Int J Clin Exp Med 2016;9(7):14722-14727
www.ijcem.com /ISSN:1940-5901/IJCEM0026338

Original Article

The association of renal function with arterial stiffness

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Received February 21, 2016; Accepted May 15, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Objective: This study aimed to investigate the relationship between renal function and arterial stiffness. Methods: A longitudinal study was conducted which included 1447 people who with on severe disease and finished median 4.8 years follow-up, then the estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration equations (CKD-EPI) and aortic arterial stiffness was representative with pulse wave velocity (PWV) (carotid-femoral PWV and carotid-radial PWV) at first visit (from 2007 to 2009) and second visit (2013). The baseline data were calculated according to eGFR by quartile. A Pearson regression analysis and a stepwise multiple linear regression analysis were performed to evaluate the association between baseline parameters and PWV. Results: There were 361 cases in Quartile 1 (eGFR ≥ 104.34 ml/min), 362 cases in Quartile 2 (96.09 ml/min ≤ eGFR < 104.34 ml/min), 365 cases in Quartile 3 (86.29 ml/min ≤ eGFR < 96.09 ml/min), 360 cases in Quartile 4 (eGFR < 86.29 ml/min). The regression analysis showed that besides age and blood pressure, eGFR also related with PWV (cf-PWV: r = -0.39, P < 0.001; cr-PWV: r = -0.068, P = 0.013), and the change of PWV during the follow-up was based on the baseline of PWV as well as eGFR change; when adjusted for age and blood pressure, cf-PWV was different in Quartile 4 and Quartile 1 with significance. Conclusion: Age, blood pressure and eGFR were all related with PWV and the changes of eGFR were associated with the change of PWV by adjusting for gender, age and multiple risk factors.

Keywords: eGFR, CKD-EPI, cf-PWV, cr-PWV

Introduction

Cardiovascular disease is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1], and the increase of arterial stiffness has been to have a significant impact on predicting mortality in end-stage renal disease patients [2]. Previous studies have shown that impaired renal function may predispose to increased arterial stiffness and most of them indicated negative relationship between arterial stiffness index (pulse wave velocity (PWV), blood pressure (BP), augmentation index (AI)) and CKD) [3-5] via multiple pathogenic mechanisms, and associated with increased cardiovascular morbidity and mortality [6]. In fact, impaired renal function is always regarded as a risk factor for vascular disease, and is associated with an increasing PWV [7]. In addition, the treatment targeting blood vessel stiffness could also protect the kidney function [8].

Previous studies have shown that increased arterial stiffness is associated with higher proteinuria [9] but not with CKD [10]. Some longitudinal study results are controversial. The study from Framingham indicated that PWV in baseline had no association with incident renal disease [11]. Arterial stiffness using PWV was not correlated with decline in renal function [12]. But in ABC study, PWV was associated with CKD among older adults [13]. Decline in renal function is related to higher levels of PWV in a community sample [14]. Although previous studies have reported relationship between renal function and arterial stiffness, but most of them was cross-section study, involved CKD patients only, or arterial stiffness affected renal function. So we performed a large longitudinal study which measured arterial stiffness affected by renal function in community not only CKD.

The purpose of this study was to find the relationship between renal function and arterial stiffness in a large community-based sample in China. (1) Relationship between renal function and PWV in baseline; (2) relationship between renal function in baseline and changes of PWV with follow-up; (3) relationship between chang-

es of renal function and changes of PWV with follow-up. (4) Observe different part of the measurement of PWV.

Materials and methods

Study population

A total of 1859 communal people living in Pingguoyuan area in Beijing in China joined this cross-sectional study as described previously [15]. When we finished the first follow-up in September 2007 and January 2009, 1680 people were involved, people who suffered severe disease such as collagenases, endocrine and metabolic diseases (except diabetes mellitus), inflammation, neoplastic disease, or severe liver or renal disease was excluded. 233 people were lost and exclude from analysis during 4.8 years follow-up. There are totally, 1447 persons were included in the statistics.

This study has been approved by the ethics committee of People's Liberation Army General Hospital, and written informed consent was obtained from all participants.

Follow-up and outcome assessment

People were second interviewed during February 1 to September 30, 2013 with a standardized questionnaire and visited by physician investigators. We gathered demographic information, medical history, blood pressure, anthropometric measurements and biochemical measurements. 1680 people were followed during a median 4.8 years, 233 people were lost or excluded. 1447 people were absorbed in analysis (follow-up rate 86.1%).

Clinical data collection

We collected age, sex, height, weight, prevalent diseases, family history of CVD, lifestyle factors through a standardized questionnaire and measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) by trained doctors. Height and weight were acquired in erect position and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was taken two times in the right brachial artery within 5 minutes, and calculated the average. Lifestyle included smoking status and drinking status that subdivided into current, former, or never.

Biomarker variable determination

We achieved lipid profile, liver and kidney function indices with an automated analyzer (Roche Cobas e601). Blood samples were collected between 8 am and 10 am at least fasting 12 h. Blood sample were measured include total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), creatinine (Cr). The estimated glomerular filtration rate (eGFR) was calculated using the following Chronic Kidney Disease Epidemiology Collaboration equations (CKD-EPI): $GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]. Scr is plasma creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of Scr/κ or 1, max is the maximum of Scr/κ or 1. All biochemical variables were acquired in the same laboratory, obeyed the criteria of the World Health Organization Lipid Reference Laboratories.

Measurements of arterial properties

Aortic arterial stiffness was representative with pulse wave velocity (PWV), which was assessed in the morning, quiet environment and stable temperature by using the Complior SP device (Artech Medical, PANTIN, France). The strain-gauge transducers were placed at the fixed right side of carotid-femoral or femoral-radial arteries. PWV was automatic calculated according the pulse transit time and distance between two sites. PWV (m/s) = distance (m)/transit time (s) [16]. The carotid-femoral PWV (cf-PWV), carotid-radial PWV (cr-PWV) was acquired. Measurements were repeated over 10 cardiac cycles repeat, the mean value of PWV was used in the further analysis.

Definition of variables

Essential hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or someone was taking antihypertensive therapy. Diabites mellitus (DM) was defined as (i) fasting blood-glucose ≥ 7.0 mmol/l or blood-glucose ≥ 11.1 mmol/l with OGTT (ii) symptom of hyperglycemia and random blood-glucose ≥ 11.1 mmol/l (iii) someone was taking hypoglycemic therapy. Smoking was defined as someone smoked ≥ 1/d cigarettes lasting at least 1 year.

Table 1. Characteristics of the subjects categorized by eGFR (CKD-EPI, ml/min) levels at baseline

Variable	Overall	Quartile 1 (≥ 104.34)	Quartile 2 (96.09-104.33)	Quartile 3 (86.29-96.08)	Quartile 4 (≤ 86.29)	P
No. of subjects	1447	361	362	365	360	
Age (y)	61.40±11.4	50.89±8.73	55.44±7.91*	62.60±9.25*	67.70±9.79*	< 0.001
Current smoking [n (%)]	380 (26.26)	75 (20.77)	98 (27.07)*	94 (25.75)*	112 (31.11)*	< 0.001
Hypertension (n)	755 (52.17)	125 (34.62)	157 (43.37)*	237 (64.93)*	235 (65.28)*	< 0.001
Diabetes (n)	302 (20.8)	71 (19.66)	76 (20.99)	78 (21.36)※	77 (21.38)※	0.135
BMI	25.41±3.32	25.31±3.30	25.51±3.36	25.45±3.53	25.53±3.25	0.819
TG (mmol/l)	1.90±1.24	1.73±1.12	1.88±1.32	1.83±1.36	1.76±1.13	0.319
TC (mmol/l)	5.03±0.93	4.91±0.96	5.03±0.86	5.17±0.95※	4.98±0.89	0.001
HDL-C (mmol/l)	1.38±0.36	1.41±0.36	1.38±0.36	1.41±0.37	1.33±0.35※	0.003
LDL-C (mmol/l)	2.91±0.71	2.85±0.75	2.87±0.69	3.01±0.72※	2.91±0.71	0.012
SBP (mmHg)	128.74±17.71	123.13±15.99	126.57±16.28	131.57±18.03*	133.25±18.62*	< 0.001
DBP (mmHg)	76.92±10.23	77.60±9.66	77.73±10.17	76.53±9.97	76.41±10.89	0.168
FBG (mmol/L)	5.39±1.65	5.48±1.94	5.43±1.59	5.33±1.58	5.28±1.30	0.306
eGFR (ml/min/1.73 m^2)	94.2±14.3	11.40±5.09	100.14±2.35*	91.56±2.65*	74.53±9.76*	< 0.001
cf-PWV	11.20±2.79	9.76±1.84	10.52±1.89*	11.84±2.98*	12.37±3.43*	< 0.001
cr-PWV	9.085±2.47	8.53±1.37	8.86±1.69	9.49±1.87	9.45±3.94	< 0.001

* < 0.01, ※ < 0.05. Notes: Continuous variables (Age, BMI, TG, TC, HDL-C, LDL-C, SBP, DBP, FBG, eGFR, cf-PWV, cr-PWV) were expressed as mean (± SD) or median (interquartile range), and categorical variables (Current smoking, hypertension, diabetes) were expressed as counts and percentages. Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; cf-PWV, carotid- femoral PWV; cr-PWV, carotid-radial PWV.

Table 2. Univariate and Multiple linear regression analysis of baseline parameters and follow-up arterial stiffness

	Pearson Correlation		Multiple Linear Correlation		
	r	P	β	95% CI	P
cf-PWV					
CKD-EPI	-0.39	< 0.001	-1.455	-2.469~-0.441	0.005
Age	0.474	< 0.001	0.097	0.080~0.113	< 0.001
SBP	0.032	< 0.001	0.038	0.027~0.050	< 0.001
DBP	-0.003	0.904	-0.039	-0.057~-0.021	< 0.001
LDL	0.033	0.233	0.296	-0.116~0.709	0.159
HDL	-0.081	0.003	0.394	-0.131~0.919	0.142
cr-PWV					
CKD-EPI	-0.068	0.013	-0.071	-0.720~0.577	0.829
Age	-0.164	< 0.001	-0.025	- 0.036~-0.015	0.006
SBP	0.101	< 0.001	0.005	-0.002~0.013	0.182
DBP	0.208	< 0.001	0.014	0.003~0.026	0.017
LDL	-0.065	0.017	0.09	-0.174~0.353	0.505
HDL	-0.03	0.271	0.35	0.015~0.686	0.041

Notes: Adjust for age, BMI, TC, TG, HDL, LDL, SBP, DBP, hypertension, diabetes. Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; cf-PWV, carotid-femoral PWV; cr-PWV, carotid-radial PWV.

Drunk was defined as someone drunk once a week. Body mass index (BMI) equal weight (kilograms) divided by the square of height (meters).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) and analyzed with Student's t-tests. Dichotomous variables are presented as numbers and percentages and analyzed with χ^2 test. A Pearson regression analysis and a stepwise multiple linear regression analysis was performed to evaluate the association between baseline parameters and follow-up arterial stiffness.

All analyses were conducted using SPSS software for Windows, version 13.0 (SPSS, Chicago, IL, USA). P < 0.05 were considered statistically significant.

Result

Clinical characteristics of the subjects categorized by eGFR level

There are total 1447 subjects in the study, summarized in **Table 1**. Mean age in baseline was 61.4 years, 59.98% was women. The baseline data were calculated according to eGFR by

Table 3. Effect of Baseline CKD-EPI and Change of CKD-EPI on Change of arterial stiffness

	Pearson Correlation		Multiple Linear Correlation		
	r	P	β	95% CI	P
Change of cf-PWV					
Change of CKD-EPI*	0.077	0.394	0.05	-0.247~0.348	0.739
Baseline CKD-EPI*	-0.072	0.008	-3.047	-5.966~-0.129	0.041
Baseline cf-PWV	-0.403	< 0.001	-0.645	-0.806~-0.484	< 0.001
Change of cr-PWV					
Change of CKD-EPI*	0.012	0.897	0.027	-0.196~0.251	0.809
Baseline CKD-EPI*	0.041	0.137	-0.015	-2.219~2.190	0.99
Baseline cr-PWV	-0.523	< 0.001	-0.909	-1.120~-0.698	< 0.001

Notes: *natural logarithm transformed. Covariates in the multiple-adjusted models included age, gender, baseline CKD, change in CKD, baseline PWV. Time between visits.

quartile, There were 361 cases in Quartile 1 (eGFR ≥ 104.34 ml/min), 362 cases in Quartile 2 (96.09 ml/min ≤ eGFR < 104.34 ml/min), 365 cases in Quartile 3 (86.29 ml/min ≤ eGFR < 96.09 ml/min), 360 cases in Quartile 4 (eGFR < 86.29 ml/min). The average age increased with eGFR increasing, smoking rate and hypertension rate was much higher in Quartile 3 and 4 than Quartile 1 and 2, so as the PWV baseline.

Correlation between baseline parameters and follow-up arterial stiffness

We analyzed baseline parameters with follow-up PWV. Adjusted for age, BMI, TC, TG, HDL, LDL, SBP, DBP, hypertension, diabetes, eGFR in baseline was related with cf-PWV over 4.8 years follow-up in Pearson and Multiple linear correlation. Age, SBP was related with follow-up cf-PWV (**Table 2**).

Correlation between baseline CKD-EPI, change CKD-EPI and PWV

With Pearson and Multiple linear correlation analysis, baseline CKD-EPI has relationship with change of cf-PWV follow-up 4.8 years. Baseline PWV has relationship with change of PWV. Change of CKD-EPI has no relationship with change of PWV (**Table 3**).

Correlation between change of eGFR and change of PWV

Comparison quartile data between change of eGFR and change of PWV over follow-up, quartile 4 was significant association with quartile 1 (OR, 1.126; 95% CI, 1.013-1.251; P = 0.028). There was same results adjusted gender and age (OR, 1.004; 95% CI, 1.146-1.308; P = 0.043), or adjusted gender, age, BMI, TC, TG, HDL, LDL, SBP, DBP, hypertension, diabetes (OR, 1.453; 95% CI, 1.095-1.928; P = 0.010) (**Table 4**).

Discussion

PWV is a noninvasive, reliable parameter of regional arterial stiffness that integrates the vascular geometry and arterial wall intrinsic elasticity and is capable of predicting cardiovascular mortality in this patient population [17]. On renal function and PWV, there are some contradictory results. Some studies have indicated that relationship between PWV and the renal function [11-13]. The study from Framingham indicated that PWV in baseline had no association with incident renal disease [11]. But in ABC study, PWV was associated with CKD among older adults [18]. These longitudinal data were examined PWV in baseline and compared with change of renal function in follow-up. A cross-sectional study showed that Mild and moderate CKD was related with the arterial stiffness in elderly adult [19]. A significant association between PWV and renal function was suggested in type 2 diabetes patients [18]. These study indicated relationship between PWV and diseases. The pathological mechanisms underlying the interaction between arterial stiffness and renal function have been reported. It's hypothesized that decline in renal functioning is associated with atherosclerosis due to endothelial dysfunction and to arteriosclerosis related to thickening of the media, calcification, and fibrosis. It has also related that oxidative stress, inflammation, uremic toxins, and dyslipidemia play a role in endothelial dysfunction and vascular calcification, vascular smooth muscle hypertrophy, and collagen deposition and that cross-linking influences medial thickening, calcification, and fibrosis [20, 21].

Most research is committed to the clear PWV affect kidney function. That means increased arterial stiffness can be adverse effects on the renal function. But instead, can the changes of renal function affect arterial stiffness? We

Table 4. Logistic with change of PWV and change of CKD-EPI

	Quartile 2 vs. Quartile 1 (-11.57-(-21.72) vs. ≥ -21.72)		Quartile 3 vs. Quartile 1 (-4.57-(-11.56) vs. ≥ -21.72)		Quartile 4 vs. Quartile 1 (≤ -4.56 vs. ≥ -21.72)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Change of cf-PWV						
Unadjusted	1.126 (0.823-1.539)	0.459	1.100 (0.941-1.286)	0.231	1.126 (1.013-1.251)	0.028
Model 1	1.109 (0.807-1.523)	0.524	1.136 (0.965-1.338)	0.126	1.004 (1.146-1.308)	0.043
Model 2	1.706 (0.783-3.720)	0.179	1.859 (1.256-2.753)	0.002	1.453 (1.095-1.928)	0.01

Model 1: Adjusted gender and age. Model 2: Adjusted gender, age, BMI, TC, TG, HDL, LDL, SBP, DBP, hypertension, diabetes.

need a community-based longitudinal study to uncover the relationship between renal function and arterial stiffness in general population. One longitudinal study which was community-based showed that decline in renal function was associated with higher cf-PWV [14]. This study involved 482 subjects and follow-up 4-5 year and only adopted cf-PWV. We have completed larger research based on the community people.

The first finding of this study is that through the large sample, longitudinal study definite about the relationship between kidney function and PWV in Chinese. Kawamoto had found that decreased eGFR is associated with an increased risk of arterial stiffness in community residents [22]. We had found renal function of women in communist was associated with arterial stiffness in cross-section study before [23]. In this study, eGFR has been found relationship with PWV at baseline. During the follow-up period of 4.8 years, we still found baseline renal function was associated with arterial stiffness.

The second important finding of this study is relationship between changes of PWV and changes of renal function. During the follow-up 4.8 years, baseline renal function does not represent the future changes of PWV, but renal function changes is associated with future PWV changes. That means a person whose kidney function is poor, not necessarily PWV is poor in the future; if the deterioration of renal function, so his PWV is deteriorating.

eGFR has been found relationship with cf-PWV and cr-PWV at baseline. eGFR is also related to follow-up cf-PWV and cr-PWV. But the baseline eGFR did not correlate with variations in PWV. The changes of renal function associated with the change of PWV.

Disclosure of conflict of interest

None.

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