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ORIGINAL ARTICLE

Decreased estimated glomerular filtration rate (eGFR) is not an independent risk factor of arterial stiffness in Chinese women

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Abstract

Recent studies suggest that decreased estimated glomerular filtration rate (eGFR) and uric acid (UA) may be independent risk factors for arterial stiffness (AS). As serum UA level is linked to renal function, we hypothesize that decreased eGFR may be not an independent risk factor of AS, but may be related to UA level. In this study, we aimed to validate this hypothesis in a large community-based Chinese population. A total of 13,899 people were selected from the Cardiovascular Risk Survey (CRS) from October 2007 to March 2010. Pulse wave velocity (PWV) was calculated using the established methods. The relationships between eGFR, fasting blood glucose (FBG), UA and PWV were analyzed with multivariate linear regression. We found that PWV was significantly correlated to FBG ($r = 0.173$, $p < 0.001$) and UA ($r = 0.177$, $p < 0.001$), and inversely correlated to eGFR ($r = -0.161$, $p < 0.001$). A multivariable regression analysis revealed that FBG ($\beta = 0.056$, $p < 0.001$) and UA ($\beta = 0.039$, $p < 0.001$), but not eGFR ($\beta = -0.011$, $p = 0.062$) were significantly related to elevation of PWV. In women, eGFR was not an independent risk factor of AS with progressively decreasing renal function (all $p > 0.05$). However, in men, eGFR was associated with PWV in subjects with eGFR < 60 ml/min/1.73 m^2. Our results suggest that decreased eGFR is not independently associated with AS in Chinese women.

Key Words: *arterial stiffness, estimate glomerular filtration rate, fasting blood glucose, pulse wave velocity, uric acid*

Introduction

There is a high prevalence of coronary artery disease (CAD) in chronic kidney disease (CKD) patients, which is associated with a decrease in the estimated glomerular filtration rate (eGFR) (1). Several studies have revealed that arterial stiffness (AS) is both a predictor of cardiovascular disease (2–4) and a correlate of reduced glomerular filtration rate (GFR) (5–7). The pulse wave velocity (PWV), one of the most studied parameters of AS, is a strong, independent predictor of cardiovascular events and mortality (8), and is one of the commonly used methods for measuring AS (9,10). It is a useful method in large clinical studies (4,11–13) because it provides a simple measurement that can be performed in primary care settings, without expensive or elaborate equipment, extensive training or experience.

Some studies indicate that AS measured by PWV is associated with renal dysfunction not only in CKD patients (14), but also in hypertensive patients (15,16), even within the normal range of eGFR (17). Accumulated evidence also suggests that serum uric acid (UA) level is associated with PWV and that hyperuricemia is an independent risk factor of AS (18–20). Therefore, we hypothesize that decreased eGFR may be not an independent risk factor of AS, but that its effect on PWV may be related to the increased serum UA level. In this study, we aimed to validate this hypothesis in a large community-based Chinese population.

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Methods

Subjects

The Cardiovascular Risk Survey (CRS) study is a multi-ethnic, community-based, cross-sectional study designed to investigate the prevalence and risk factors for cardiovascular diseases and determine the genetic and environmental contributions to atherosclerosis, CAD and cerebral infarction (CI) of Chinese Han, Uygur and Kazakh population in Xinjiang of western China from October 2007 to March 2010. We used a stratified sampling method to select a representative sample of the general population of Chinese Hans, Uygurs and Kazakhs of this area. Seven cities (Urumqi, Kelamayi, Hetian, Zhaosu, Fukang, Tulufan and Fuhai) were chosen and, based on the government record of registered residence, one participant was randomly selected from each household. In this way, a total of 14,618 participants (5757 Hans, 4767 Uygurs and 4094 Kazakhs), were randomly selected from 26 villages of these seven cities and were invited to participate. Those whose data were incomplete were excluded (182 Hans, 332 Uygurs and 205 Kazakhs). Finally, 13,899 individuals (95.08%) were analyzed in the present study.

The present study was conducted in accordance with the Declaration of Helsinki guidelines, and informed consent was obtained from each individual according to a protocol approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University.

PWV measurement

Bilateral brachial-ankle PWV (baPWV) was measured in all subjects using the form ABI/PWV (VP1000; Colin Co., Ltd., Komaki, Japan), which is a device with four cuffs that can simultaneously measure blood pressure levels in both arms and legs, and automatically calculate the ankle brachial pressure index (ABI). In addition, it can also record pulse waves through sensors in the cuffs, store data from the start point of each pulse wave in the right arm and both the legs in memory, record the time difference between transmission time to arm and transmission time to ankle as "transmission time", calculate the transmission distance from the right arm to each ankle according to body height, and automatically compute and output the baPWV values by transmission time and transmission distance. As there was a significant positive correlation between left and right baPWV, we used the mean right/left baPWV value during our analysis (21,22).

Covariates

We collected information on each subject's medical history and lifestyle characteristics using standardized questionnaires. Systemic arterial hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg and/or a diastolic blood pressure (DBP) $\geq$ 90 mmHg (23), on at least two separate occasions, or antihypertensive treatment. Hypercholesterolemia was defined as a documented total cholesterol (TC) of $\geq$ 240 mg/dl ($\geq$ 6.2 mmol/l) or current treatment with cholesterol-lowering medication. Diabetes mellitus was defined as the presence of an active treatment with insulin or an oral antidiabetic agent; for patients on dietary treatment, documentation of an abnormal FBG or glucose tolerance test based on the World Health Organization criteria (24) was required to establish this diagnosis. Smoking status classifications were current smokers, former smokers and never-smokers. All the participants underwent a standardized physical examination performed by experienced research staff. Anthropometric measurements were conducted in light clothing and without shoes. Height was measured to the nearest 0.1 cm and weight was measured with a standard scale in the upright position to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided

Table I. Participant characteristics (n = 13,899).

	Mean ± SD or no. (%)
Age, years	50.84 ± 12.60
Male, *n* (%)	6439 (46.3)
BMI, kg/m^2	25.75 ± 4.20
Smoking, *n* (%)	3975 (29.6)
SBP, mmHg	134.54 ± 2.43
DBP, mmHg	84.64 ± 17.11
Creatinine, µmol/l	72.96 ± 26.05
eGFR, ml/min/1.73 m^2	99.74 ± 32.86
Uric acid, mmol/l	275.29 ± 85.30
FBG, mmol/l	5.16 ± 1.69
Triglyceride, mmol/l	1.55 ± 1.25
TC, mmol/l	4.61 ± 1.13
HDL-C, mmol/l	1.27 ± 0.45
LDL-C, mmol/l	2.88 ± 0.92
PWV, cm/s	1526.45 ± 368.28

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PWV, pulse wave velocity. Continuous variables are presented as mean ± SD and median (range), whereas categorical variables are presented as counts and percentages.

Table II. Correlation coefficients among pulse wave velocity (PWV), age, body mass index (BMI), systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR) and fasting blood glucose (FBG).

Variable	Age	BMI	SBP	eGFR	Uric acid	FBG
PWV	0.604*	0.197*	0.720*	− 0.161*	0.177*	0.173*
Age		0.119*	0.442*	− 0.223*	0.134*	0.092*
BMI			0.362*	− 0.083*	0.228*	0.122*
SBP				− 0.115*	0.153*	0.160*
eGFR					− 0.328*	− 0.223*
Uric acid						0.177*

*$p < 0.01$.

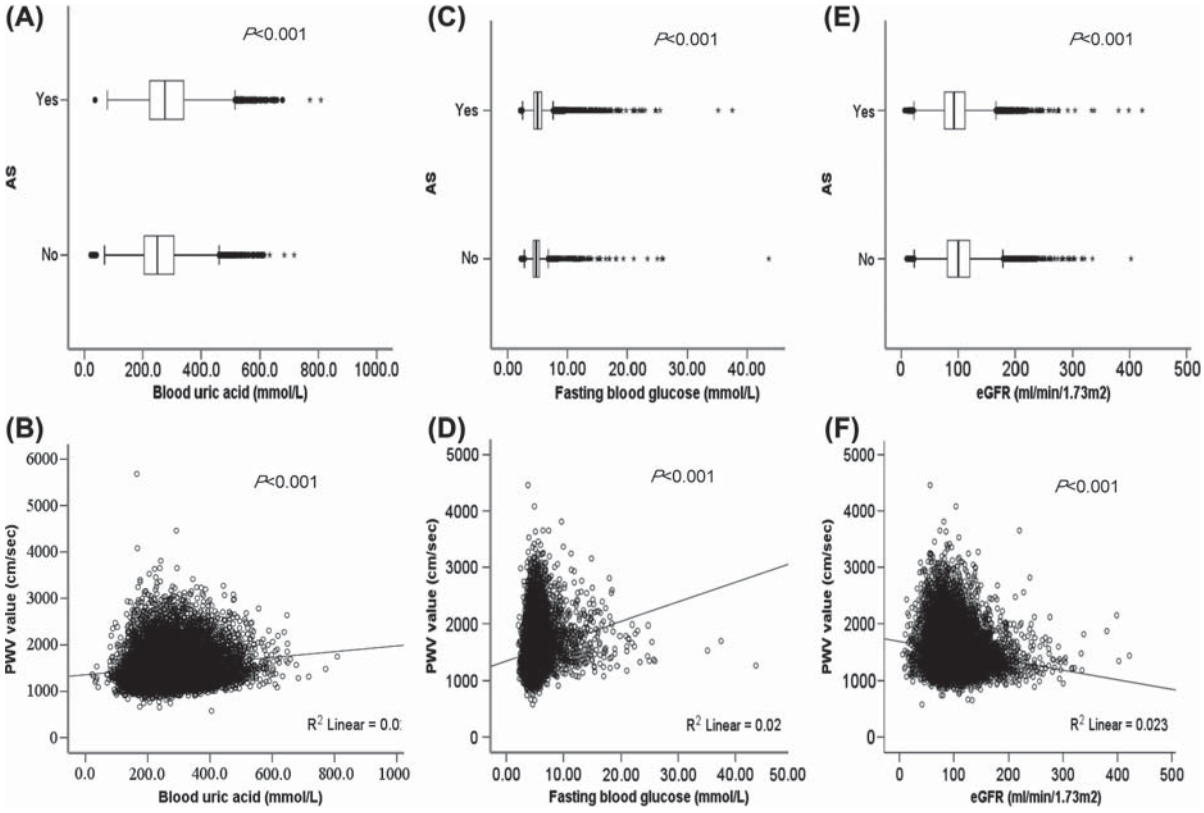

Figure 1. Relationship between fasting blood glucose (FBG), uric acid (UA) and estimated glomerular filtration rate (eGFR) and the presence of arterial stiffness (AS) and pulse wave velocity (PWV) values. (A) Box plots showing the distribution of UA in participants with and without AS (PWV > 1400 cm/s); (B) scatter plot showing the correlation between UA and PWV; (C) box plots showing the distribution of FBG in participants with and without AS (PWV > 1400 cm/s); (D) scatter plot showing the correlation between FBG and PWV; (E) box plots showing the distribution of eGFR in participants with and without AS (PWV > 1400 cm/s); (F) scatter plot showing the correlation between eGFR and PWV.

by height squared (m^2). Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower border of the rib cage and the upper hip bone (iliac crest) during expiration.

Biochemical analysis

Serum was separated from the samples within 30 min and stored at −80°C until analysis. We measured the serum concentration of UA, creatinine, triglycerides (TG), TC, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting glucose using equipment for chemical analysis (Dimension AR/AVL Clinical Chemistry System, Newark, NJ, USA) employed by the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University. Glomerular filtration rate was estimated by using the following equation: $\text{eGFR} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) (25).

Statistical analysis

Data analysis was performed using the computer software *Statistical Package for Social Sciences-SPSS* for Windows version 17.0 (SPSS, Inc., Chicago, IL, USA). Demographic and clinical characteristics of the study population were expressed as the mean ± standard deviation or as a ratio based on the renal function categories. The bivariate associations between variables were examined using Pearson's correlation coefficients. All parametric data were analyzed using Student's *t*-test, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) wherever appropriate. Multivariable linear regression was used to assess whether eGFR and UA were independent predictors of AS. Within each multivariable regression analysis, five models were constructed. In Model 1, the variables included AS risk factors, such as age, SBP, BMI, TC and TG. To assess whether FBG was a significant predictor, in Model 2, we added it to the variables used in Model 1. In Model 3, we added UA to the variables employed in Model 1 to assess whether it was an independent predictor of AS. To assess whether eGFR was an independent predictor of AS, in Model 4, we added it to the variables used in Model 1. Finally, in Model 5, we added FBG, UA and eGFR to the variables employed in Model 1 to assess whether these three factors were independent of each other and other risk factors. We also investigated the interactions between eGFR and age, SBP, BMI, FBG, and UA in the statistical models. Statistical significance was determined at $p < 0.05$.

Results

The mean age of the participants was 50.84 years, and 46.3% of the participants were men and 29.6% were smokers (Table I). As shown in Table II, PWV was statistically significant and directly correlated to age, SBP, BMI, fasting blood glucose (FBG) and UA, and was inversely correlated to eGFR.

FBG level in participants with AS (PWV > 1400 cm/s) was significantly higher than that in participants without AS (PWV ≤ 1400 cm/s) [(5.34 ± 1.89 mmol/l) vs (4.92 ± 1.36 mmol/l); $p < 0.001$; Figure 1A], and was significantly related to PWV ($p < 0.001$; Figure 1B). The UA level in participants with AS was significantly higher than that in participants without AS [(286.64 ± 86.98 mmol/l) vs (260.76 ± 80.80 mmol/l); $p < 0.001$; Figure 1C], and was significantly related to PWV ($p < 0.001$; Figure 1D). Furthermore, the eGFR level in participants with AS was significantly lower than that in participants without AS [(104.06 ± 34.14 ml/min/1.73 m^2) vs (96.37 ± 31.42 ml/min/1.73 m^2); $p < 0.001$; Figure 1E]; and was significantly related to PWV ($p < 0.001$; Figure 1F).

In a multivariable linear regression model, variables significantly associated with PWV included age, BMI, SBP and TG (Model 1, Table III). After adjustment for these risk factors in Model 1, FBG, UA and eGFR were independently related to PWV (Models 2, 3 and 4, respectively; Table III). Nevertheless, after adjustment for UA and FBG as well as Model 1, the independent effect of eGFR disappeared (Model 5, Table III, $p = 0.062$), but the effect of TC was significant (Model 5, Table III, $p = 0.012$), suggesting that eGFR is not independently related to PWV. In a gender-specific model, we divided these subjects into three groups according to the eGFR categories. As shown in Table IV, in women, the eGFR was not independently related to PWV in each category of renal function (all $p > 0.05$); however, in men, the eGFR was associated with PWV only in subjects with eGFR < 60 ml/min/1.73 m^2.

Discussion

In this study, we investigated the relationships between UA, FBG, eGFR and PWV in a large sample of Chinese population. Our main results suggest that elevated UA and FBG levels, but not decreased eGFR level, are independently associated with AS in Chinese women.

Several studies have suggested that AS measured by PWV is associated with renal dysfunction (14–17). However, our results are not in agreement with those findings. Through simple analysis, we observed a significant association of eGFR with PWV, and in a multivariable linear regression model including age, SBP, BMI and TC, this association remained significant; however, in a multivariable

Table III. Association of uric acid (UA), fasting blood glucose (FBG) and estimated glomerular filtration rate (eGFR) with pulse wave velocity (PWV): multivariable linear regression models.

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*
UA, mmol/l	–	–	–	–	–	–	–	–	–	0.041	0.025	< 0.001	0.039	0.026	< 0.001
FBG, mmol/l	–	–	–	–	–	–	0.056	1.211	< 0.001	–	–	–	0.056	1.216	< 0.001
eGFR, ml/min/ 1.73 m^2	–	–	–	− 0.027	0.063	**< 0.001**	–	–	–	–	–	–	− 0.011	0.066	**0.062**
SBP, mmHg	0.594	0.104	< 0.001	0.595	0.104	< 0.001	0.590	0.104	< 0.001	0.595	0.104	< 0.001	0.591	0.103	< 0.001
BMI	− 0.105	0.512	< 0.001	− 0.105	0.512	< 0.001	− 0.106	0.510	< 0.001	− 0.111	0.516	< 0.001	− 0.111	0.514	< 0.001
Age, years	0.350	0.174	< 0.001	0.346	0.176	< 0.001	0.348	0.173	< 0.001	0.347	0.174	< 0.001	0.343	0.175	< 0.001
TC	0.000	1.872	0.877	− 0.007	1.915	0.237	− 0.006	1.872	0.307	− 0.008	1.895	0.179	− 0.015	1.921	0.012
TG	0.040	1.676	< 0.001	0.041	1.675	< 0.001	0.030	1.695	< 0.001	0.031	1.714	< 0.001	0.022	1.741	< 0.001

SBP, systolic blood pressure; BMI, body mass index; TC, total cholesterol; TG, total triglycerides. The β coefficients represent the amount of change in the predicted response (PWV) for a unit change in a continuous variable.

Table IV. Association of estimated glomerular filtration rate (eGFR) with pulse wave velocity (PWV) in subgroups: multivariable linear regression models.

	Men								Women							
	eGFR ≥ 90 (ml/min/1.73 m^2)			60 < eGFR < 90 (ml/min/1.73 m^2)			eGFR ≤ 60 (ml/min/1.73 m^2)			eGFR ≥ 90 (ml/min/1.73 m^2)			60 < eGFR < 90 (ml/min/1.73 m^2)			eGFR ≤ 60 (ml/min/1.73 m^2)		
Variables	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*
Age, years	7.628	0.672	**< 0.001**	7.863	0.329	**< 0.001**	10.127	0.412	**< 0.001**	139.51	61.835	**0.024**	11.206	0.359	**< 0.001**	13.136	0.486	**< 0.001**
SBP, mmHg	9.262	0.438	**< 0.001**	10.128	0.216	**< 0.001**	10.232	0.253	**< 0.001**	8.920	0.584	**< 0.001**	9.206	0.195	**< 0.001**	9.681	0.241	**< 0.001**
TG, mmol/l	− 1.329	5.493	0.809	1.970	3.068	0.521	1.191	3.966	0.764	8.036	0.349	**< 0.001**	12.563	3.670	**0.001**	11.323	5.373	**0.035**
TC, mmol/l	− 5.610	6.945	0.419	− 1.651	3.904	0.672	− 4.844	4.938	0.327	14.938	6.364	**0.019**	− 4.132	3.787	0.275	− 13.886	4.713	**0.003**
BMI, kg/m^2	− 9.259	2.009	**< 0.001**	− 9.033	1.124	**< 0.001**	− 7.848	1.423	**< 0.001**	4.227	5.679	0.457	− 9.164	0.906	**< 0.001**	− 12.626	1.219	**< 0.001**
UA, mmol/l	0.274	0.119	**0.021**	0.132	0.055	**0.017**	0.104	0.060	0.084	− 8.108	1.456	**< 0.001**	0.170	0.063	**0.007**	0.035	0.073	0.635
FBG, mmol/l	11.221	5.248	**0.033**	14.009	2.278	**< 0.001**	7.634	2.548	**0.003**	0.170	0.121	0.161	17.395	2.576	**< 0.001**	12.208	3.257	**< 0.001**
eGFR, ml/min/1.73 m^2	0.108	0.349	0.757	0.027	0.494	0.956	− 1.487	0.467	**0.001**	3.968	3.949	0.315	0.340	0.460	0.460	− 0.785	0.424	0.064

SBP, systolic blood pressure; TG, total triglycerides; TC, total cholesterol; BMI, body mass index; UA, uric acid; FBG, fasting blood glucose.

linear regression model including UA, besides FBG, age, SBP, BMI and TC, this relationship disappeared. These results suggest that eGFR is not independent of serum UA levels. Both Miyatake et al. (26) and Kawamoto et al. (21), who did not consider serum UA level in the mutivariable model, observed a positive association of eGFR with AS.

UA is the end product of purine metabolism in humans. Sources of purine are either endogenous or exogenous, with the former from *de novo* synthesis and nucleic acid breakdown, and the latter from dietary purine intake. In the steady state, this daily production and ingestion of approximately 700 mg of UA is balanced by daily elimination of an equal amount of UA from the body, of which approximately 70% (roughly 500 mg daily) needs to be excreted by the kidneys (20). Therefore, elevated UA level is not only associated with diet, but also related to renal function. Recently, two large prospective population studies from Japan examined the relationship between serum UA level and development of kidney disease. Tomita et al. (27) observed a strong association between serum urate level and renal failure, even when adjusted for covariate effects. Similarly, Iseki et al. (28) found that hyperuricemia was associated with a greater risk of end-stage renal disease even after adjustment for comorbidities. Nevertheless, not only serum UA, but also decreased renal function was considered an independent risk factor for cardiovascular event, including CAD, AS and stroke.

Schillaci et al. (17) demonstrated that a mildly reduced kidney function was responsible for increased AS. Interestingly, in a large longitudinal study of patients with essential hypertension, Benetos et al. (29) found that serum creatinine level was a major determinant of accelerated progression of AS. Tsai et al. (18) suggested that UA was an independent predictor of AS in hypertensive patients. Nevertheless, these studies did not consider UA and eGFR simultaneously in the multivariable analysis. In the present study, although an inverse relationship was found between eGFR and AS through simple analysis, in the multivariable regression analysis, the independent effect of eGFR was not observed in the total population.

Although several studies have indicated that eGFR is associated with PWV, the mechanisms linking PWV to renal function are largely unknown. Several studies have indicated that increased AS may be a cause or an effect of reduced renal function, and may result in an increase in SBP leading to high pulse pressure. The high pressure waves generated may cause injury to the renal vascular system, and thus result in lowering of GFR (30,31). In addition, impaired renal function may lead to stiffening of the large arteries (32,33) through several mechanisms, including accumulation of advanced glycosylation end products, increased collagen cross-linking and

activation of the renin–angiotensin system (34). Nevertheless, the association between UA and renal function may be an important factor contributing to AS, which was not considered in several previous studies. As elevated UA level not only results from increased intake, but also decreased renal function, serum UA level may be a better predictor of AS than eGFR.

There are several advantages with respect to the inclusion of a large community-based cohort of individuals from the community. We used uniform protocols in groups, including questionnaires, anthropometric measurements, assessment of conventional risk factors and the PWV measure. A potential weakness of this study is the cross-sectional study design, which cannot establish causality relations.

Conclusions

Our results suggest that elevated serum UA and FBG are independent risk factors of AS, and that decreased eGFR is not independently associated with AS in Chinese women.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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