Original Paper

The Relationships of the Fractional Excretion of Uric Acid with Brachial-Ankle Pulse Wave Velocity and Ankle Brachial Index in Chinese Young Adults

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Key Words

UA • FEUA • BaPWV • ABI

Abstract

Background/Aims: Elevated serum uric acid (UA) was intimately correlated with vascular stiffness and abnormal ankle brachial index (ABI) in various populations. These correlations lost significance after adjustment for estimated glomerular filtration rate (eGFR), indicating that the association of UA and brachial-ankle pulse wave velocity (baPWV) or ABI might be driven by kidney function. UA is predominantly eliminated through the kidneys, and metabolic disorders can influence the clearance of UA. In this study, we aimed to explore the putative correlation between FEUA and baPWV or ABI to determine to what extent the associations with UA were affected by renal function. **Methods:** This cross-sectional study enrolled 2351 participants, who underwent general health screening in Hanzhong people's hospital from March to June of 2017. BaPWV and ABI were measured using a volume-plethysmographic apparatus (BP-203RPEII; Nihon Colin, Tokyo, Japan). FEUA was divided into quartiles: Q1:FEUA≤3.07; Q2:3.07<FEUA≤5.32; Q3: 5.32<FEUA≤9.19; and Q4: FEUA> 9.19. **Results:** Lower FEUA predicted a higher prevalence of high baPWV and low ABI (p for trend <0.001). The respective ORs for high baPWV from the first to the third quartiles of FEUA were 1.777(1.323, 2.387); 1.561(1.158, 2.104); and 1.680 (1.250, 2.259). The prevalence of low ABI was greatly elevated with the decrement of FEUA [ORs for the first to third FEUA quartiles were 6.977(2.062, 23.610); 5.123(1.475, 17.790); and 2.685(0.709, 10.171), respectively]. The association of FEUA and ABI was independent of related confounding factors. However, the association between FEUA and baPWV was greatly influenced by corresponding confounders, especially gender. The efficacy of FEUA in the prediction of low ABI was stronger than that of serum UA. However, serum UA

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was more powerful in the prediction of high baPWV. **Conclusion:** Kidney function exerted a profound influence on the relationship between UA and baPWV or ABI, revealing complex interactions among cardiovascular risk factors.

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Introduction

Uric acid (UA), the final oxidative metabolite of purine nucleotide in humans, has been identified as a prominent risk factor for atherosclerotic diseases [1]. Compelling evidence has addressed the concept that increased UA intimately correlated with cardiovascular risk factors, such as metabolic syndrome (MetS), dyslipidaemia, obesity, and hypertension [1-3]. The interactions of these factors synergistically contributed to the pathogenesis and progression of cardiovascular disease (CVD). Several clinical and animal studies have identified that lowering UA levels prevented or reversed the progression of the MetS and hypertension [4, 5].

The brachial-ankle pulse wave velocity (baPWV) for large and media arterial elasticity and ankle brachial index (ABI) for systemic atherosclerosis status are two easy-access and effective indices reflecting overall vascular status. Increased baPWV and lowered ABI are associated with higher morbidity and mortality of CVD in high risk or even general populations [6-8]. All-cause and CVD mortality were 16.983-fold and 18.441-fold higher in patients with $ABI \leq 0.4$ and $UA > 536 \mu\text{mol/L}$, respectively, than in those with $0.9 < ABI \leq 1.4$ and $UA \leq 357 \mu\text{mol/L}$ [9]. A Japanese study in the general population suggested that every 20% increment in baPWV predicted a 1.30-fold greater cardiovascular risk after adjusting for confounders [10].

Clinical observational studies have proved that increased serum UA levels were intimately correlated with vascular stiffness and abnormal ABI in various populations independent of other cardiovascular risk factors [11-13]. However, these associations lost significance after adjustment for eGFR, indicating that the association of UA and baPWV or ABI might be driven by kidney function [12]. UA is mainly eliminated by the kidney, which diminishes in obese, hypertensive and MetS subjects [5]. It has been found in gout patients that metabolic disorders influenced the clearance of uric acid [14]. Thus, the decreased excretion of UA might modify the relationship between UA and metabolic parameters. Nevertheless, few studies have paid attention to this.

In this study, we aimed to explore whether the putative association still holds in UA and baPWV or ABI after taking kidney function into consideration by using fractional excretion of uric acid (FEUA), a good indicator of the balance of UA, and determine to what extent the associations were affected by renal function.

Materials and Methods

Participants

A total of 2351 participants, who underwent general health screening in Hanzhong people's hospital and were available for the results of UA, baPWV, and ABI, were recruited from March to June of 2017. The exclusion criteria were as follows: secondary hypertension; history of infectious diseases or abnormal liver function; $eGFR < 60 \text{ mL/min/1.73 m}^2$; $ABI > 1.4$; pregnancy; and alcohol abuse. All procedures complied with the Declaration of Helsinki and the research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Medical School, Xi'an Jiaotong University (code: 2015-128). Upon admission, written informed consent was obtained from each participant.

Demographic and anthropometric data

Basic demographic information (including age, sex, history of diseases, smoking habits and alcoholic

Table 1. CKD-EPI equation for non-blacks. Abbreviations: Scr =serum creatinine; eGFR =estimated glomerular filtration rate

Gender	Scr(umol/L)	Equation
Female	≤62	$eGFR=144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$
	>62	$eGFR=144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$
Male	≤80	$eGFR=144 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$
	>80	$eGFR=144 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$

consumption) was obtained by trained staff using a standard questionnaire. Participants took off their shoes and wore light clothes for anthropometric parameter measurements. Body mass index (BMI) was calculated using weight in kilograms (kg) divided by the square of height in metres (m²). Blood pressure (BP) was measured by certified physicians using electric sphygmomanometers. Participants were instructed to sit in a resting position for more than 5 min and refrain from exercise, smoking, alcohol, coffee, or tea prior to BP measurement. BP was measured three times at 1-min intervals. Hypertension was defined as a mean systolic blood pressure (SBP) of ≥ 140 mmHg, and/or mean diastolic blood pressure (DBP) of ≥ 90 mmHg, and/or a history of hypertension with current use of antihypertensive medications.

Laboratory analyses

Blood samples were obtained after an overnight fast and were centrifuged at 2500 g for 15 min within 2 h. Morning urine samples were collected after blood drawing. Samples were packaged in aliquots for further analysis. Basic biochemistry parameters (including lipid profiles, fasting serum glucose, serum creatinine, serum uric acid, urinary creatinine and urinary uric acid) were analysed using a Hitachi 7600-110 Chemistry Autoanalyzer (Hitachi, Ltd., Tokyo, Japan). FEUA was calculated as the ratio of urinary uric acid in umol/L to serum uric acid in umol/L divided by the ratio of urinary creatinine in umol/L to serum creatinine in umol/L [15]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation as shown in Table 1.

Measurement of BaPWV and ABI

BaPWV and ABI were measured using a volume-plethysmographic apparatus (BP-203RPEII; Nihon Colin, Tokyo, Japan)[16, 17]. Participants were in the supine position with cuffs, which were connected to a plethysmographic sensor and an oscillometric pressure sensor, wrapped around both the brachium and ankles. BaPWV was calculated according to the following equation adjusted for age, weight, and height. Averages of baPWVs from both sides were used for analysis:

$$BaPWV = \frac{La - Lb}{\Delta Tba} \text{ cm/s}$$

La: the path lengths from the suprasternal notch to the ankle,

Lb: the path lengths from the suprasternal notch to the brachium,

ΔTba: the time interval between the wavefront of the brachial waveform and that of the ankle waveform.

The ABIs of both sides were calculated by the highest pressure of the ankle on the corresponding side divided by the highest brachial pressure on either side. The lower ABI of both sides was used for analysis.

Definition of MetS

Subjects with three or more of the following five conditions were defined as having MetS[18]: Abdominal obesity: waist circumference ≥ 88 cm for females and ≥ 102 cm for males; high blood pressure: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, or taking antihypertensive drug; hypertriglyceridaemia: (TC) ≥ 150 mg/dL or treatment of dyslipidaemia; high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in males or < 50 mg/dL in females; fasting plasma glucose ≥ 100 mg/dL or treatment for diabetes mellitus (DM).

Statistical analysis

IBM SPSS Statistics 22.0 (IBM Corp., Chicago, IL, USA) was used for all statistical analyses. Demographic and clinical features of participants were compared across quartiles of FEUA subgroups. Categorical variables were expressed as percentages. Continuous variables were presented as means ± standard

Table 2. Demographic and clinical characteristics of participants by quartiles of FEUA. * compared with Q1; † compared with Q2; ‡ compared with Q3; Abbreviations: FEUA= fractional excretion of uric acid; Q=quartile; DM=diabetes mellitus; SBP=systolic blood pressure; DBP=diastolic blood pressure; TC=total cholesterol; TG=triglycerides; LDL-C=low-density lipoprotein triglycerides cholesterol; HDL-C= High-density lipoprotein triglycerides cholesterol; CREs=serum creatinine; UAs=serum uric acid; CREu=urinary creatinine; UAu=urinary uric acid; eGFR=estimated glomerular filtration rate; baPWV=brachial-ankle pulse wave velocity; ABI= ankle brachial index

Variables	FEUA				p for trend
	Q1 (n=588)	Q2(n=587)	Q3(n=589)	Q4(n=587)	
Age(years)	43±3	43±3	43±3	42±3	0.211
Sex(male,%)	69.6	60.8 *	55.3 *	35.9 * † ‡	<0.001
Smokers(%)	56.3	47.3 *	42.1 *	26.7 * † ‡	<0.001
Alcohol drinkers(%)	36.7	33.1	28 *	19.4 * † ‡	<0.001
Hypertension(%)	12.4	11.4	11.2	8.4	0.030
DM(%)	2.6	2.6	3.0	2.9	0.613
SBP(mmHg)	125±20	123±16 *	124±17	121±16 *	0.002
DBP(mmHg)	79±12	77±11	77±12 *	76±13 *	<0.001
BMI(kg/m ²)	24.5±3.3	24.1±3.1	24.0±3.2 *	23.7±3.1 *	<0.001
Laboratory parameters					
Glucose(mmol/L)	4.69±0.91	4.80±1.24	4.78±1.22	4.8±1.43	0.150
TC(mmol/L)	4.65±0.80	4.58±0.85	4.54±0.81	4.50±0.75 *	0.001
TG(mmol/L)	1.73±1.08	1.70±1.37	1.70±1.42	1.45±1.21 * † ‡	<0.001
LDL-C(mmol/L)	2.63±0.80	2.54±0.68	2.50±0.65 *	2.48±0.60 *	<0.001
HDL-C(mmol/L)	1.15±0.26	1.17±0.27	1.16±0.26	1.23±0.27 *	<0.001
TG/HDL-C	1.33[0.78-2.14]	1.23[0.79-1.95]	1.17[0.76-1.84]	0.98[0.66-1.52] * † ‡	0.004
CREs(μmol/L)	79.2±14.6	77.3±13.2	76.5±13.8 *	73.2±13.3 * †	<0.001
UAs(μmol/L)	320.9±81.8	294.7±70.6 *	279.7±71.0 * †	245.0±64.1 * † ‡	<0.001
CREu(μmol/L)	14947±6413	10221±5496 *	7203±4603 * †	4135±3257 * † ‡	<0.001
UAu(μmol/L)	1042[811-1312]	1321[991-1921] *	1463[972-2272] *	1643[1031-2424] * †	<0.001
eGFR(ml/min/1.73m ²)	96.74±13.95	96.76±12.28	96.62±12.42	96.58±13.10	0.803
baPWV(cm/s)	1263±229	1250±232	1255±246	1204±224 * † ‡	<0.001
ABI	1.07±0.08	1.08±0.08	1.09±0.07 *	1.13±0.07 * † ‡	<0.001

deviation or medians (inter-quartile range) as appropriate. The Chi-squared test for categorical variables and analysis of variance for continuous variables were used to analyse the differences across FEUA groups followed by post-hoc analysis. Partial correlation and multivariate logistic regression analysis were used to explore the association between FEUA and baPWV or ABI. During logistic regression analysis, baPWV and ABI were transformed to dichotomous variables: baPWV<1400cm/s or baPWV≥1400cm/s; ABI≤0.9 or ABI>0.9. FEUA was log-transformed to achieve normality during analysis. Two-tailed p < 0.05 was considered significant.

Results

Characteristics of the subjects

Participants were divided into four groups according to quartiles of FEUA: Q1:FEUA≤3.07; Q2:3.07<FEUA≤5.32; Q3: 5.32<FEUA≤9.19; and Q4: FEUA> 9.19. The basic characteristics of participants across quartiles of FEUA are summarized in Table 2. Participants in the lowest quartile of FEUA tended to be male, a smoker and an alcoholic drinker and their BP, BMI, total cholesterol (TC), TG, and low-density lipoprotein-cholesterol (LDL-C) were significantly higher than those in the highest quartile of FEUA(all p<0.05). HDL-C of group Q1was lower than that of group Q4 (p<0.05). Age, history of hypertension or DM, fasting glucose and eGFR showed no significant inter-group differences. Sex-specific analysis showed that baPWV and serum UA were higher in men, while ABI and FEUA were higher in women (Fig. 1).

Correlations between FEUA and baPWV or ABI

Compared with subjects in the highest quartile of FEUA, baPWV increased (Q1 vs Q4: 1263±228 vs 1204±224cm/s) and ABI decreased(Q1 vs Q4: 1.07±0.08 vs 1.13±0.07) in those of the lowest FEUA group (Table 2). Correlation analysis showed a significantly positive relationship between ABI and log-FEUA (r=0.229, p<0.001) and a negative relationship

between baPWV and log-FEUA ($r=-0.100$, $p<0.001$). However, these two correlations lost significance after adjusting for age, sex, BMI, smoking habits, alcohol consumption, history of hypertension and DM (Table 3).

Logistic regression analysis between FEUA and baPWV or ABI

To explore the predictive role of FEUA on high baPWV or low ABI, further multiple logistic regression analysis was performed. When FEUA was modeled continuously, the prevalence of high baPWV (≥ 1400 cm/s) and low ABI (≤ 0.9) decreased with an increase in FEUA [odds ratio(OR) for high baPWV: 0.597, 95% confidence interval(CI): 0.454, 0.786; OR for low ABI: 0.214, 95%CI: 0.099, 0.462]. After adjustment for age, sex, smoking habits, alcohol consumption, history of hypertension, and history of DM, the OR for low ABI was 0.181(0.083, 0.399) but the prevalence of high baPWV was no longer related to FEUA. When adjusted for metabolic components including SBP, DBP, waist circumference, glucose, TC, TG, LDL-C, and HDL-C, the respective adjusted ORs for high baPWV and low ABI were 0.653(0.464, 0.920), and 0.180(0.082, 0.395). When FEUA was modelled in quartiles, the respective ORs for high baPWV from the first to the third quartiles of FEUA were 1.777(1.323, 2.387); 1.561(1.158, 2.104); and 1.680 (1.250, 2.259), respectively. The ORs for high baPWV still held significance after adjusting for metabolic components or age, smoking habits, alcohol consumption, history of hypertension, and history of DM but lost significance after adjusting for gender. The prevalence of low ABI was greatly elevated with the decrement of FEUA [ORs for the first to third FEUA quartiles were 6.977(2.062, 23.610); 5.123(1.475, 17.790); and 2.685(0.709, 10.171), respectively] where the first and second ORs were significant and still held significance after adjusting for multiple confounders (Table 4).

Fig. 1. The differences of baPWV, ABI, serum UA, FEUA by gender.

Table 3. Comparison of the correlations of serum UA or FEUA with baPWV or ABI. Abbreviations: UA=uric acid; FEUA= fractional excretion of uric acid; baPWV= brachial-ankle pulse wave velocity; ABI= ankle brachial index. Model1 unadjusted model. Model2 adjusted for age, smoke habits, alcohol consumption, history of hypertension, history of DM. Model3 based on model 2 and further adjusted for sex

Characteristics		Correlation coefficients			
Model	Index	baPWV	p values	ABI	p values
Model 1	Serum UA	0.338	<0.001	-0.117	<0.001
	FEUA	-0.100	<0.001	0.229	<0.001
Model 2	Serum UA	0.268	<0.001	-0.014	0.511
	FEUA	-0.55	0.007	0.033	0.110
Model 3	Serum UA	0.166	<0.001	-0.009	0.674
	FEUA	-0.004	0.829	0.032	0.127

Table 4. Logistic analysis between FEUA and baPWV or ABI. Abbreviations: FEUA= fractional excretion of uric acid; baPWV= brachial-ankle pulse wave velocity; ABI= ankle brachial index. BaPWV and ABI were divided into two groups: baPWV<1400cm/s or baPWV $\geq$ 1400cm/s; ABI $\leq$ 0.9 or ABI>0.9. Model1 unadjusted model. Model2 adjusted for age, smoke habits, alcohol consumption, history of hypertension, history of DM. Model3 based on model 2 and further adjusted for sex. Model4 adjusted for metabolic components including SBP, DBP, waist, glucose, TC, TG, LDL-C, HDL-C

Variables	OR (95% confidence interval)				p values	for trend
	Q1	Q2	Q3	Q4		
High baPWV (baPWV≥1400cm/s)						
Model 1	1.78 (1.32, 2.39)	1.56 (1.16,2.10)	1.68 (1.25, 2.26)	1(Reference)	<0.001	
Model 2	1.37 (1.00, 1.88)	1.34 (0.98, 1.84)	1.47 (1.07, 2.01)	1(Reference)	0.002	
Model 3	1.23 (0.89, 1.69)	1.22 (0.89, 1.68)	1.37 (1.00, 1.87)	1(Reference)	0.380	
Model 4	1.53 (1.07, 2.20)	1.50 (1.04, 2.15)	1.62 (1.13, 2.33)	1(Reference)	0.056	
Low ABI(ABI≤0.9)						
Model 1	6.98 (2.06, 23.61)	5.12 (1.48, 17.79)	2.69 (0.71, 10.17)	1(Reference)	<0.001	
Model 2	7.72 (2.27, 26.52)	5.36 (1.53, 18.74)	2.78 (0.73, 10.57)	1(Reference)	<0.001	
Model 3	8.56 (2.48, 29.60)	5.78 (1.65, 20.26)	3.00 (0.79, 11.44)	1(Reference)	<0.001	
Model 4	8.67 (2.50, 30.05)	5.95 (1.69, 21.03)	3.17 (0.82, 12.21)	1(Reference)	<0.001	

Fig. 2. Subgroup analysis of the relationship between FEUA and high baPWV or low ABI.

Subgroup analysis

Considering the profound effects of gender and MS on the excretion of UA, baPWV and ABI, we conducted further analysis by dividing participants into two groups separately according to gender and MS to assess the influence of gender and MS on the interrelationship between UA and baPWV or ABI. As shown in Fig. 2, the risk of lower ABI decreased as FEUA increased which was independent of gender. This was attenuated but remained significant after adjusting for confounders. However, the relationship between FEUA and high baPWV was greatly influenced by sex and lost significance in both gender during disaggregated analysis. While subdivided according to MetS status, this relationship between FEUA and high baPWV or low ABI was significant in MetS (-) participants but lost significance in MetS (+). Additionally, higher FEUA predicted lower risk of abnormal baPWV or ABI after excluding hypertensive patients (Fig. 2).

Fig. 3. The efficacies for FEUA and serum UA in the prediction of low ABI (a) and high baPWV (b).

The differences between FEUA and serum UA

To compare the efficacies of FEUA and UA in the prediction of high baPWV or low ABI, we further analysed the correlations between UA and baPWV or ABI. As shown in Table 3, serum uric acid was significantly associated with baPWV ($r=0.338$, $p<0.001$) and remained significant after adjusting for confounding factors. The weak but significant association of serum UA and ABI ($r=-0.117$, $p<0.001$) became non-significant after corresponding confounding factor adjustment. In the prediction of the prevalence of high baPWV, serum UA was more effective than FEUA (areas of ROC curves: 0.662 vs 0.553, $p<0.001$). Nevertheless, FEUA was more effective than serum UA in the prediction of lower ABI (areas of ROC curves: 0.664 vs 0.554, $p=0.027$) (Fig. 3 a, b).

Discussion

In the present study, we found that lower FEUA predicted a higher prevalence of high baPWV and low ABI. The association of FEUA and ABI was independent of related confounding factors. However, the association between FEUA and baPWV was greatly influenced by corresponding confounders, especially gender. The efficacy of FEUA in the prediction of low ABI was stronger than that of serum UA. However, serum UA was more powerful in the prediction of high baPWV. These results indicated that kidney function exerts an influence on the relationship between UA and baPWV and ABI, revealing the complex interactions among cardiovascular risk factors.

The relationship between UA and baPWV or ABI has been discussed for years, but the results have been inconsistent. In this study, we firstly assessed the correlation of UA and baPWV or ABI using FEUA to determine the influence of renal function. The balance of UA was largely dependent on the kidneys, through which two-thirds of UA is excreted [19]. However, elevated UA was independently associated with the progression of renal damage, which indicated a vicious cycle between renal function and elevated UA [20, 21]. The multi-ethnic study of atherosclerosis indicated that lower arterial elasticity predicted faster kidney function decline in subjects with $eGFR>60\text{ml}/(\text{min} \cdot 1.73\text{m}^2)$. In addition, renal function also declined as ABI decreased [22]. These results revealed the intimate correlations of renal function with various cardiovascular risk factors. Through the influence of renal function, there are some indirect effects of UA on baPWV and ABI. Thus, renal function could modify the correlation between UA and baPWV or ABI. In this study, we found that the association of UA and baPWV or ABI was greatly influenced by kidney function. For the reason that the extents of influence of renal function on baPWV and ABI are quite divergent, the relationships of baPWV and ABI with serum UA or FEUA are different. Elevated UA could contribute to arteriosclerosis of the renal afferent vessels and aggravate inflammation, endothelial dysfunction of kidney, resulting in salt-sensitive hypertension [23]. UA may also influence

skin microvascular function [24]. These effects exposed people to a higher susceptibility to arterial stiffness. In addition, elevated UA and arterial stiffness also contributed to insulin resistance [25, 26]. Insulin inhibited the excretion of UA and was inversely associated with FEUA. Thus, kidney could simultaneously influence the progression of arterial stiffness and UA elevation and may therefore enforce the relationship between UA and baPWV. Adjustment of renal function by using FEUA may mask some effects of the kidney. However, to a lesser extent, ABI was influenced by renal function. Oxidative stress was a major contributor of the pathogenesis of low ABI [27]. Though as a risk factor of CVD, UA could also act as an antioxidant and protect against oxidative damage [28]. Thus, accompanied with the decline of renal function, the detrimental effects and the antioxidative effect of UA are all enhanced. The enhancement of antioxidant effect may weaken the relationship between ABI and UA. Therefore, though the correlation of UA and baPWV or ABI still existed while using FEUA, baPWV was more intimately correlated with serum UA but the correlation with low ABI was stronger while using FEUA. In other words, renal function influences the strength of the correlation and the efficacy of assessment. The correlations of serum UA and other cardiovascular indices, to some extent, were also influenced by kidney function [29]. These results further strengthened the profound interaction of cardiovascular risk factors that synergetically promoted the progression of CVD.

Compelling studies revealed that the relationships between serum UA and arterial stiffness indices were different between genders, although their conclusions might not be consistent. Cristina et al. only found a positive link between serum UA and cfpWV in men [30]. But most studies supported that women were more vulnerable to the detrimental effects of UA. The morbidity and mortality of CVD or the decline of renal function attributed to elevated UA were all higher in female [31-33]. Gomez-Marcos et al. showed a positive result of the correlation between UA and cfpWV in women [29]. Asian studies also found a prominent correlation between UA and baPWV in female [34, 35]. A similar condition was found for the correlation of UA and ABI. A cross-sectional study among 6262 Chinese patients proposed that the association between UA and low ABI was stronger in women than in men and held significance after adjusting for eGFR only in women [12]. Given these facts, a gender-specific analysis was performed in the present study. The association between FEUA and low ABI was observed in men and women, with the association being stronger in women than in men. Our results were consistent with previous findings on this topic, which reported the effect size of UA and PAD association being stronger in women. Previous studies have found that women were exposed to a higher level of oxidative stress indicating by higher allantoin/UA ratio [36]. In addition, serum UA was more intimately associated with mean platelet volume and insulin resistance in women [37]. These might synergetically contribute to a poor clinical outcome in females. Whether there are some sex-dependent pathogenesis pathways of UA is far from clear and further experimental researches are warranted.

Several studies have proposed that the associations of UA with cardiovascular risk factors were influenced by MetS status [38]. Two cross-sectional studies from Japan found that the prevalence of carotid atherosclerosis and carotid plaque increasing with elevated UA quartile was prominent in subjects without MetS [39, 40]. A Chinese cohort also found that higher UA predicted higher prevalence of CVD in a MetS(-) group [41]. In line with those results, our study also found that the relationship between FEUA and baPWV or ABI was only significant in MetS (-) participants rather than MetS (+) participants. These might be attributed to the abnormal metabolism of UA in MS status. Under-excretion of UA partly contributed to high serum UA level in MS patients [9]. This fact further emphasized that kidney function modified the relationship of UA with other parameters. However, the generalization of this conclusion still needs further evidence for the limited number of individuals in the MetS(+) group in this study.

The mechanisms underlying the association of UA and baPWV or ABI are far from clear. Experimental studies found that elevated UA could promote the process of vascular inflammation by enhancing the expression of pro-inflammatory factors and oxidative stress

[42, 43]. UA could also contribute to endothelial dysfunction and dysregulate the proliferation of vascular smooth muscle cells and endothelial cells [43]. Furthermore, animal models indicated that mild hyperuricemia contributed to renal afferent arteriolar fibrosis and media membrane thickening independent of BP [44]. However, temporary administration of UA in healthy men did not exert obvious effects on haemodynamics and endothelium-dependent vasodilation [45]. Future studies concentrating on the long-term effects of UA may shed light on better explanations.

There are some limitations that should be addressed. The study participants were all restricted in middle-aged Chinese and the range of age was quite small. Thus, the results of this study might not represent the whole population. Moreover, due to the cross-sectional nature of the present study, little causal inference or information regarding mechanisms could be drawn from the results. Longitudinal studies and basic research on the mechanisms are urgently needed to figure out the innate relationship between UA and baPWV or ABI. Furthermore, the interactions among various cardiovascular risk factors are full of complexity, thus residual confounders may still potentially account for our results, though many confounders have been adjusted.

Conclusion

Lower FEUA confers an increased risk of high baPWV and low ABI. The correlation between UA and baPWV or ABI was influenced by kidney function. These results revealed the complex interactions among cardiovascular risk factors and may provide further evidence for drug-selection and dietary intervention for relevant patients.

Disclosure Statement

The authors declare that there is no Disclosure Statement.

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