.412	0.138
Cre (μmol/L)	845.04 ± 439.26	730.76 ± 357.92	-0.896	0.387
BUN (mmol/L)	32.95 ± 18.19	26.75 ± 1.37	-0.794	0.395
Ca (mmol/L)	1.91 ± 0.26	1.97 ± 0.28	0.397	0.619
P (mmol/L)	2.19 ± 0.74	2.00 ± 0.66	-0.798	0.528
Ca*P (mg/dL)^2	51.46 ± 11.02	47.99 ± 14.49	-0.718	0.456
TG (mmol/L)	1.45 ± 1.08	1.72 ± 1.11	0.593	0.661
TC (mmol/L)	3.78 ± 1.59	4.27 ± 1.44	0.839	0.458
LDL-C (mmol/L)	2.62 ± 0.66	2.78 ± 0.92	0.482	0.713
ALB (mmol/L)	35.30 ± 4.25	36.41 ± 6.13	0.516	0.585
HB (g/L)	83.14 ± 21.30	89.98 ± 22.45	1.461	0.090
FBG (mmol/L)	4.61 ± 0.75	6.35 ± 3.87	1.263	0.244
iPTH (pg/ml)	234.14 ± 201.07	296.26 ± 222.74	0.585	0.679
AOPP (μmol/L)	39.57 ± 6.25	60.32 ± 15.43	2.578	0.001

Abbreviation: Cre: creatinine, BUN: blood urea nitrogen, TG: triglycerides, TC: total cholesterol, HDL: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, ALB: albumin, HB: hemoglobin, FBG: fasting blood glucose, iPTH: immunoreactive parathyroid hormone, AOPP: advanced oxidation protein product.

Table IV. Comparison of AOPP among groups with abdominal aortic calcification in different degrees.

	Negative (n = 10)	Mild (n = 19)	Moderate (n = 27)	Severe (n = 16)	F	p
AOPP (umol/L)	39.57 ± 6.25	52.04 ± 10.36	56.75 ± 11.62	70.72 ± 18.18	3.847	0.013

Abbreviation: AOPP: advanced oxidation protein product.

Table V. Comparison of serum AOPP in different disease groups.

	AOPP (umol/L)	t	p
Non-hypertension group (n = 24)	38.75 ± 6.59	0.646	0.233
Hypertension group (n = 60)	59.37 ± 11.68		
Non-diabetes group (n = 49)	39.04 ± 7.13	1.742	0.158
Diabetes group (n = 35)	60.30 ± 13.86		

Abbreviation: AOPP: advanced oxidation protein product.

tion analysis showed that AOPP had a significantly positive correlation with inferior AACI (Table VI).

Discussion

In addition to the traditional risk factors of CVD, such as advanced age, hypertension, abnormal glucose tolerance and dyslipidemia, VC is considered to be an important risk factor for the increased incidence rate and mortality rate of cardiovascular events in dialysis patients in recent years[2,3].

Table VI. Correlation analysis between AOPP and CACS/AACI.

	r	p
AOPP *vs.* $\log_{10}^{[CACS+1]}$	0.416	0.039
AOPP *vs.* AACI	0.562	0.000

Abbreviation: : AOPP: advanced oxidation protein product, CACS: coronary arterial calcification score, AACI: abdominal aortic calcification index.

AOPP is the firstly-discovered oxidize-modified protein that is significantly increased in the hemodialysis patients[5]. AOPP is mainly the product of oxidative stress reaction between albumin in the body and hypochlorous acid, which is an important marker of oxidation-mediated protein damage and a reliable indicator reflecting the oxidative stress status of uremic patients[4-8]. Descamps-Latscha et al[6] studied and suggested that AOPP is a risk factor for atherosclerotic cardiovascular events. So, what is the relationship between AOPP and VC that is also a risk factor for cardiovascular disease? This study investigated the relationship between blood AOPP level and VC in uremic patients.

In this report, 60 uremic patients received the detection of CACS and AOPP simultaneously, and the results showed that AOPP in positive coronary arterial calcification group was significantly increased compared with that in negative group, which was consistent with previous researches. The calcification score was further classified according to the different degrees of calcification. The results showed that AOPP showed an increasing trend with the gradual aggravation of coronary arterial calcification, but there was no statistically significant difference, which was related to the small sample size. Previous studies have shown that CACS is positively correlated with AOPP, and some showed that AOPP is positively correlated with $\log_{10}^{[CACS+1]}$[9]. The results of this work showed that AOPP was positively correlated with $\log_{10}^{[CACS+1]}$, suggesting that high AOPP may be an important non-traditional risk factor for VC in uremic patients.

AACI can be used as an independent predictor of cardiovascular events in uremic patients. Studies have shown that AACI has a significantly positive correlation with CACS[10]. In this study, 72 uremic patients received the detection of AACI and AOPP simultaneously, and the results showed that AOPP in positive abdominal aortic calcification group was significantly increased compared with that in negative group, and the positive group was further divided into mild group, moderate group and severe group. AOPP in severe calcification group was significantly increased compared with that in negative group, and there were no significant differences among the other groups. The correlation study showed that AOPP had a significantly positive correlation with inferior AACI.

Some investigations have shown a significant increase in AOPP level in hypertension patients compared with that in non-hypertension patients[11,12]. This paper suggested that there was no significant difference in AOPP between hypertension group and non-hypertension group, which was considered to be related to the use of antihypertensive drugs and blood pressure control level in hypertension group. Diabetic nephropathy is the most common cause of end-stage renal disease in developed countries. Diabetes is associated with oxidative stress and inflammatory status, and levels of serum inflammatory markers in patients with diabetic nephropathy are higher than those in patients with non-diabetic nephropathy[13]. Herrmann et al[14] found that the AOPP level in patients with diabetic nephropathy is significantly increased with the progression of renal injury. Increased AOPP in diabetic nephropathy may be associated with insulin resistance, protein and amino acid metabolic disorders. It was observed in this investigation that there was no significant difference in AOPP level between diabetic nephropathy group and non-diabetic nephropathy group, which was considered to be related to the small sample size.

Conclusions

AOPP in positive coronary arterial calcification group and positive abdominal aortic calcification group was higher than that in negative group and AOPP in severe calcification group was significantly higher than that in negative group. AOPP of uremic patients has a significantly positive correlation with CACS and AACI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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