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Original Paper

Pulse Pressure, Instead of Brachium-Ankle Pulse Wave Velocity, is Associated with Reduced Kidney Function in a Chinese Han Population

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Key Words
Pulse wave velocity • eGFR • Smoking • Healthy • Chinese

Abstract
Background/Aims: In this study, we aim to investigate the association between renal function and arterial stiffness in a Chinese Han population, and further to discuss the effects of smoking on renal function. ***Methods:*** We collected the data of the brachium-ankle pulse wave velocity (baPWV), blood pressure, blood chemistry and smoking status. Then, the multiple linear regression was done to explore the relationship between estimated glomerular filtration (eGFR) and baPWV. Further, the parameters were compared among the four groups divided according to the quartiles of baPWV. Finally, the baPWV, eGFR and albuminuria values were compared between smokers and non-smokers. ***Results:*** baPWV is associated with eGFR in the correlation analysis and univariate linear regression model. After adjustment, the pulse pressure (PP) instead of baPWV showed a significant association with eGFR. Nevertheless, the eGFR values differed among the four baPWV groups; the baPWV values were significantly higher in the subjects at the CKD (eGFR<60 mL/min/1.73 m^2) and the early CKD stage (eGFR60–80 mL/min/1.73 m^2). The baPWV values and the ratio of proteinuria were significantly increased in smokers. ***Conclusion:*** PP but not baPWV is a predictor of declined renal function. Smokers have worse arterial stiffness and worse renal function.

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Introduction

Cardiovascular disease (CVD) and chronic kidney disease (CKD) share some risk factors like hypertension and diabetes mellitus [1]. CKD per se, even at its early stage, may increase the morbidity and the mortality of patients with CVD [2-7]. Kidney is a high-flow organ and therefore any changes in arterial stiffness may affect its function.

Many indicators have been used to evaluate arterial stiffness, including the stiffness index [8], the cardio-ankle vascular index [9] and the pulse wave velocity (PWV) [10, 11]. Among others, PWV is a widely-accepted method for measuring arterial stiffness in clinical practice [12] and a strong predictor of CVD mortality [10]. The brachium-ankle pulse wave velocity (baPWV) as an easy and well-standardized method, is closely correlated to central aortic PWV [11, 13]. Since glomerular filtration rate (GFR) is difficult to measure, GFR is calculated from the serum concentrations of endogenous filtration markers, which is called estimated glomerular filtration rate (eGFR) [14-16]. As a surrogate parameter for renal function, eGFR has been widely used in the diagnosis and clinical management of CKD [14-25]. To date, studies on the relationship between PWV and renal function have yielded inconsistent results [17-24]. Some researchers reported a strong correlation between arterial stiffness and renal function by finding that an increased PWV was accompanied by reduced eGFR [17-19], whereas others failed to find a correlation [23, 24]. In the Framingham study, the PWV values were associated with albuminuria (urine protein > 150mg/24h or urine protein quantitative check is positive, $P< 0.0001$) but not a decline in renal function [22]. Taken together, it remains controversial whether increased PWV correlates with decreased renal function.

Smoking is a risk factor for various diseases including CVD [26, 27]. Previous studies revealed that smokers with CKD have a higher incidence of CVD than non-smokers and smokers without CKD [28]. Nicotine may decrease renal function by inducing apoptosis [29]. It is possible that the effects of smoking on decreasing renal function and increasing arterial stiffness may interact with each other during the ageing process [28].

In the current study, we collected data of 890 community subjects in 2014, and investigated the association between baPWV and renal function in the Chinese Han population. We further discussed whether smoking influences renal function.

Materials and Methods

Study population

At first 1368 residents of urban Beijing were recruited in 2014 (Fig. 1). All volunteers were asked to finish an interview of past medical history before medical examination. Participants were excluded from the study if they had surgeries or one of the following diseases in the 6-month period: stroke, cancer, diabetes, heart failure, coronary heart disease, peripheral artery disease, mental disorder, trauma or pulmonary disease. Subjects who failed to complete any of the tests were excluded. Finally, 890 volunteers with an average age of 58.1 ± 14.4 years who met the inclusion criteria were enrolled in the study (Fig. 1). The study protocol was approved by the Ethics Committee of the General Hospital of Chinese People's Liberation Army and by the Ethics Committee of Jilin University. Written informed consents were obtained from all participants.

Pulse wave velocity, blood pressure and electrocardiograph measurements

PWV, blood pressure and electrocardiograph measurements were taken using an OMRON VP-1000 Artery Stiffness Detector at the General Hospital of Chinese People's Liberation Army. The artery stiffness detector was operated by a senior physician. Before the test, participants were asked to rest for at least 5 min, and information regarding the age, gender, height and weight of the subject was input to the system. Then, participants lay on the bed with four inflatable bands wrapped around their upper arms and ankles to test the blood pressure and baPWV. Meanwhile, electrocardiography leads were placed on the chest to record the heart rate and activity. A higher baPWV value means greater brachium-arterial stiffness. All of the subjects were divided into four groups (very hard, hard, normal and soft) according to the baPWV quartile. Finally, there were 222 subjects in the very hard group, 223 subjects in the hard group, 223 subjects in the normal group and 222 subjects in the soft group.

Calculating the estimated glomerular filtration rate

Fast blood samples (20 mL) were collected for blood chemistry, and serum creatinine (Scr) was measured in the clinical laboratory. eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [30], because CKD-EPI equation is regarded to more appropriately categorize individuals at risk of CKD and CVD [31], and is more accurate than Modification of Diet in Renal Disease (MDRD) equation in subjects with eGFR>60 mL/min/1.73 m^2 [32]:

eGFR (mL/min/1.73 m^2) = $a \times (Scr/b)^c \times (0.993)^{age}$,

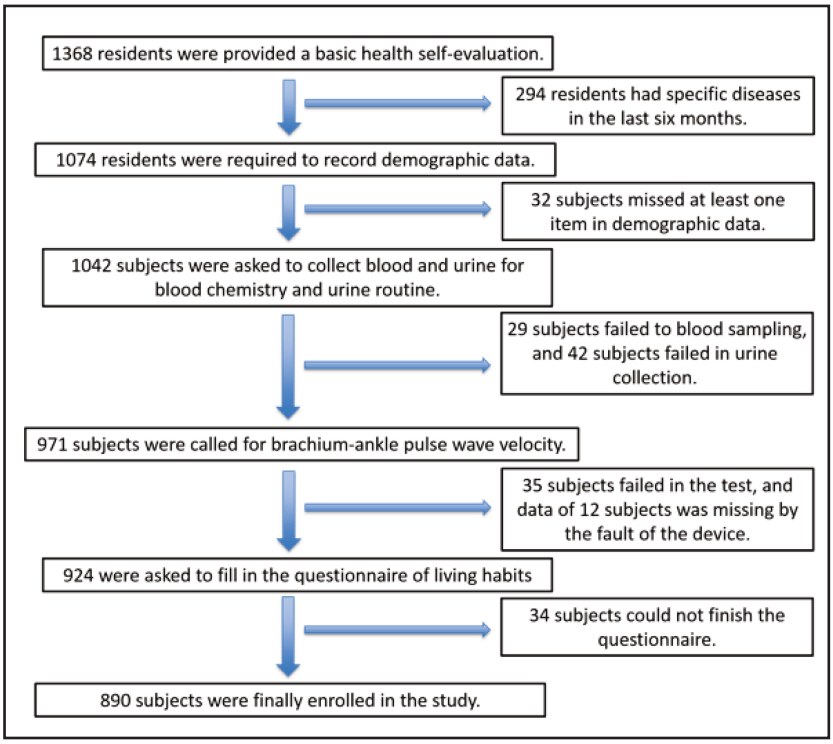

Fig. 1. Flow chart of subjects screening. Initially, 1368 volunteers took part in the study. After physical examinations and questionnaires, 890 were finally enrolled.

Here a values 144 for females and 141 for males, and b values 0.7 for females and 0.9 for males. For females, c values –0.329 when Scr ≤0.7 mg/dL and –1.209 when Scr>0.7 mg/dL. For males, c values –0.411 when Scr ≤0.7 mg/dL and –1.209 when Scr> 0.7 mg/dL.

According to K/DOQI (Kidney Disease Outcome Quality Initiative) [33], the subjects were divided into the following groups: normal (eGFR>90 mL/min/1.73 m^2), the early CKD stage (eGFR 60–90 mL/min/1.73 m^2) and the CKD stage (eGFR<60 mL/min/1.73 m^2).

Other variables

Demographic data, including name, gender, date of birth, height, weight, waist circumference and hip circumference, were collected. The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). The waist to hip ratio (WHR) was computed as dividing waist circumference by hip circumference. The blood chemistry variables measured including fasting glucose (GLU), blood urea nitrogen (BUN), total cholesterol (TC), triglyceride (TG), urea acid (UA), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Urine samples were collected for urine routine tests. Smoking status was recorded using a questionnaire as follows: Have you ever smoked? How many cigarettes do/did you have every day? How long have you smoked?

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 software (SPSS, IBM, West Grove, PA, USA). First, pair-wise correlation tests were run between each index and eGFR to screen indicators that were related to kidney function. Variables with a correlation coefficient $|r|> 0.30$, $p< 0.05$ were selected, because Wedam has interpreted r as follows: $r> 0.7$ means a strong correlation; $0.5 < r< 0.7$ means moderate correlation; $0.3 < r< 0.5$ means weak to moderate correlation; $r< 0.3$ means weak correlation [34]. The P value only indicated whether the test of $r = 0$ is right [34]. In order to select all the possible indicators, we only excluded the indicators of weak correlation with eGFR.

Then the linear regression analyses were performed to investigate the association between significant indicators and eGFR before and after adjustment respectively. Third, all of the subjects were divided into

four groups according to baPWV quartiles. The data from each variable are presented as means ± SDs. One-way ANOVA was used to compare each variable among the four PWV groups. Last, to explore the effects of smoking on eGFR and baPWV, we calculated the smoking rates in each CKD groups, the smokers' albuminuria rates and compared the smokers' and non-smokers' baPWV in different eGFR groups.

Results

baPWV is closely correlated to eGFR

The general characteristics of the 890 subjects and correlation coefficients with eGFR were listed in Table 1. The eGFR value was 91.51 ± 19.10 mL/min/1.73 m^2, and the baPWV value was 1509.46 ± 338.93 cm/s. Variables were selected based on the strength of their relationship with eGFR using the following the criteria: $|r|>0.30$ and $P<0.05$ [34]. Among the 15 variables measured, four met the requirements (Table 1): age, systolic blood pressure (SBP), pulse pressure (PP) and mean baPWV. Age and baPWV were highly correlated with eGFR (r = –0.725 and –0.438, respectively).

Table 1. General characteristics of the study subjects and the correlation of variables with estimated glomerular filtration rate (r is the correlation coefficient and P is the significance level). Data for variables with |r|> 0.30 and P < 0.05 are shown in bold

	Mean ± SD	*r*	*P*
Age (y)	58.0 ± 14.4	**–0.725**	**<0.01**
Body mass index (kg/m^2)	24.28 ± 3.35	–0.062	0.066
Waist hip ratio	0.87 ± 0.07	–0.105	<0.01
Fasting glucose (mM)	5.48 ± 1.43	–0.043	0.200
Blood urea nitrogen (mM)	5.12 ± 2.18	–0.228	<0.01
Total cholesterol (mM)	4.57 ± 0.91	–0.144	<0.01
Triglyceride (mM)	1.46 ± 1.35	0.013	0.704
Uric acid (μM)	324.16 ± 107.27	–0.094	<0.01
High-density lipoprotein (mM)	1.35 ± 0.36	–0.100	<0.01
Low-density lipoprotein (mM)	2.80 ± 0.79	–0.092	<0.01
Heart rate (bpm)	67.6 ± 10.4	0.005	0.892
Systolic blood pressure (mmHg)	128.76 ± 17.26	**–0.312**	**<0.01**
Diastolic blood pressure (mmHg)	76.11 ± 10.48	-0.083	0.013
Pulse pressure (mmHg)	52.77 ± 11.18	**–0.401**	**<0.01**
Mean baPWV (cm/s)	1509.46 ± 338.93	**–0.438**	**<0.01**
eGFR (mL/min/1.73 m^2)	91.51 ± 19.10		

Abbreviations: baPWV, brachium-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate.

baPWV and eGFR are not correlated in multiple linear regression analysis

In the univariate linear regression model, baPWV (β = –0.438, P < 0.001; Fig. 2a), age (β = –0.725, P < 0.001; Fig. 2b), PP (β = –0.401, P < 0.001; Fig. 2c) and SBP (β = –0.312, P < 0.001; Fig. 2d) were associated with eGFR, respectively. However, in the multiple linear regression, after adjustment for age, PP, SBP and gender, the association between baPWV and eGFR was no more significant (β_a = 0.043, P = 0.231) (Table 2).

Blood lipid and UA do not vary according to baPWV

According to the quartiles of the baPWV, we divided the subjects into soft (823.5 cm/s ≤ baPWV ≤ 1269.0 cm/s), normal (1269.0 cm/s <baPWV ≤ 1453.0 cm/s), hard (1453.0 cm/s <baPWV ≤ 1688.0 cm/s) and very hard (1688.0 cm/s <baPWV ≤ 3243.5 cm/s) groups. Clinical characteristics among the four baPWV groups were compared by one-way ANOVA. Results are shown in Table 3. Age, BMI, WHR, GLU, BUN, TG, heart rate, SBP, diastolic blood pressure (DBP), PP and eGFR varied significantly in subjects with different baPWV levels. While UA and indicators of blood lipid, including TC, HDL and LDL, did not vary among the four baPWV groups. Generally, subjects with a higher baPWV value had a lower eGFR value. Furthermore, worse blood vessel elasticity was accompanied with the older age, higher GLU, BUN, TG, blood pressure and the lower heart rate. However, the changes of BMI and WHR were not regular.

Smokers have worse blood vessel elasticity and higher albuminuria rate than non-smokers

A total of 25.96% of the study subjects were smokers, defined as at least one cigarette daily in current or before (Fig. 3a). To investigate whether smoking influenced renal function and blood vessel elasticity, the subjects were divided into groups according to smoking status and the values of eGFR. The mean eGFR of non-smokers and smokers was 91.06 and 92.79 mL/min/1.73 m^2, respectively. The early CKD group had the highest proportion of smokers (Fig. 3b), and smokers had a higher rate of proteinuria than non-smokers did (12.67% vs 10.61%)(P < 0.05). Compared with subjects in the normal group, subjects in the early CKD

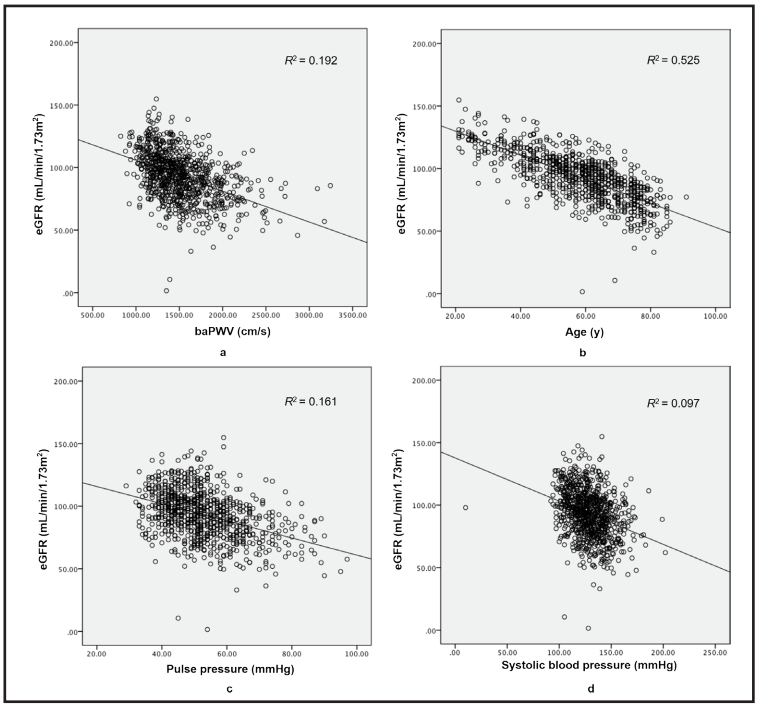

Fig. 2. The association between predictive variables and estimated glomerular filtration rate (eGFR). In the univariate regression analysis, brachium-ankle pulse wave velocity (baPWV, β = –0.438, P < 0.001; Fig. 2a), age (β = –0.725, P < 0.001; Fig. 2b), pulse pressure (PP, β = –0.401, P < 0.001; Fig. 2c) and systolic blood pressure (SBP, β = –0.312, P < 0.001; Fig. 2d) exhibit correlations with eGFR separately. After adjustment for age, PP, SBP and gender, no correlation was observed between baPWV and eGFR (β_a =0.043, P=0.231).

Table 2. The results of adjusted multiple linear regression analysis assessing the association between the estimate glomerular filtration rate and clinical characteristics

Variables	Adjusted standardized Coefficient / β_a	P
Age	–0.713**	<0.01
Systolic blood pressure	0.035	0.389
Pulse pressure	-0.102**	<0.01
Mean baPWV	0.043	0.231

**p< 0.01. Abbreviations: baPWV, brachium-ankle pulse wave velocity.

Table 3. The clinical characteristics of the study population according to baPWV

Level of baPWV	Very hard (1688.4 m/s <baPWV ≤ 3243.5 cm/s)	Hard (1453.0 m/s <baPWV ≤ 1688.0 cm/s)	Normal (1269.0 m/s <baPWV ≤ 1453.0 cm/s)	Soft (823.5 m/s ≤ baPWV ≤ 1269.0 cm/s)	P
General Characteristics	(N = 222)	(N = 223)	(N = 223)	(N = 222)	
Age (y)	70.8 ± 8.4	61.2 ± 10.6	54.7 ± 11.2	45.4 ± 13.4	<0.01
Males (%)	44.2	52.7	52.2	39.2	0.015
Body mass index (kg/m²)	24.42 ± 3.31	24.75 ± 3.29	24.54 ± 3.16	23.42 ± 3.51	< 0.01
Waist hip ratio	0.89 ± 0.06	0.88 ± 0.08	0.87 ± 0.06	0.84 ± 0.07	< 0.01
Fasting glucose (mM)	6.03 ±2.04	5.56 ± 1.34	5.31 ± 0.94	5.02 ± 0.89	< 0.01
Blood urea nitrogen (mM)	5.38 ± 1.32	5.44 ± 3.66	5.07 ± 1.35	4.58 ± 1.27	< 0.01
Total cholesterol (mM)	4.57 ± 0.87	4.68 ± 0.97	4.58 ± 0.91	4.44 ± 0.87	0.440
Triglyceride (mM)	1.51 ± 0.93	1.71 ± 2.21	1.43 ± 0.99	1.21 ± 0.65	<0.05
Uric acid (μM)	330.4 ± 79.3	335.26 ± 77.46	323.14 ± 77.56	308.1 ± 160.0	0.01
High-density lipoprotein (mM)	1.37 ± 0.36	1.34 ± 0.39	1.32 ± 0.34	1.39 ± 0.36	0.238
Low-density lipoprotein (mM)	2.77 ± 0.75	2.89 ± 0.81	2.84 ± 0.81	2.68 ± 0.77	0.029
Heart rate (bpm)	71.1 ± 11.9	68.1 ± 10.2	65.94 ± 9.40	65.2 ± 8.8	<0.01
Systolic blood pressure (mmHg)	144.79 ± 14.23	133.15 ± 12.61	123.87 ± 11.14	113.09 ± 12.61	<0.01
Diastolic blood pressure (mmHg)	81.59 ± 10.00	79.52 ± 9.73	75.38 ± 8.85	67.91 ± 7.64	<0.01
Pulse pressure (mmHg)	63.23 ± 11.00	53.63 ± 9.36	48.47 ± 8.12	45.67 ± 6.90	<0.01
eGFR (mL/min/1.73 m²)	80.50 ± 16.64	87.45 ± 16.48	94.44 ± 18.45	103.67 ± 16.80	<0.01

Abbreviation: baPWV, brachium-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate.

and CKD groups had a higher baPWV (1400.89 ± 269.28 cm/s vs. 1636.13 ± 349.72 cm/s vs. 1870.16 ± 452.58 cm/s, P < 0.001). When baPWV was analysed according to eGFR group, a stepwise decreasing trend in baPWV was observed in both smokers and non-smokers (Table 4). In addition, smokers in each group appeared to have worse blood vessel elasticity (P < 0.001).

Table 4. The mean, maximum and minimum baPWV based on eGFR and smoking status

	GFR (mL/min/1.73 m²)					
	<60		60–89		>90	
	Smoke (–)	Smoke (+)	Smoke (–)	Smoke (+)	Smoke (–)	Smoke (+)
baPWV	(N = 33)	(N = 4)	(N = 252)	(N = 122)	(N = 374)	(N = 105)
Mean (cm/s)	1716.50 ± 388.44*	1888.78 ± 461.50+	1510.74 ± 254.85*	1665.64 ± 362.63+	1386.16 ± 280.72	1436.09 ± 236.96
Maximum (cm/s)	2087.50	3174.00	2173.50	3243.50	2275.50	2553.50
Minimum (cm/s)	1247.50	1269.50	1115.00	922.00	823.50	926.50
Smoking rate	10.81%		32.62%		21.9%	

Abbreviation: baPWV, brachium-ankle pulse wave velocity; eGFR, estimated glomerular filtration rat

Discussion

In the current study, we investigated the relationship between baPWV and renal function in a Chinese Han population. The baPWV was highly associated with eGFR in the correlation and univariate linear regression analyses; however, only PP and age showed a significant association with eGFR in multiple linear regression analysis.

Our results were inconsistent with previous studies that evaluated the association of PWV changes and decline of eGFR. The Maine Syracuse Longitudinal Study (MSLS) reported that a decline in renal function was related to higher levels of PWV after adjustment for covariates [19]. The Rotterdam study also found a relationship between PWV and eGFR, and suggested that vascular stiffness could be a target for delaying the decline in kidney function [17, 18]. However, these studies did not include PP as a parameter [17-19]. Of note is that our findings are consistent with those of Kim et al. [20], who reported that PP was more strongly related to kidney function than baPWV and cfPWV. The Ageing and Body Composition (ABC) study also stressed the necessity of adjustment by PP [23]. Investigators of the ABC Study confirmed that adjustment with PP could attenuate the relationship of PWV and eGFR [23].

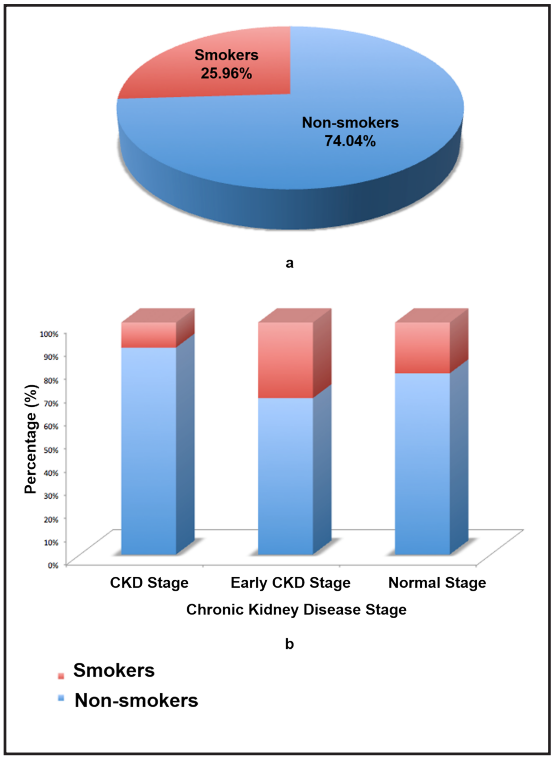

Fig. 3. Comparison of the smoking status between patients with different stages of chronic kidney disease (CKD). There were 231 smokers and 659 non-smokers in the study population (25.96% and 74.04%, respectively (a). The early CKD stage has the highest proportion of smokers compared with the normal and CKD stages (b).

Various mechanisms could explain how arterial stiffness influences kidney function. Since the kidney is a high-flow organ, the renal vasculature may be easily affected by haemodynamic stress, which could result in microvascular ischaemia, endothelial dysfunction and ultimately kidney dysfunction [35]. However, baPWV may not be a direct indicator of eGFR in a multiple regression model. This is because PP is related to both arterial stiffness and non-stiffness-related factors, such as left ventricle ejection patterns [23]. The special structure of the glomerular capillaries forms the basis of how PP influences renal function. Because the pressure in the efferent artery is higher than that in the afferent artery, the pulsation pressure is higher in the glomerulus than in other organs. When PP changes, the self-regulation system of the kidney might be more easily affected [36, 37]. Thus, baPWV had a high correlation coefficient with eGFR, but was excluded from the multiple linear regression analysis.

We also verify the conclusion of previous studies that renal function decreases with age. With age increasing, kidney is associated with various histological changes such as interstitial fibrosis and tubular atrophy [38]. These histological changes lead to a reduced blood flow and decreased eGFR. It was reported that eGFR declines with age after 30 years old at a rate of 1 mL per year [39].

A previous study reported that smoking might aggravate the risk of cardiovascular and CKD, and even all-cause mortality [28]. The current study investigated whether smoking status influenced arterial stiffness and renal function. The results demonstrated that smokers had worse arterial stiffness, which might explain why smokers are more easily affected by some aspects of CVD. Among all of the CKD groups, subjects with early CKD included the highest proportion of smokers. However, the proportion of the smokers in the normal group is higher than the CKD group. The interesting distribution of smoking rate may be explained as that smoking may increase the metabolite and then increase the eGFR values [40-42]. Thus the eGFR values of some smokers with CKD may appear higher than 60mL/min/1.73 m^2. Smokers are easier to have proteinuria than non-smokers [40, 41]. In this study, we also found a higher albuminuria rate in smokers, which may indicate the decreasing of kidney function. A large cohort of Chinese Han population was recruited in the current study. However, our study has some limitations. First, dynamic changes in the relationship between baPWV and eGFR cannot be observed in such a cross-sectional study. Second, the mechanisms behind the association between arterial stiffness and renal function require in-depth investigations in both rural residents and in other kinds of kidney diseases.

Conclusion

In summary, we investigated the relationship between baPWV and kidney function in a Chinese Han population, and our results revealed that arterial stiffness is not an independent marker of renal function. Age and PP may play a more important role in the changes of eGFR in different CKD stages. Smokers usually have higher baPWV values and worse kidney function.

Disclosure Statement

The authors state that they do not have any conflict of interests and nothing to disclose.

Acknowledgement

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