Acta Cardiol Sin 2016;32:75–80
Original Article
doi: 10.6515/ACS20150429A

General Cardiology

Serum Paraoxonase Levels are Correlated with Impaired Aortic Functions in Patients with Chronic Kidney Disease

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Background: The correlation between aortic functions and paraoxonase levels has been previously demonstrated by several earlier studies. In this study, we aimed to investigate the correlation between serum paraoxonase levels and aortic functions among patients with chronic kidney disease.

Methods: Our study enrolled 46 chronic kidney disease patients and 45 healthy controls. From these patients, serum cholesterol, creatinine, hemoglobin, and paraoxonase-1 levels were analyzed.

Results: Paraoxonase-1 levels were significantly lower in patients with chronic kidney disease compared to the controls ($p < 0.001$). Additionally, the extent of aortic stiffness index (%) was significantly higher in chronic kidney disease patients, but aortic strain and aortic distensibility were significantly higher in healthy controls ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). We further found that paraoxonase-1 levels were correlated with aortic stiffness index, aortic strain, and aortic distensibility ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

Conclusions: Our study demonstrated that serum paraoxonase-1 levels were significantly correlated with impaired aortic functions. The results of this study highlight the impact of serum paraoxonase-1 activity on atherosclerosis and cardiovascular adverse events.

Key Words: Aortic functions • Atherosclerosis • Chronic kidney disease • Echocardiography • Paraoxonase

INTRODUCTION

Studies have shown that paraoxonase-1 (PON-1) confers protection of low density lipoprotein (LDL) cholesterol from oxidation by removing oxidized phospholipids on LDL cholesterol.[1] PON-1 activity is determined by genetic, dietary, life-style, and environmental factors.[2,3] Clinical studies have reported that PON-1 activity was reduced in patients with high cardiovascular risk, including patients with diabetes mellitus, heterozygous familial hypercholesterolemia, and myocardial infarction.[4] High density lipoprotein (HDL) cholesterol has a antiatherogenic role independent from inverse cholesterol transport, and protects LDL cholesterol against oxidative modification. The latter is attributed to PON-1 enzyme located on HDL cholesterol itself.

Cardiovascular disease (CVD) is the major cause of morbidity and mortality among patients with chronic kidney disease (CKD).[5] Epidemiological and clinical studies have shown that damage to large arteries is a major contributing factor to high cardiovascular morbidity and mortality of CKD patients.[6]

Arterial stiffness (AS) is affected by elastic fiber de-

Received: July 19, 2014 Accepted: April 29, 2015
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generation, increased collagen, and hypertrophy in vascular smooth muscle layers, all of which are related to oxidative stress. Conditions associated with increased AS are advanced age, hypertension, diabetes mellitus, atherosclerosis, and CKD.[7-10]

In this study, we aimed to investigate whether serum PON-1 levels correlate with aortic functions (distensibility, strain and stiffness index) among patients with chronic renal failure.

MATERIALS AND METHODS

The study enrolled 46 chronic kidney disease patients (22 women and 24 men) with glomerular filtration rate (GFR) of less than 30 mg/min/1.73 m^2. The mean age and body mass index (BMI) of this group was 43.52 $\pm$ 9.34 years, and 25 $\pm$ 5 kg/m^2, respectively. We also enrolled 45 healthy controls (23 women and 22 men) who were sex, age, and BMI matched with the disease group from cardiology outpatients. The mean age of healthy controls was 43.36 $\pm$ 9.33 years, and BMI was 26.77 $\pm$ 4.11 kg/m^2. All participants underwent physical examination and 2D echocardiography, and each subject provided a detailed medical history. The designated criteria for exclusion included patients with coronary artery disease, heart failure and/or left ventricular ejection fraction (LVEF) < 50%, diabetes mellitus, thyroid disorders, hypertension, connective tissue or other inflammatory disorders, moderate or severe valvular insufficiency or stenosis, hepatic dysfunction, and use of medications affecting aortic functions (calcium channel blockers, beta blockers).

Echocardiographic evaluation

Echocardiographic evaluation was performed at rest, with the patient in the left lateral decubitus position, using 2D echocardiography (VIVID 7 Dimension, GE Healthcare, Horten, Norway) with a 3-MHz transducer. Long-axis measurements were obtained at the level distal to the mitral valve leaflets with M mode echocardiography as noted in the current recommendations of the American Society of Echocardiography.[11]

Left atrial diameter, left ventricular end-systolic and end-diastolic diameters (LVSd and LVDd, respectively), end-diastolic interventricular septal thickness (IVSth), and left ventricular end-diastolic posterior wall thickness (PWth) were also measured.

The diameters of the aortas (Ao) were measured at the same view on the M-mode tracing at a level 3 cm above the aortic valve. The systolic diameter (AoSD) was measured at the maximum anterior motion of the aorta, and the diastolic diameter (AoDD) was measured at the peak of the QRS complex on the simultaneously recorded electrocardiography (ECG). Systolic and diastolic blood pressures (SBP and DBP, respectively) were simultaneously measured by sphygmomanometer during echocardiography. Aortic functions (i.e. distensibility, strain and stiffness index) were calculated as previously described.[12-14]

Aortic stiffness (%) = 100X (aortic systolic diameter – aortic diastolic diameter)/AoDD; Aortic distensibility = 2X (aortic systolic diameter – aortic diastolic diameter)/(aortic diastolic diameter X pulse pressure) = cm^2 X dyn^{-1} X 10^{-6}; Aortic stiffness index (AStI) = ln (systolic blood pressure/diastolic blood pressure)/(aortic systolic diameter – aortic diastolic diameter)/Aortic diastolic diameter.

Serum samples were obtained by venipuncture with vacutainer tubes after each patient fasted for 12 hours to measure serum lipid and biochemical profile. Serum creatinine, hemoglobin, total cholesterol, LDL cholesterol, HDL lipoprotein, triglycerides, thyroid stimulating hormone (TSH), and high sensitive CRP (hsCRP) were measured by automated enzymatic methods using an Olympus AU 600 auto analyzer (Beckman Coulter, Fullerton CA, USA). GFR was calculated with MDRD formula.

Measurement of serum PON-1 level

Paraoxonase assays were performed in the absence of sodium chloride (NaCl) (basal activity). The initial rates of hydrolysis of paraoxon (O,O-diethyl-O-p-nitrophenylphosphate; Sigma Chemical Co, London, UK) were determined by measuring liberated p-nitrophenol at 405 nm at 37 C on a Technicon RA-1000 autoanalyzer (Bayer, Milan, Italy). The basal assay mixture included 2.0 mmol/L paraoxon and 2.0 mmol/L of calcium chloride (CaCl2) in 0.1 mol/L Tris-HCl buffer, pH 8.0. Thereafter, 10 L of serum was added to 350 L of the reagent mixture.

Two groups of participants were studied after having given written informed consent. The study protocol was approved by the institutional ethics review board and conforms to the principles outlined in the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed with the SPSS package program for Windows version 18.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and median [min-max]. Categorical variables were summarized as frequencies and percentages. Distributions of the numerical variables were analyzed for normality by use of the Kolmogorov-Smirnov test. For numerical variables, differences between the groups were determined by the independent samples t-test or the Mann-Whitney U test. The Chi-square test was used to determine the associations between categorical variables, and any relation between the numerical variables was determined by Pearson correlation coefficient. Multivariate linear regression analysis was performed to determine the predictors of high PON-1. Those p values less than 0.05 ($p < 0.05$) were tabulated to be statistically significant.

RESULTS

Demographic and clinical features of the subjects are summarized in Table 1. In the CKD group, weight and serum creatinine levels were significantly higher, and serum hemoglobin, GFR and hsCRP were significantly lower. Furthermore, PON-1 levels were significantly lower in the CKD group when compared to healthy controls ($p < 0.001$).

Echocardiographic data are summarized in Table 2. Left ventricular septal and posterior wall thickenings, and left atrial diameter were higher in CKD patients when compared to controls. There were no significant differences between CKD patients and controls in terms of LVEF, LV fractional shortening (LVFS), and LV diameter. The aortic stiffness index (%) was significantly higher in CKD subjects, but aortic strain and aortic distensibility were also significantly higher in the control group as well ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

As shown in Table 3, serum PON-1 levels were correlated with aortic stiffness index, aortic strain, and aortic distensibility in the study subjects ($r = -0.88$, $p < 0.001$; $r = 0.96$, $p < 0.001$; $r = 0.95$, $p < 0.001$, respectively). Multivariate regression analysis revealed that serum PON-1 level was an independent factor for aortic functions, including aortic stiffness index ($p < 0.001$), aortic strain ($p < 0.001$), and aortic distensibility ($p < 0.001$) (Table 3).

Table 1. Characteristics of chronic kidney disease patients and healthy control groups

	Healthy control (n = 45)	Chronic kidney disease (n = 46)	p-value
Mean age (years ± SD)	43.36 ± 9.33	43.52 ± 9.34	0.93
Men % (n)	48.9 (22/45)	52.2 (24/46)	0.88
Weight (kg ± SD)	75.1 ± 12.83	70.12 ± 15.11	0.051
Height (cm ± SD)	168.16 ± 10.09	167.48 ± 9.371	0.74
BMI (kg/m² ± SD)	25.00 ± 5.00	26.77 ± 74.11	0.07
Systolic blood pressure (mmHg ± SD)	119.2 ± 14.55	121.33 ± 17.95	0.40
Diastolic blood pressure (mmHg ± SD)	75.62 ± 8.87	76.52 ± 11.09	0.58
Heart rate (bmp ± SD)	43.58 ± 10.0	44.7 ± 10.74	0.67
Serum creatinine level (mg/dl ± SD)	1.06 ± 0.13	4.95 ± 2.33	< 0.001
Blood hemoglobin level (g/dl ± SD)	14.57 ± 1.36	11.11 ± 1.69	< 0.001
GFR (mg/min/1.73 m² ± SD)	95.44 ± 19.16	21.82 ± 9.56	< 0.001
Total cholesterol level (mg/dl ± SD)	181.60 ± 40.9	178.43 ± 48.02	0.74
LDL cholesterol level (mg/dl ± SD)	109.92 ± 38.3	106.64 ± 43.03	0.70
HDL cholesterol level (mg/dl ± SD)	39.011 ± 10.41	39.71 ± 12.70	0.78
hsCRP (mg/l ± SD)	2.97 ± 2.83	5.95 ± 3.35	< 0.001
Serum TSH level (mg/dl ± SD)	1.607 ± 1.23	2.33 ± 2.56	0.16
Tobacco smoking % (n)	26.7 (12/45)	10.9 (5/46)	0.053
Paraoxonase-1 (U/L ± SD)	203.11 ± 82.70	104.26 ± 52.28	< 0.001

GFR, glomerular filtration rate; hsCRP, high sensitive CRP; TSH, thyroid stimulating hormone.

Table 2. Echocardiographic parameters of chronic kidney disease and healthy control groups

	Chronic kidney disease (n = 46)	Healthy control (n = 45)	p-value
Left ventricular end-diastolic diameter (mean cm ± SD)	4.56 ± 0.539	4.50 ± 0.54	0.56
Left ventricular end-systolic diameter (mean cm ± SD)	3.04 ± 0.77	2.95 ± 0.43	0.86
Left ventricular end-diastolic volume (mean ml ± SD)	67.22 ± 28.67	74.96 ± 22.82	0.16
Left ventricular end-systolic volume (mean ml ± SD)	23.93 ± 15.59	27.18 ± 9.96	0.24
Left ventricular ejection fraction (mean % ± SD)	65.22 ± 7.59	65.85 ± 4.88	0.64
Left ventricular fractional shortening (mean % ± SD)	36.07 ± 5.54	36.83 ± 4.21	0.47
Left ventricular septal wall thickness (mean cm ± SD)	1.15 ± 0.20	0.94 ± 0.14	< 0.001
Left ventricular posterior wall thickness (mean cm ± SD)	1.11 ± 0.15	0.94 ± 0.13	< 0.001
Left atrial volume (mean ml ± SD)	3.66 ± 0.55	3.45 ± 0.34	0.05
Aortic systolic diameter (mean cm ± SD)	3.31 ± 0.41	2.94 ± 0.41	< 0.001
Aortic diastolic diameter (mean cm ± SD)	3.21 ± 0.42	2.84 ± 0.42	< 0.001
Aortic strain (median ± SD)	2.94 ± 1.76	8.00 ± 4.24	< 0.001
Aortic stiffness index (median ± SD)	1.68 ± 0.54	1.01 ± 0.48	< 0.001
Aortic distensibility (median ± SD)	5.43 ± 3.63	16.50 ± 8.14	< 0.001

Table 3. Univariate and multivariate logistic regression analysis of aortic functions and PON-1 among patients with CKD

	Univariate analysis		Multivariate analysis	
	Spearman correlation coefficient	p	β	p
Aortic strain	0.96	< 0.001	0.96	< 0.001
Aortic distensibility	0.95	< 0.001	0.95	< 0.001
Aortic stiffness index(%)	-0.88	< 0.001	-0.88	< 0.001

Correlation is significant at the 0.01 level (p value).

DISCUSSION

PON-1 protects LDL cholesterol from oxidative modification by reactive oxygen species (ROS), and thus contributes significantly to the atheroprotective effect of HDL cholesterol.[14] The anti-atherosclerotic effect of PON1 was demonstrated in animal studies including PON1 knock-out mice and overexpressing mice. PON1 knockout mice developed atherosclerosis faster than the control mice on a high fat, high cholesterol diet, while PON1 overexpressing transgenic mice showed a decrease in atherosclerotic lesion size and improved oxidation status of the aorta and peritoneal macrophage.[15,16] PON-1 binds to HDL molecule and protects HDL and LDL from peroxidation, hence improving reverse cholesterol transport.[17-19] HDL-bound PON1 hydrolyzes particular oxidized lipids on macrophages, atherosclerotic lesions and lipoproteins. PON-1 was shown to inhibit cholesterol biosynthesis and decrease its accumulation.[20] It also prevents the conversion of macrophages into foam cells.[21]

CKD is associated with decreased activity of PON-1.[22-24] The decrease in PON-1, hence the reduction in its antioxidant and antiatherogenic properties could be an essential factor for premature vascular aging.[25] An unfavorable uremic environment due to the retention of uremic toxins and/or “middle molecules” including advanced glycation end products (AGE), free adducts and peptides might play a mechanistic role in decreasing PON-1 activity. Besides, these advanced glycation end products and urea-derived cyanate remains might cause inhibition via posttranslational modification of paraoxonase.[19,26] Reduced paraoxonase activity may cause decreased HDL antioxidant capacity in hemodialyzed uremic patients, and would therefore be expected to contribute to the increased risk of premature atherosclerosis found in these patients.[27] As suggested before, increased oxidative stress, and consumption of antioxidants during free radical production can also contribute to both atherosclerosis and reduced PON-1 activity.[28,29] Dialysis itself may also change enzyme activity and contribute to oxidative stress.[30] Recovery of paraoxonase activity has also been

reported after renal transplantation.[25]

One of the most important factors contributing to the development of cardiac dysfunction is arterial sclerosis or uremic arteriopathy and activation of the renin-angiotensin system.[31,32] Oxidative stress leads to vascular dysfunction. It has been observed that the balance between oxidants and anti-oxidants is important in the pathophysiology of aortic stiffness as well as several other conditions.[33]

Furthermore, it has been reported that the presence of vascular calcifications in CKD patients was associated with increased stiffness of large, capacitant, elastic-type arteries including the aorta and common carotid artery.[27] Serum PON-1 activity is decreased among patients with coronary artery disease, and it is inversely correlated with the severity of coronary lesions.[34] Yang et al. reported that PON-1 activity was negatively associated with high frequency pulse wave velocity even after adjusting for age, blood pressure and lipid profiles.[35] PON-1 activity was also found to be inversely correlated with the severity of aortic valvular stenosis.[36] Arterial stiffness is due mostly to the degeneration of elastic fibers, increased collagen and hypertrophy of vascular smooth muscle cell, all of which are closely related to oxidative stress.[35] Gungor et al. showed that PON-1 activity was a predictor of AS in renal transplant patients. In addition, researchers found that PON-1 was a novel predictor of AS in these patient populations.[37] We demonstrated that PON-1 levels were correlated with impaired aortic parameters and may be used as a marker of AS in CKD patients. Therefore, both decreases in PON-1 activity and arterial stiffness might originate from increased oxidative stress.

In our study, there were no statistical differences between the predialysis and hemodialysis patient groups in terms of aortic strain, aortic distensibility, aortic stiffness index and also PON-1 levels. Prakash et al. have shown significantly decreased PON-1 levels in CKD patients who were on conservative management, while CKD patients on hemodialysis therapy had significantly lower levels.[38]

Study limitations

Some limitations should be underlined. Our study sample size was small, and we did not investigate the levels of other markers of oxidative stress.

CONCLUSIONS

Our study demonstrated that serum PON-1 levels were significantly associated with impaired aortic functions. The decrease in PON-1 levels are likely to be linked with more severe atherosclerosis. The results of this study might highlight the role of PON-1 in CKD patients. Therefore, PON-1 activity levels may be used as a marker of oxidative status, AS and atherosclerosis in this population.

CONFLICT OF INTEREST

None declared.

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