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Original Article

Relationship between Serum Uric Acid and Vascular Function and Structure Markers and Gender Difference in a Real-World Population of China-From Beijing Vascular Disease Patients Evaluation Study (BEST) Study

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***Aim*: The study was done to establish the relationship between serum uric acid (UA) and vascular function and structure parameters including carotid femoral pulse wave velocity (CF-PWV), carotid radial pulse wave velocity (CR-PWV), cardio ankle vascular index (CAVI), ankle brachial index (ABI), and carotid intima-media thickness (CIMT), and the gender difference in a real-world population from China.**

***Methods*: A total of 979 subjects were enrolled (aged 60.86 ± 11.03 years, male 416 and female 563). Value of UA was divided by 100 (UA/100) for analysis.**

***Results*: Body mass index (BMI), diastolic blood pressure (DBP), fasting plasma glucose (FPG), UA, and UA/100 were significantly higher in males compared with females (all $p<0.05$); pulse pressure (PP), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were lower in males than females (all $p<0.05$). All vascular parameters including CF-PWV, CR-PWV, CAVI, ABI, and CIMT were higher in males than females (all $p<0.05$). Multiple linear regression analysis showed that UA/100 was independently positively linearly correlated with CAVI (B = 0.143, $p=0.001$) and negatively correlated with ABI in the male population (B = −0.012, $p=0.020$). In people with higher UA, the risk of higher CF-PWV was 1.593 ($p<0.05$).**

***Conclusions*: 1. All vascular parameters were higher in males than females. There was no gender difference in the relationship between UA and vascular markers except in ABI. 2. UA was independently linearly correlated with CAVI. 3. In people with higher UA level, the risk of higher CF-PWV increased. Therefore, higher UA may influence the vascular function mainly instead of vascular structure.**

Key words: Serum uric acid (UA), Carotid femoral pulse wave velocity (CF-PWV), Cardio ankle vascular index (CAVI), Ankle brachial index (ABI), Carotid intima-media thickness (CIMT).

Introduction

Serum uric acid (UA) is the major product of purine metabolism and is formed from xanthine, a reaction catalyzed by dehydrogenase/oxidase. UA may have both beneficial functions (acting as an antioxidant) as well as detrimental actions (to stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction)[1]. It has been clearly associated with oxidative stress and inflammation in several pathological conditions[2, 3], and UA was considered to be associated with cardiovascular diseases[1, 4, 5].

Noninvasive markers of vascular function and structure have been confirmed as alternative indicators of risk for future cardiovascular disease (CVD). Carotid femoral pulse wave velocity (CF-PWV) was a gold standard for evaluation of arterial stiffness[6]. Cardio ankle vascular index (CAVI) was another new index of arterial stiffness independently of instant blood pressure and was related to several cardiovascular risk factors[7]. The ankle brachial index (ABI) also predicts CVD risk and further development and has been used

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for cardiovascular disease prevention in clinical practice[8, 9]. The carotid intima-media thickness (CIMT) was a measurement of early atherosclerosis which was also related to future cardiovascular risk[8]. ABI, CIMT, carotid plaque, CF-PWV were all recommended for risk assessment of future vascular disease by domestic and international guidelines[8, 10, 11].

High UA has been associated with several vascular related diseases[12]. Many studies indicated that high levels of UA were independently related with myocardial infarction[13], silent brain infarction[14], white matter atrophy and worse cognition[15] and vascular dementia[16], hypertension and metabolic syndrome prevalence[17], diabetic vascular complications[18]. In addition, high UA has been confirmed as an independent risk factor for cardiovascular mortality and sudden cardiac death[19]. However, in the relationship between UA and vascular diseases there still exists some inconsistency. Another study showed lower UA levels were independently correlated with vascular events in the first year in acute ischemic stroke patients[20].

UA has been confirmed to be related to markers of vascular injuries and vascular related diseases. CF-PWV was a marker reflecting vascular function, CAVI was a reflection of both vascular function and structure, and CIMT was a parameter of vascular structure. Therefore, the present study was designed to evaluate the relationship between UA and various vascular function and structure markers and gender differences in a real-world population.

Methods

The Beijing Vascular Disease Patients Evaluation Study (BEST) enrolled a sample of individuals through clinics or hospitals from the community of the western region of Beijing, China, since 2010. The western region of Beijing was chosen as the site of the study because of the homogeneity of life-style among its residents, with a very low rate of immigration. For the present investigation, we included participants from part of the BEST study with complete data of vascular parameters and UA. Subjects with ABI <0.9 and medication on UA lowering agents were excluded.

The ethics committee of Peking University Shougang Hospital approved the study protocol, and all participants provided written informed consent before participating, which was conducted in accordance with the Declaration of Helsinki.

Clinical and Laboratory Evaluation

The personal history including life-style habits such as pharmacological treatments, history of vascular related diseases, such as hypertension, diabetes mellitus, coronary artery disease, stroke, and peripheral artery disease (PAD) was obtained by medical records or a questionnaire. In the present study, pharmacological treatments included hypoglycemic drugs and lipid-lowering drugs. Cardiovascular drugs were described as ABCD drugs, namely one of the medications including angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker, or beta-receptor antagonist, or calcium channel blocker, or diuretic. The basic parameters recorded with standardized methods by trained personnel are: fasting plasma glucose (FPG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), high sensitive C reactive protein (hs-CRP). Fasting UA was measured using an auto-analyzer with a phosphotungstic acid reagent.

Vascular Measurements

CF-PWV and Carotid Radial Pulse Wave Velocity (CR-PWV) Measures

CF-PWV and CR-PWV were simultaneously measured by an automatic equipment Compliar SP (Artech Medical, Pantin, France). The measurement was undertaken with the participant in a supine position after 5 to 10 minutes of rest and CF-PWV and CR-PWV were calculated by knowing the pulse transit time and distance.

CAVI and ABI Measures

CAVI and ABI were recorded using a VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) with the participants resting in a supine position for 5 to 10 minutes and cuffs were wrapped around both the arms and ankles. The value of CAVI, ABI, heart rate, and blood pressure of both arms were obtained automatically. And we chose the mean level of left and right CAVI and ABI for the analysis.

CIMT Measures

CIMT was measured as recommended by the Mannheim Consensus[21], i.e., in supine position in the left and right common carotid arteries in anterolateral, posterolateral, and mediolateral directions. The extracranial carotid arteries were bilaterally examined with ultrasound EUB-7500 (Hitachi, Japan), equipped with a linear array transducer. The analysis of CIMT was calculated as the mean of bilateral CIMT measurements, namely CIMT = (left CIMT + right CIMT)/2.

Statistical Methods

The researchers conducted a cross-sectional analysis of UA levels and CF-PWV, CR-PWV, CAVI, ABI, CIMT of 979 participants according to gender. The researchers then performed multiple linear regression

Table 1. General characteristics of participants in global, male and female population.

Variables	Total $n=979$	Male $n=416$	Female $n=563$	t value	p value
Age (year)	60.86 ± 11.03	60.93 ± 12.58	60.81 ± 9.74	0.157	.875
BMI (kg/m^2)	24.95 ± 3.48	25.66 ± 3.43	24.43 ± 3.43	5.556	.000*
HR (beats/min)	67.95 ± 10.97	68.28 ± 11.67	67.71 ± 10.43	0.784	.433
SBP (mmHg)	136.59 ± 17.30	137.44 ± 16.42	135.96 ± 17.92	1.320	.187
DBP (mmHg)	83.65 ± 10.07	86.06 ± 10.40	81.87 ± 9.45	6.578	.000*
PP (mmHg)	52.94 ± 12.88	51.38 ± 12.10	54.09 ± 13.31	−3.328	.001*
FPG (mmol/L)	5.87 ± 1.42	6.13 ± 1.71	5.69 ± 1.13	4.485	.000*
hs-CRP (mg/L)	1.18	1.26	1.12		.309
TC (mmol/L)	4.84 ± 1.13	4.58 ± 1.17	5.03 ± 1.06	−6.282	.000*
TG (mmol/L)	1.73 ± 1.22	1.82 ± 1.49	1.67 ± 0.98	1.742	.082
HDL-C (mmol/L)	1.28 ± 0.30	1.17 ± 0.27	1.36 ± 0.30	−10.592	.000*
LDL-C (mmol/L)	3.00 ± 0.86	2.87 ± 0.87	3.09 ± 0.83	−3.949	.000*
UA (umol/L)	316.94 ± 81.54	361.05 ± 82.35	284.35 ± 63.70	15.819	.000*
UA/100 (umol/L)	3.17 ± 0.82	3.61 ± 0.82	2.84 ± 0.64	15.819	.000*

Values are described as mean ± SD for continuous variables and percentage or median for categorical variables. * indicated $p < 0.05$.
Abbreviations: BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FPG, fasting plasma glucose; UA, serum uric acid; UA/100, serum uric acid divided by 100; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C reactive protein

(stepwise) and logistic regression analyses (enter) in total, male and female populations respectively, adjusting for traditional risk factors, to evaluate the independent effect of UA levels on measures of arterial parameters. The researchers assessed the independent relations between UA and vascular indices using multiple linear regression with adjustment for age, gender, body mass index (BMI), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), high sensitive C reactive protein (hs-CRP), medication for hyperlipidemia, hypoglycemic agents, and ABCD drugs. CF-PWV, CR-PWV, CAVI, ABI, and CIMT were dependent variables, and UA/100 was an independent variable. Finally, the researchers adopted multivariable binary logistic regression analysis by translating the number variables to two-categorical variables. Higher CF-PWV, CAVI, and CIMT were described as higher than the fourth quartile in the total population. Descriptive values, expressed as mean ± SD or numbers and percentages, were reported by gender. A *P*-value less than 0.05 (bilateral) was regarded as statistically significant. Statistical analyses were performed using the SPSS 20.0 statistical software package. UA was divided by 100 (UA/100) to reduce heteroscedasticity and still restore directionality of associations.

Results

1. General Clinical Characteristics in Total, Male and Female Populations

The level of BMI, DBP, FPG, UA, and UA/100 were significantly higher in males than that in females; and PP, TC, HDL-C, and LDL-C were lower in males than females (see **Table 1**). In addition, the value of all vascular parameters, including CF-PWV, CR-PWV, CAVI, ABI, and CIMT were significantly higher in males than that in females (see **Table 2**). In the present population, percentages of records with history of vascular related diseases and medications are shown in **Table 3**. In about one third participants, the history of hypertension, diabetes mellitus, coronary artery disease, stroke, peripheral artery disease were not recorded. And a total of 152 (15.5%) participants were without any of the above vascular related diseases (see **Table 3**). The prevalence rate of hyperuricemia was significantly higher in males than that in females. And the prevalence rate of coronary artery disease and rate of medication on ABCD drugs were different between males and females (see **Table 4**).

2. Results of Multivariable-Adjusted Linear Regression Analyses

We further evaluated the independent linear association between UA/100 and vascular parameters adjusted for age, gender, BMI, HR, SBP, DBP, PP, FPG, TC, TG, HDL-C, LDL-C, hs-CRP, medication of ABCD

Table 2. Vascular parameters according to gender and total population

Variables	Total $n=979$	Male $n=416$	Female $n=563$	t value	p value
CF-PWV (m/s)	10.59 ± 2.28	10.77 ± 2.31	10.46 ± 2.26	2.108	.035*
CR-PWV (m/s)	8.75 ± 1.63	9.03 ± 1.86	8.54 ± 1.40	4.554	.000*
CAVI	8.35 ± 1.22	8.44 ± 1.26	8.28 ± 1.18	2.070	.039*
ABI	1.13 ± 0.08	1.15 ± 0.08	1.12 ± 0.07	6.429	.000*
CIMT (mm)	0.09 ± 0.04	0.10 ± 0.05	0.08 ± 0.03	6.093	.000*

Values are described as mean ± SD. *indicated $p<0.05$.
Abbreviations: CF-PWV, carotid femoral pulse wave velocity; CR-PWV, carotid radial pulse wave velocity; CAVI, cardio ankle vascular index; ABI, ankle brachial index; CIMT, carotid intima-media thickness.

drugs and hypoglycemic drugs, lipid-lowering drugs. The results showed that only UA was positively linearly correlated with CAVI. UA was negatively linearly correlated with ABI in the male population. However, UA was not linearly correlated with CF-PWV, CR-PWV, and CIMT in total, male and female populations (see **Table 5**).

3. Results of Multivariable-Adjusted Logistic Regression Analyses

We evaluated the independent association between higher UA and higher vascular parameters adjusted for age, gender, BMI, HR, SBP, DBP, PP, FPG, TC, TG, HDL-C, LDL-C, hs-CRP, medication of ABCD drugs and hypoglycemic drugs, lipid-lowering drugs. The results showed that in people with higher UA, the risk of higher CF-PWV was 1.593 times than people with normal UA. In addition, people with higher UA had a risk tendency of higher CAVI ($p=0.088$). However, higher UA was not correlated with higher CIMT ($p=0.280$). We further analyzed the gender difference between UA with CAVI and CIMT in both genders, and found UA also not logistically related with CAVI and CIMT in males or females (see **Table 6**). The value and meaning of variables are shown in **Table 7**.

Discussion

The present study was done to evaluate the relationship between UA and various vascular function and structure markers and gender difference in a real-world population. The results showed that all the vascular markers including CF-PWV, CR-PWV, CAVI, ABI, and CIMT were different between males and females, with a higher level in males. The differences between the prevalence rate of hyperuricemia may be the cause of the higher vascular parameters. We further explored the linear and logistic regression association between UA and various vascular function and structure markers and gender difference. The results indicated that

Table 3. Percentage of records with of history vascular related diseases and medications in total population

Variables	With records of disease history
Hypertension, NO. (%)	616 (62.9)
Diabetes Mellitus, NO. (%)	594 (60.7)
Coronary artery disease, NO. (%)	611 (62.4)
Stroke, NO. (%)	602 (61.5)
Peripheral artery disease, NO. (%)	609 (62.3)
ABCD drugs, NO. (%)	169 (17.3)
Hypoglycemic drugs, NO. (%)	59 (6.0)
Lipid-lowering drugs, NO. (%)	186 (19.0)
Without above diseases, NO. (%)	152 (15.5)

only UA was linearly correlated with CAVI and independent of traditional risk factors, gender, and medications. However, UA was not linearly correlated with CF-PWV, CR-PWV, ABI, and CIMT independently. We further explored whether gender differences existed in the linear association between CF-PWV, CR-PWV, ABI, and CIMT, and found that only ABI was negatively linearly correlated with UA in males, the other vascular markers were not linearly correlated with UA, in male and female populations respectively. We further explored the logistic regression association between UA and vascular parameters; the results showed that in people with higher UA, the risk of higher CF-PWV was 1.593 times and independent of traditional risk factors, gender and medications. People with higher UA had a higher risk tendency of higher CAVI which was not independently correlated with higher CIMT. In addition, higher UA was not logistically related with CAVI and CIMT in both genders. CF-PWV was a marker that reflects arterial stiffness and is regarded as a function marker. CAVI was a parameter reflecting both vascular function and structure. And CIMT indicated the changes in vascular structure. Therefore, we speculate that UA may mainly influence the vascular function instead of the vascular structure. The relation-

Table 4. The history of medications and vascular related diseases in total, male and female population.

Variables	Total $n=979$	Male $n=416$	Female $n=563$	Chi-square Value	p value
Hyperuricemia	264 (27.0)	201 (48.3)	63 (11.2)	167.44	.000*
Hypertension, NO. (%)	362 (37.0)	165 (39.7)	197 (35.0)	1.536	.215
Diabetes Mellitus, NO. (%)	114 (11.6)	57 (13.7)	57 (10.1)	2.224	.136
Coronary artery disease, NO. (%)	185 (18.9)	97 (23.3)	88 (15.6)	8.545	.003*
Stroke, NO. (%)	119 (12.2)	59 (14.2)	60 (10.7)	2.601	.107
Peripheral artery disease, NO. (%)	40 (4.1)	23 (5.5)	17 (3.0)	3.575	.059
ABCD drugs, NO. (%)	169 (17.3)	84 (20.2)	85 (15.1)	4.347	.037*
Hypoglycemic drugs, NO. (%)	59 (6.0)	31 (7.5)	28 (5.0)	2.595	.107
Lipid-lowering drugs, NO. (%)	186 (19.0)	83 (20.0)	103 (18.3)	0.427	.514

*indicated $p<0.05$.

Table 5. Multivariable-adjusted linear regression analyzes the association of CF-PWV, CR-PWV, CAVI, ABI and CIMT with UA/100, global and by gender.

Variables	Total ($n=979$)		Male ($n=416$)		Female ($n=563$)	
	B	p value	B	p value	B	p value
CF-PWV (m/s)						
UA/100	0.016	.627	0.036	.423	−0.003	.939
CR-PWV (m/s)						
UA/100	−0.012	.745	−0.024	.639	−0.011	.811
CAVI						
UA/100	0.143	.001*				
ABI						
UA/100	−0.072	.056	−0.012	.020*	0.015	.732
CIMT (mm)						
UA/100	−0.011	.766	−0.030	.538	0.065	.117

Adjusted for age, gender, BMI, HR, SBP, DBP, PP, FPG, TC, TG, HDL-C, LDL-C, hs-CRP, medication of ABCD and hypoglycemic drugs, lipid-lowering drugs.
*indicated $p<0.05$.

ship between UA and ABI was a negative linear association (B = −0,072, $p=0.056$), and UA was significantly correlated with ABI in the male population (B = −0.012, $P=0.020$). We speculated that this maybe because of the high level of BMI, DBP, FPG, UA, and the high prevalence rate of hyperuricemia. Thus, further studies need to confirm this finding.

Many studies reported have confirmed nearly consistently an association of elevated UA level with CVD, although not all have found that the correlation is independent of other risk factors. Several studies showed UA was independently negatively correlated with vascular endothelial function[22, 23]. UA was also a determinant of arterial stiffness independently from conventional risk factors[24] and was associated with vascular inflammation (hs-CRP)[25], coronary artery calcification (CAC)[26], and PAD[27]. Studies on the relationship between vascular markers and UA showed an independent association between UA and CF-PWV, CR-PWV, CAVI, CIMT, lower ABI in several populations[28-31]. However, the associations between UA and vascular markers have been reported inconsistently. Some studies showed no independent associations between higher UA and endothelial dysfunction[29, 32], CF-PWV[17], microalbuminuria, arterial stiffness, carotid plaque[29, 33], CIMT[17], CAC[25], which were consistent with the partial results of ours. Furthermore, the relationships between UA and vascular markers were different in males and females. Although advancing age is accompanied by increased aortic stiffness in both males and females, a significant sex difference exists, with females showing a steeper decline in aortic elasticity[34]. In addition, UA is associated with alterations in systemic arterial stiffness that differ in men and women. Women might be more sus-

Table 6. Multivariable-adjusted logistic regression analyzes the association of higher CF-PWV, higher CAVI and higher CIMT with higher UA, global and by gender.

Subjects	Dependent variable	B	Wals	OR	95% C.I.	*P*
Total	Higher CF-PWV	0.466	4.395	1.593	1.031-2.463	.036*
	Higher CAVI	0.390	2.904	1.478	0.943-2.315	.088
	Higher CIMT	−0.244	1.168	0.784	0.503-1.220	.280
Male	Higher CAVI	0.189	0.410	1.208	0.678-2.153	.522
	Higher CIMT	−0.480	3.393	0.619	0.371-1.031	.065
Female	Higher CAVI	0.658	2.911	1.931	0.907-4.113	.088
	Higher CIMT	0.416	0.936	1.516	0.652-3.524	.333

Adjusted for age, gender, BMI, HR, SBP, DBP, PP, FPG, TC, TG, HDL-C, LDL-C, hs-CRP, medication of ABCD and hypoglycemic drugs, lipid-lowering drugs.
*indicated $p<0.05$.

ceptible to large vascular damage associated with hyperuricemia[35]. However, in our study population, we did not find gender differences between UA and vascular markers. A positive association between pulse wave velocity (PWV) and UA was observed after adjusting for classical risk factors in women only[36] and a gender difference was also observed in the UA range for increase in CAVI[30], which was not consistent with our results which showed that the relationship between UA and CAVI was independent of gender. UA was more strongly associated with metabolic syndrome (MS) in women than in men[37], and was associated with the prevalence of carotid atherosclerosis only in women with MS[38] and only in men without MS[37]. In addition, a trial provided evidence that control of UA can rectify prehypertension[39]. Therefore, further studies will be needed to establish the mechanisms and there may be a window of opportunity in which uric acid-lowering therapy could prevent or delay the development of vascular damage. About the inconsistent results with other studies, we inferred that the following reasons may have contributed. Firstly, the research population in the present study included a real-world population from China, including healthy subjects and vascular related patients. Secondly, the mean age (60.86 ± 11.03 years) was higher; in addition, the age span was relatively large from 20 years to 94 years. The relation between UA and vascular markers maybe different during this age span. Thus, further studies will be needed to explore the deeper relationship between UA and vascular function and structure parameters.

In conclusion, in our population sample, all vascular parameters were higher in males than females. Gender differences did not exist between the relationship between UA and vascular markers except ABI. UA was independently linearly correlated with CAVI rather than CF-PWV, ABI, and CIMT. In people with higher UA level, the risk of higher CF-PWV increased. People with higher UA also showed the trend of increased risk of higher CAVI. However, higher UA was not associated with higher CIMT. Therefore, higher UA may influence the vascular function mainly instead of vascular structure.

Table 7. The value and meaning of variables

Variable	Value and meaning
UA	0: normal UA 1: higher UA, with male UA > 420 umol/L or female UA > 360 umol/L
CF-PWV	0: CF-PWV ≤ 11.7 m/s 1: Higher CF-PWV, CF-PWV > 11.7 m/s
CAVI	0: CAVI ≤ 9.1 1: Higher CAVI, CAVI > 9.1
CIMT	0: CIMT ≤ 0.10 mm 1: Higher CIMT, CIMT > 0.10 mm

Study Strengths and Weakness

The strengths of the present study include its large sample size involving all kinds of vascular related diseases and healthy subjects in a real world. In addition, the present study included various non-invasive vascular function and structure parameters and analyzed the relationship between them and UA and gender difference in a single population. However, there are also some limitations. First, the study was a cross-sectional study and could not provide some predicting value of UA and vascular parameters. Second, the history of vascular related disease and medication was not complete, and about one third data of participants

were missing. Therefore, further studies are needed to evaluate the predicting value of UA for vascular related disease and vascular markers.

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Disclosure

The authors declare no conflict of interest.

Clinical Trials Registration

Clinical Trials.gov Identifier: NCT02569268.

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