Int J Clin Exp Med 2017;10(8):12250-12258
www.ijcem.com /ISSN:1940-5901/IJCEM0055363

Original Article

Association between serum uric acid and the characteristics of coronary plaque burden: assessment with coronary CT angiography

Ruiyi Tan[1], Chunyan Jiang[2], Hang Xiang[3], Nan Hong[1]

[1]Department of Radiology, Peking University People's Hospital, Beijing, China; [2]Orthopedics Institute of Chinese PLA, 89 Hospital, Weifang, Shandong Province, China; [3]Health Management of PLA General Hospital, Beijing, China

Received February 22, 2017; Accepted June 13, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: It is controversial whether serum uric acid (UA) is an independent risk factor for cardiovascular diseases (CVD). The aim of this study was to investigate the correlation between the serum UA level and coronary plaque burden characteristics evaluated by coronary CT angiography (CCTA). Methods: In total, 1315 patients who underwent CCTA were divided into the hyperuricemia group and normal serum UA group according to their serum UA level and stratified by gender. The low-attenuation plaque volume (LPV) and total plaque volume (TPV) were separately measured in each main coronary artery. The correlation of serum UA or hyperuricemia with coronary plaque burden was assessed using multivariate-adjusted linear regression analyses. Results: The TPV and LPV significantly differed between males and females ($P < 0.0001$ each). The TPV values in female with hyperuricemia group were higher than in subjects without hyperuricemia ($P = 0.0124$). The serum UA level significantly correlated with the TPV in both genders ($\beta = 0.4231$ and $P = 0.0441$ for males and $\beta = 0.4996$ and $P = 0.0149$ for females). However, the serum UA and LPV did not correlate with either gender after adjusting for multivariates. Conclusion: The serum UA level was significantly associated with the coronary TPV in both genders. However, the serum UA was not associated with the LPV. We found that the serum UA may play an independent role in the pathophysiology of total plaque burden.

Keywords: Uric acid, coronary plaque burden, coronary CT angiography, gender

Introduction

Serum UA is the end product of purine nucleotides metabolism, and several epidemiological studies investigated the use of the serum UA level as a risk factor for CVD, including metabolic syndrome, coronary artery disease (CAD), carotid atherosclerosis and thoracic aortic atherosclerosis [1-4]. With regard to the correlation between hyperuricemia and CVD, a meta-analysis of studies involving more than 400,000 patients has confirmed the independent association between hyperuricemia and the incidence and mortality due to CAD [5], suggesting that hyperuricemia is strongly associated with CVD, especially in women at high risk for CAD [6]. In contrast, recent studies showed that the serum UA level is not associated with coronary atherosclerosis and carotid atherosclerosis in either gender [7-9]. Based on these contrasting opinions, the association between the serum UA level and CVD remains controversial.

Several imaging methods are used to quantify coronary plaque volume, such as intravascular ultrasound (IVUS), CCTA and optical coherence tomography (OCT) [10-12]. Currently, CCTA is the preferred method because it is an accurate and non-invasive imaging tool for quantifying atherosclerosis plaque volume [13, 14]. CCTA can also acquire additional information with respect to plaque morphology, plaque composition, plaque remodelling and the severity of coronary atherosclerosis [15]. To the best of our knowledge, the relationship between the serum UA level and coronary plaque burden as assessed by CCTA has not yet been published. Thus, we aimed to assess this relationship in patients with or without a history of CAD.

Materials and methods

Study population

We conducted a retrospective observational study of 1597 Chinese patients underwent consecutive CCTA from April 2015 to December 2016 at our outpatient centre. 105 patients who had coronary artery bypass grafting or coronary stenting were excluded from the participants, 83 patients were excluded for poor image quality or interim coronary revascularization procedures, 50 patients with renal dysfunction (serum creatinine levels ≥ 100 μmol/L) were excluded, and 44 patients were also excluded for intake of diuretics or serum UA-lowering medications. Finally, 1315 patients were enrolled in the study. This study was approved by the local ethics committee, complied the Declaration of Helsinki, and informed consent was obtained from each participant.

Data collection and measurements

Information was obtained from medical records systems or telephone follow-up. Height and weight information was gathered from patients, and the body mass index (BMI) was calculated (in kg/m^2). The blood pressure was measured in a sitting position after the patient had been seated for at least 5 min, and hypertension was defined as the use of antihypertensive medications or a blood pressure higher than 140/90 mmHg. Patients with a history of smoking were classified as current smokers. A positive family history was defined as CAD in a parent or sibling noted under the age of 55 for men and 65 for women.

Laboratory evaluations were performed using venous blood samples, which were acquired after overnight fasting. The blood samples were analysed for biochemical markers the same day they were obtained. A Beckman Coulter AU 5800 Auto Analyser (Beckman Coulter Inc., Brea, CA, USA) was used to determine the levels of serum UA, creatinine, triglyceride, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, urea, Ca^{2+} and fasting serum glucose.

CCTA scanning protocols

All subjects were scanned using a 256-slice multi-detector CT scanner (Revolution CT, GE Healthcare, Milwaukee, USA). Controlling the heart rate was not necessary. All data were acquired prospectively from an electrocardiogram-triggered axial scan during one tube rotation and within one R-R interval, without moving the table. Revolution CT was used with collimation of 256×0.625 mm; the gantry rotation time was 0.28 s; the slice thickness and interval were both 0.625 mm, and the matrix was 512×512; a voltage of 80 or 100 kV was used, and a 100-kV tube potential was used for patients with a BMI > 30 kg/m^2, whereas 80 kV was used for patients with BMIs < 30 kg/m^2. The X-ray tube current was adjusted individually for each patient and ranged from 200 to 720 mA, depending on BMI. Approximately 50 mL of the undiluted iodine contrast agent Iopromide (370 mg I/mL) was injected via the antecubital vein at a flow rate of 5 mL/s, followed by an injection of 20 mL of saline at the same rate. Automatic bolus tracking was applied to trigger the acquisition. The region of interest (ROI) was located in the descending aorta at the level of tracheal bifurcation, and the scan was started after a delay of 6-s to allow the CT value in the ROI to reach an enhancement of 80 Hounsfield units (HU). CT scanning and contrast medium injection protocols were recorded at baseline. The standard reconstruction type was applied with a hybrid iterative reconstruction algorithm (adaptive statistical iterative reconstruction-Veo, ASIR-V, GE Healthcare) at 60% blending percentage [16].

Plaque assessment

All primary scan data were then conveyed to a computer workstation (Advantage Workstation Ver.4.6, GE Healthcare) for 3-dimensional image reconstruction, including volume rendering, curved multi-planar reformation and maximum intensity projection. Two skilled heart specialists who were blinded to the demographics and clinical materials analyzed the coronary vessels separately. Plaque detection and measurements were performed using the PlaqID function of the attenuation-based semi-automated software (PlaqID [CardIQ Xpress™ 2.0 Reveal, GE Medical Systems SCS, FRANCE]). First, the 3-dimensional coronary tree containing centrelines was obtained using an automatic tree extraction algorithm, and curved planar reformation images of the coronary arteries were created based on these centrelines. The coronary plaques were then identified on the curved planar reformation images and con-

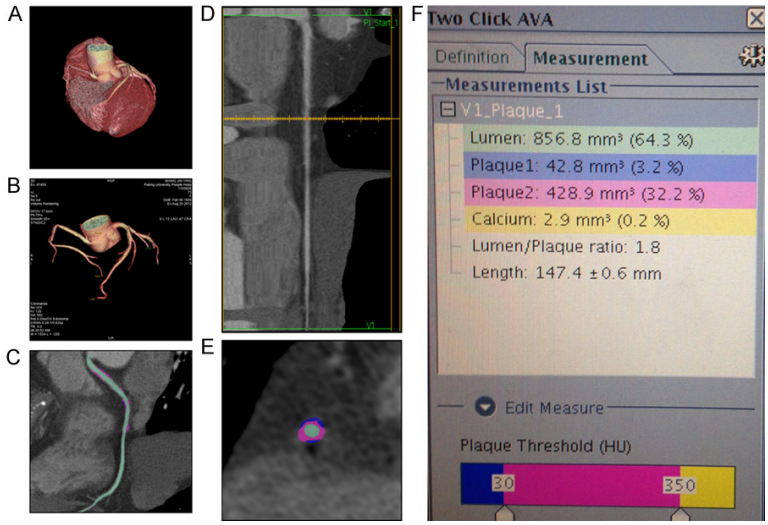

Figure 1. An example of a plaque measurement. A, B. The 3-dimensional heart and coronary tree were created. C. This plaque was identified on the curved planar reformation image and confirmed against a color-coded image map derived from the dedicated plaque analysis software. D. The manual adjustment was started and end of the plaque for the RCA. E. Color-coded cross-sectional image. F. Plaque burden measurement results. RCA: right coronary artery.

firmed against a color-coded image map derived from the dedicated plaque analysis software. For plaque measurement, we manually adjusted the plaque threshold slider to separate the HU values and stratify different plaque characteristics into low-attenuation plaque (< 30 HU), lumen (150 - 350 HU), and calcified plaque (> 350 HU) [17-19]. The coronary plaque characteristics were separately measured in each main coronary artery, including the right coronary artery (RCA), left main (LM), left anterior descending (LAD) and left circumflex (LCX) using plaque analysis software. The TPV and LPV were calculated using the four main coronary arteries. An example plaque measurement is shown in **Figure 1**. The inter-observer and intra-observer correlations for plaque quantification using this software have already been published elsewhere [20].

Statistical analysis

All analyses were carried out separately for males and females. Hyperuricemia was defined as a serum UA level > 357 μmol/L in females and > 420 μmol/L in males [21].

Continuous variables are presented as the mean ± standard deviation (SD), and categorical variables are presented as numbers and percentages. Student's t-test and the Chi-squared test were used for continuous and categorical variables, respectively, to compare baseline characteristics between different groups.

Univariate and multivariate stepwise linear regression models were used to determine the association between the serum UA levels or hyperuricemia and TPV or LPV. As a result, age, BMI, fasting serum glucose, HDL cholesterol, total cholesterol, triglyceride, creatinine, Ca^{2+}, hypertension and cigarette smoking were adjusted in the multivariate linear regression models.

A two-sided *P* value of less than 0.05 was considered to indicate a significant difference. The statistical analysis was conducted using the SAS statistical software (version 9.4, Cary, North Carolina, USA).

Results

Clinical characteristics

Males comprised 38.9% (n = 728) and females comprised 61.1% (n = 587) of the 1315 study participants (**Table 1**). The mean age (± SD) of the participants was 61.5 years (± 12.8) for males and 65.8 years (± 10.5) for females. The mean serum UA level (± SD) of the participants was 374.6 (± 81.2) for males and 323.6 (± 78.6) μmol/L for females, and this difference was significant (P < 0.0001). Similarly, the creatinine level (± SD) of the participants significantly differed by gender (P < 0.0001); it was 78.1 (± 21.7) for males and 63.4 (± 25.2) μmol/L for females. Moreover, the HDL cholesterol, total cholesterol, TPV, LPV, cigarette smoking, Ca^{2+} and LDL cholesterol also significantly differed by gender (P < 0.0001). However, the other baseline characteristics shown in **Table 1** did not differ between male and female participants.

Comparison of TPV and LPV according to gender and hyperuricemia

When comparing indicators for TPV and LPV, female subjects had lower TPV values than male subjects (513.3 ± 409.1 for females vs. 623.4 ± 466.0 for males, P < 0.0001) (**Figure 2A**). In addition, a significantly lower LPV value

Table 1. Baseline characteristics of the study participants

Variable	Males (n = 728)	Females (n = 587)	*P* value
Age (years)	61.4 ± 12.7	65.8 ± 10.4	< .0001
BMI (kg/m^2)	25.5 ± 3.1	25.3 ± 3.3	0.2216
Uric acid (μmol/L)	374.6 ± 81.2	323.6 ± 78.6	< .0001
Fasting serum glucose (mmol/L)	5.7 ± 2.3	5.6 ± 1.6	0.1292
LDL cholesterol (mmol/L)	2.5 ± 0.8	2.7 ± 1.0	0.0001
HDL cholesterol (mmol/L)	1.0 ± 0.3	1.1 ± 0.3	< .0001
Total cholesterol (mmol/L)	4.2 ± 0.9	4.6 ± 1.0	< .0001
Triglyceride (mmol/L)	1.8 ± 1.6	1.7 ± 1.0	0.0985
Creatinine (μmol/L)	78.1 ± 21.7	63.4 ± 25.2	< .0001
Urea (mmol/L)	6.1 ± 9.4	5.9 ± 12.1	0.6718
Ca^{2+} (mmol/L)	2.1 ± 0.1	2.2 ± 0.3	0.0061
TPV (mm^3)	623.4 ± 466.0	513.3 ± 409.1	< .0001
LPV (mm^3)	64.7 ± 58.1	38.0 ± 36.3	< .0001
Hypertension			0.2885
No	200 (28%)	146 (25%)	
Yes	527 (73%)	440 (75%)	
Cigarette smoking			< .0001
No	292 (40%)	551 (94%)	
Yes	436 (60%)	36 (6%)	
Family history of CAD			0.3550
No	633 (87%)	500 (85%)	
Yes	95 (13%)	87 (15%)	
Chest pain			0.4192
No	196 (40%)	155 (38%)	
Yes	292 (60%)	258 (63%)	

Data are expressed as the mean ± SD for continuous variables and n (%) for categorical variables. BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TPV: total plaque volume; LPV: low-attenuation plaque volume; CAD: coronary artery disease.

was observed in females than in males (38.0 ± 36.3 for females vs. 64.7 ± 58.1 for males, P < 0.0001) (**Figure 2B**).

Furthermore, 27.2% (n = 198) of males and 28.6% (n = 168) of females had hyperuricemia, as shown in Supplementary Table 1. At baseline, age, BMI, total cholesterol, triglyceride, creatinine and hypertension were significantly differed in males with hyperuricemia compared with males with normal serum UA levels. Similarly, age, BMI, fasting serum glucose, HDL cholesterol, triglyceride, creatinine, Ca^{2+}, hypertension and cigarette smoking significantly differed between women with hyperuricemia and women with normal serum UA levels.

The TPV values were higher in female subjects with hyperuricemia than in subjects without hyperuricemia (579.8 ± 438.7 vs. 486.0 ± 394.0, P = 0.0124) (**Figure 2C**). However, when comparing indicators for TPV and LPV, the TPV did not differ between the non-hyperuricemia and hyperuricemia groups in males (663.5 ± 471.2 vs. 608.4 ± 463.7, P = 0.1556), similarly, the LPV did not differ between the non-hyperuricemia and hyperuricemia groups in either males or females (64.9 ± 60.3 vs. 64.1 ± 51.9 for males and 36.7 ± 36.8 vs. 41.3 ± 35.1 for females, respectively) (**Figure 2D**).

Correlations between serum UA level and TPV or LPV

When comparing the serum UA level with LPV in a crude model, no significant association was found in either gender. Specifically, an increase in the serum UA level did not linearly correlate with the LPV in either gender after adjusting for multivariates (**Table 2**).

The linear regression between the serum UA level, a continuous variable, and the TPV is shown in **Table 2**. In the crude model, the serum UA level was significantly associated with TPV in males (β = 0.4779, P = 0.0246) and in females (β = 0.7558, P = 0.0004). In the multivariate-adjusted model, the serum UA level significantly correlated with the TPV in males (β = 0.4231, P = 0.0441) after adjusting for age, BMI, total cholesterol, triglyceride, creatinine and hypertension. After adjusting for age, BMI, fasting serum glucose, HDL cholesterol, triglyceride, creatinine, Ca^{2+}, hypertension and cigarette smoking, the serum UA level was also significantly associated with the TPV in females (β = 0.4996, P = 0.0149) (**Table 3**).

Discussion

In the present study, we aimed to assess the association between the serum UA level and

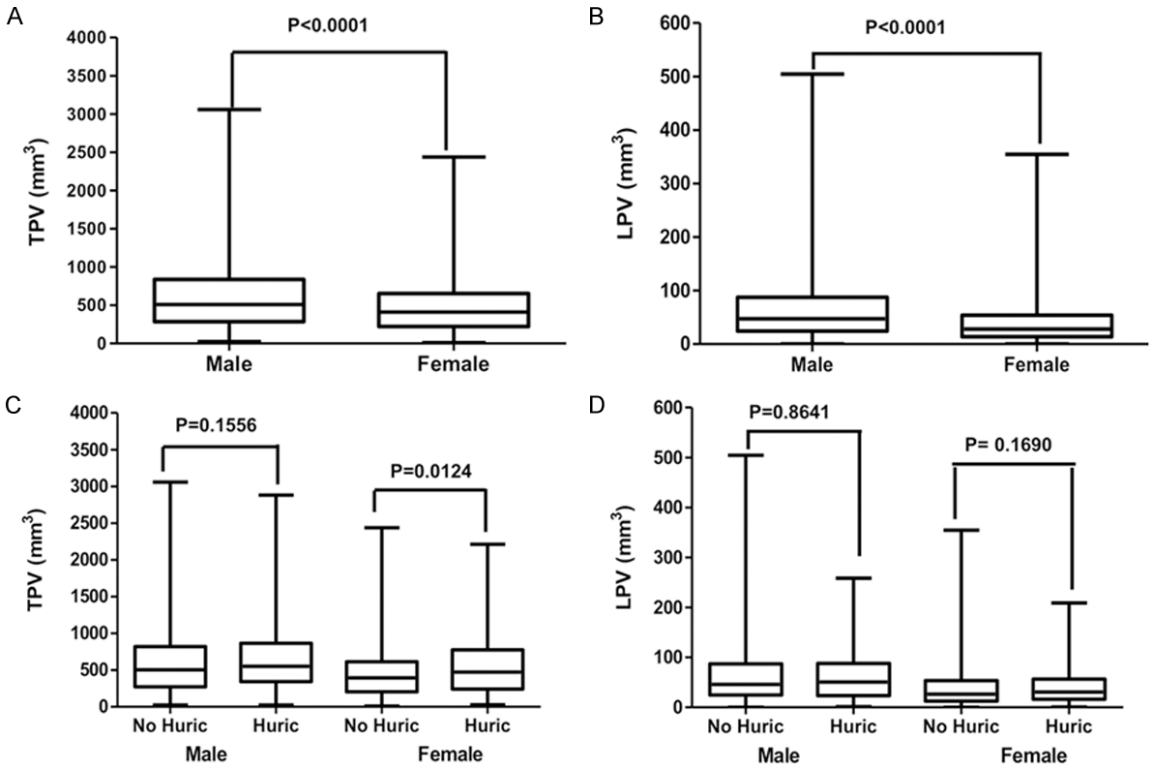

Figure 2. Comparison of TAV (mm^3) and LPV (mm^3) according to gender and the presence of hyperuricemia. Data are illustrated as the mean with minimum and maximum values. *P* values were calculated using Student's t-tests for continuous variables. TPV: total plaque volume; LPV: low-attenuation plaque volume.

Table 2. Linear regression coefficients[a] between hyperuricemia (μmol/L) and TPV (mm^3) and LPV (mm^3)

		Males		Females	
		TPV (mm^3) n = 728	LPV (mm^3) n = 728	TPV (mm^3) n = 587	LPV (mm^3) n = 587
Crude	β	0.4779	0.0292	0.7558	0.0254
	P value	0.0246	0.2715	0.0004	0.1839
	Model adjusted R^2	0.0056	0.0003	0.0194	0.0013
Multivariate-adjusted	β	0.4231	-0.0052	0.4996	0.0038
	P value	0.0441	0.8490	0.0149	0.8886
	Model adjusted R^2	0.0659	0.0664	0.1258	0.0908

[a]For males, adjusted for age, BMI, total cholesterol, triglyceride, creatinine, and hypertension; for females, adjusted for age, BMI, fasting serum glucose, HDL cholesterol, triglyceride, creatinine, Ca^{2+}, hypertension and cigarette smoking. TPV: total plaque volume; LPV: low-attenuation plaque volume.

the TPV or LPV characteristics detected by CCTA in a cohort of patients who had been admitted to our department for the evaluation of CAD. To the best of our knowledge, this paper is the first to describe a relationship between the serum UA levels and coronary plaque burden characteristics assessed by CCTA in patients. Specifically, this study found the following: 1) The serum UA level was significantly associated with the coronary TPV in both genders. 2) The serum UA level was not associated with the LPV in either gender. Therefore, these results support that the serum UA may serve as an independent risk factor to predict the pathophysiology of the total plaque burden.

Many studies have assessed the relationship between the serum UA level and CVD, but their results remain controversial. In the general population, the serum UA level is an indepen-

Table 3. Multivariate Linear regression coefficients of TPV (mm^3) separately for males and females

Variable	β	Partial R^2	*P* value
Males[a]			
Uric acid	0.4231	0.0054	0.0441
Age	6.9157	0.0259	< .0001
BMI	28.2271	0.0352	< .0001
Females[b]			
Uric acid	0.4996	0.0085	0.0149
Age	9.2866	0.0745	< .0001
Fasting serum glucose	44.6860	0.0316	< .0001
Hypertension	102.9846	0.0128	0.0068
Cigarette smoking	130.3869	0.0058	0.0488

[a]Variables not entered in the stepwise model for males: total cholesterol, triglyceride, creatinine and hypertension. [b]Variables not entered in the stepwise model for females: BMI, HDL cholesterol, triglyceride, creatinine and Ca^{2+}.

dent risk factor for hypertension, dyslipidaemia and metabolic syndrome [22, 23]. For example, Ndrepepa G et al. found that the serum UA level is an independent risk factor for CAD in both genders [24]. However, another study showed that the serum UA levels were not associated with the CVD, even when using xanthine oxidase inhibitors (XOIs) for hyperuricemia [25]. The carotid intima-media thickness (C-IMT) measured by ultrasonography is widely used as a substitutable indicator of carotid atherosclerosis and directly associated with the risk of CVD. Accordingly, the serum UA levels were directly associated with the C-IMT, independent of hypertension, and the serum UA levels were independently associated with the C-IMT [1, 2]. However, although the serum UA level was associated with cardiovascular risk factors in young adults, it was not demonstrated to be significantly associated with the C-IMT in the pathophysiology of preclinical atherosclerosis [8]. Similarly, J.S. Bae et al. found that the C-IMT was not linearly related to the serum UA levels in either gender [26]. Notably, the serum UA level differs by gender; it is higher in men than in women. However, few studies have addressed the association between the serum UA level and gender with regard to CVD. Nevertheless, several studies reported a significant association between the serum UA level and CAD only in women [27, 28].

IVUS is traditionally regarded as the gold-standard for quantifying atherosclerosis by measuring atheroma volume over time. Recently, the serum UA levels were reported to be associated with lipid-rich plaques volume, irrespective of gender [29]. In another current report, the prevalence of larger lipid-rich plaques directly correlated with the serum UA level in both genders, as assessed using IVUS [30]. However, IVUS requires is invasive and not suitable for all patients, especially non-ischemic patients with non-obstructive plaques. Thus, CCTA can be considered an effective alternative to invasive IVUS in serial studies to determine plaque burden. However, only a few studies have focused on the relationship between the serum UA level and the CCTA-derived plaque characteristics. For example, one study showed that the serum UA level was only significantly associated with calcified plaques [9]. However, calcified plaques do not represent the total plaque burden of coronary arteries, and non-calcified plaques (NCPs) are more strongly associated with acute coronary syndrome (ACS) than calcified plaques [18]. Furthermore, the low-attenuation plaque has been described as an indicator of high-risk plaques (HRPs), which are a reported risk factor for ACS [17, 19]. More recent studies of CCTA have described several "vulnerable" plaque features, most notably low-attenuation plaque which correlate with lipid-rich necrotic cores identified by IVUS [10, 31] and are independent predictors of future ACS [17]. In another cross-sectional study, elevated serum UA levels were independently associated with the prevalence of vulnerable carotid plaques in middle-aged adults [2]. Our study used CCTA to find that the serum UA level was significantly associated with the coronary TPV in both genders. However, the serum UA was not associated with LPV in either gender.

Several potential pathophysiological mechanisms may account for the significant association between the serum UA level and plaque burden. Specifically, serum UA is the final product of purine degradation, which is catalysed by xanthine oxidoreductase (XOR). Recently, XOR has also been shown to play an important role in the transformation of macrophages into foam cells and the development of atherosclerotic plaques [32]. Although serum UA has antioxidant capacities, significant paradoxical correlations have been reported between the

serum UA level and surrogate markers of atherosclerosis, such as inflammation, endothelial dysfunction and slow coronary artery flow [33-35]. Moreover, a recent study showed a relationship between the serum UA level and endothelial dysfunction in the coronary microvasculature only in women [36], which may explain the relationship between the serum UA level and CAD in women. Oestrogen has also been reported to promote the clearance of uric acid [37]. Specifically, the serum UA levels increase after menopause in females but remain lower than in males. Accordingly, the UA level was higher in postmenopausal women than premenopausal women [38]. Overall, our study suggests that the serum UA level is an independent risk factor to predict the pathophysiology of plaque burden in both genders.

Nevertheless, our study is subject to several limitations. First, it was performed at a single medical centre, and a large, multicentre, randomized controlled study of different nations is required to investigate the relationship between the serum UA level and coronary plaque volume. Second, we considered lipid-rich plaques to be vulnerable plaques, but we did not assess the relationship between the serum UA level and coronary plaque volume for intermediate density (30 - 150 HU) and calcified plaques (> 350 HU). Furthermore, the present guidelines for plaque volume measurement and progression evaluation do not recommend CCTA. Moreover, the semi-automated plaque assessment software may be associated with measurement error. Although the intra- and inter-observer reproducibility of plaque volume measurements were good, scan-rescan repeatability was not assessed in our study. Third, we did not identify a longitudinal relationship between the serum UA level and cardiovascular outcomes in a cross-sectional analysis. Therefore, prospective studies are needed to clarify the exact role of the serum UA level in the development of coronary atherosclerosis. Moreover, we did not analyse the potential effects of oestrogen, alcohol, and seafood on the relationship between the serum UA level and plaque burden. Finally, the difference in the radiation dose between CCTA and IVUS is one of the most important issues to be considered. Several dose-saving strategies, such as prospective electrocardiogram triggering, the electrocardiogram-controlled modulation of the tube current, and low kilo-voltage, have significantly reduced radiation doses.

Conclusion

The serum UA level was significantly associated with the coronary TPV in both genders, but it was not associated with the LPV in either gender. We found that the serum UA plays an independent role in the pathophysiology of the total plaque burden, and we suggest controlling the serum UA level as a meaningful strategy in the management of coronary plaque burden.

Acknowledgements

Ruiyi Tan performed most of the research. Nan Hong conceived the study and participated in the design, in the interpretation of results. All authors participated in the study conception and design and participated in the acquisition of data, and analysis and interpretation of data. All authors read and approved the manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Nan Hong, Department of Radiology, Peking University People's Hospital, 11 Xizhimen South Street, Xicheng District, Beijing 100044, China. Tel: +86-10-88325181; Fax: +86-10-88325180; E-mail: hongnan@bjmu.edu.cn

References

[1] Tavil Y, Kaya MG, Oktar SO, Sen N, Okyay K, Yazici HU and Cengel A. Uric acid level and its association with carotid intima-media thickness in patients with hypertension. Atherosclerosis 2008; 197: 159-163.

[2] Li Q, Zhou Y, Dong K, Wang A, Yang X, Zhang C, Zhu Y, Wu S and Zhao X. The association between serum uric acid levels and the prevalence of vulnerable atherosclerotic carotid plaque: a cross-sectional study. Sci Rep 2015; 5: 10003.

[3] Gur M, Sahin DY, Elbasan Z, Kalkan GY, Yildiz A, Kaya Z, Ozaltun B and Cayli M. Uric acid and high sensitive C-reactive protein are associated with subclinical thoracic aortic atherosclerosis. J Cardiol 2013; 61: 144-148.

[4] Harrington J, Pena AS, Gent R, Hirte C and Couper J. Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus. J Pediatr 2010; 156: 237-241.

[5] Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF and Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010; 62: 170-180.
[6] Baker JF, Krishnan E, Chen L and Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med 2005; 118: 816-826.
[7] Kocaman SA, Sahinarslan A, Cemri M, Timurkaynak T, Boyaci B and Cengel A. Independent relationship of serum uric acid levels with leukocytes and coronary atherosclerotic burden. Nutr Metab Cardiovasc Dis 2009; 19: 729-735.
[8] Oikonen M, Wendelin-Saarenhovi M, Lyytikainen LP, Siitonen N, Loo BM, Jula A, Seppala I, Saarikoski L, Lehtimaki T, Hutri-Kahonen N, Juonala M, Kahonen M, Huupponen R, Viikari JS and Raitakari OT. Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. Atherosclerosis 2012; 223: 497-503.
[9] Kaya EB, Yorgun H, Canpolat U, Hazirolan T, Sunman H, Ulgen A, Ates AH, Aytemir K, Tokgozoglu L, Kabakci G, Akata D and Oto A. Serum uric acid levels predict the severity and morphology of coronary atherosclerosis detected by multidetector computed tomography. Atherosclerosis 2010; 213: 178-183.
[10] Marwan M, Taher MA, El Meniawy K, Awadallah H, Pflederer T, Schuhback A, Ropers D, Daniel WG and Achenbach S. In vivo CT detection of lipid-rich coronary artery atherosclerotic plaques using quantitative histogram analysis: a head to head comparison with IVUS. Atherosclerosis 2011; 215: 110-115.
[11] Yonetsu T, Bouma BE, Kato K, Fujimoto JG and Jang IK. Optical coherence tomography- 15 years in cardiology. Circ J 2013; 77: 1933-1940.
[12] Tian J, Dauerman H, Toma C, Samady H, Itoh T, Kuramitsu S, Domei T, Jia H, Vergallo R, Soeda T, Hu S, Minami Y, Lee H, Yu B and Jang IK. Prevalence and characteristics of TCFA and degree of coronary artery stenosis: an OCT, IVUS, and angiographic study. J Am Coll Cardiol 2014; 64: 672-680.
[13] Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G and Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the society of cardiovascular computed tomography guidelines committee. J Cardiovasc comput Tomogr 2014; 8: 342-358.
[14] Fischer C, Hulten E, Belur P, Smith R, Voros S and Villines TC. Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. J Cardiovasc Comput Tomogr 2013; 7: 256-266.
[15] Kristensen TS, Kofoed KF, Kuhl JT, Nielsen WB, Nielsen MB and Kelbaek H. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. J Am Coll Cardiol 2011; 58: 502-509.
[16] Lim K, Kwon H, Cho J, Oh J, Yoon S, Kang M, Ha D, Lee J and Kang E. Initial phantom study comparing image quality in computed tomography using adaptive statistical iterative reconstruction and new adaptive statistical iterative reconstruction v. J Comput Assist Tomogr 2015; 39: 443-448.
[17] Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y and Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009; 54: 49-57.
[18] Arbab-Zadeh A and Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. J Am Coll Cardiol 2015; 65: 846-855.
[19] Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, Harigaya H, Kan S, Anno H, Takahashi H, Naruse H, Ishii J, Hecht H, Shaw LJ, Ozaki Y and Narula J. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015; 66: 337-346.
[20] Hamirani YS, Zeb I, Pagali SR, Kadakia J, Saraff G, Choi T, Ahmadi N, Isma'eel H and Budoff MJ. Normalization of automatic plaque quantification in cardiac computed tomography (CCT). Int J Cardiol 2011; 146: 282-290.
[21] Fang J and Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National health and nutrition examination survey. JAMA 2000; 283: 2404-2410.
[22] Alderman MH, Cohen H, Madhavan S and Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension 1999; 34: 144-150.
[23] Li LX, Dong XH, Li MF, Zhang R, Li TT, Shen J, Shen J, Bao YQ and Jia WP. Serum uric acid levels are associated with hypertension and metabolic syndrome but not atherosclerosis in Chinese inpatients with type 2 diabetes. J Hypertens 2015; 33: 482-490.
[24] Ndrepepa G, Braun S, King L, Fusaro M, Tada T, Cassese S, Hadamitzky M, Haase HU, Schomig A and Kastrati A. Uric acid and prognosis in

angiography-proven coronary artery disease. Eur J Clin Invest 2013; 43: 256-266.
[25] Kim SC, Schneeweiss S, Choudhry N, Liu J, Glynn RJ and Solomon DH. Effects of xanthine oxidase inhibitors on cardiovascular disease in patients with gout: a cohort study. Am J Med 2015; 128: 653, e657-653, e616.
[26] Bae JS, Shin DH, Park PS, Choi BY, Kim MK, Shin MH, Lee YH, Chun BY and Kim SK. The impact of serum uric acid level on arterial stiffness and carotid atherosclerosis: the Korean multi-rural communities cohort study. Atherosclerosis 2013; 231: 145-151.
[27] Kawabe M, Sato A, Hoshi T, Sakai S, Hiraya D, Watabe H, Kakefuda Y, Ishibashi M, Abe D, Takeyasu N and Aonuma K. Gender differences in the association between serum uric acid and prognosis in patients with acute coronary syndrome. J Cardiol 2016; 67: 170-176.
[28] Sun Y, Yu X, Zhi Y, Geng S, Li H, Liu T, Xu K, Chen L, Wu C and Qi G. A cross-sectional analysis of the relationship between uric acid and coronary atherosclerosis in patients with suspected coronary artery disease in China. BMC Cardiovasc Disord 2014; 14: 101.
[29] Saito Y, Nakayama T, Sugimoto K, Fujimoto Y and Kobayashi Y. Relation of lipid content of coronary plaque to level of serum uric acid. Am J Cardiol 2015; 116: 1346-1350.
[30] Ando K, Takahashi H, Watanabe T, Daidoji H, Otaki Y, Nishiyama S, Arimoto T, Shishido T, Miyashita T, Miyamoto T and Kubota I. Impact of serum uric acid levels on coronary plaque stability evaluated using integrated backscatter intravascular ultrasound in patients with coronary artery disease. J Atheroscler Thromb 2016; 23: 932-939.
[31] Voros S, Rinehart S, Qian Z, Vazquez G, Anderson H, Murrieta L, Wilmer C, Carlson H, Taylor K, Ballard W, Karmpaliotis D, Kalynych A and Brown C 3rd. Prospective validation of standardized, 3-dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (assessment of tissue characteristics, lesion morphology, and hemodynamics by angiography with fractional flow reserve, intravascular ultrasound and virtual histology, and noninvasive computed tomography in atherosclerotic plaques) I study. JACC Cardiovasc Interv 2011; 4: 198-208.
[32] Kushiyama A, Okubo H, Sakoda H, Kikuchi T, Fujishiro M, Sato H, Kushiyama S, Iwashita M, Nishimura F, Fukushima T, Nakatsu Y, Kamata H, Kawazu S, Higashi Y, Kurihara H and Asano T. Xanthine oxidoreductase is involved in macrophage foam cell formation and atherosclerosis development. Arterioscler Thromb Vasc Biol 2012; 32: 291-298.
[33] Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U and Ferrucci L. Uric acid and inflammatory markers. Eur Heart J 2006; 27: 1174-1181.
[34] Nieto FJ, Iribarren C, Gross MD, Comstock GW and Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000; 148: 131-139.
[35] Gagliardi AC, Miname MH and Santos RD. Uric acid: a marker of increased cardiovascular risk. Atherosclerosis 2009; 202: 11-17.
[36] Kuwahata S, Hamasaki S, Ishida S, Kataoka T, Yoshikawa A, Orihara K, Ogawa M, Oketani N, Saihara K, Okui H, Shinsato T, Kubozono T, Ichiki H, Fujita S, Takumi T, Yoshino S, Nakazaki M, Miyata M and Tei C. Effect of uric acid on coronary microvascular endothelial function in women: association with eGFR and ADMA. J Atheroscler Thromb 2010; 17: 259-269.
[37] Adamopoulos D, Vlassopoulos C, Seitanides B, Contoyiannis P and Vassilopoulos P. The relationship of sex steroids to uric acid levels in plasma and urine. Acta Endocrinol (Copenh) 1977; 85: 198-208.
[38] Feig DI, Kang DH and Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008; 359: 1811-1821.

Supplementary Table 1. Baseline characteristics of the study participants with and without hyperuricemia

Characteristics	Males (n = 728)			Females (n = 587)		
	No Huric (n = 530)	Huric (n = 198)	*P* value[a]	No Huric (n = 419)	Huric (n = 168)	*P* value[a]
Age (years)	62.2 ± 61.2	59.4 ± 57.6	0.0064	65.2 ± 10.4	67.4 ± 10.4	0.0192
BMI (kg/m^2)	25.2 ± 3.0	26.3 ± 3.2	<.0001	25.1 ± 3.2	25.9 ± 3.4	0.0135
Uric acid (μmol/L)	337.0 ± 54.3	475.3 ± 49.0	<.0001	284.7 ± 43.0	420.5 ± 61.5	<.0001
Fasting serum glucose (mmol/L)	5.8 ± 2.5	5.7 ± 2.0	0.6010	5.5 ± 1.5	5.8 ± 1.7	0.0346
LDL cholesterol (mmol/L)	2.5 ± 0.8	2.5 ± 0.8	0.7722	2.7 ± 1.0	2.6 ± 0.9	0.2957
HDL cholesterol (mmol/L)	1.0 ± 0.3	1.0 ± 0.3	0.1401	1.2 ± 0.4	1.0 ± 0.2	0.0004
Total cholesterol (mmol/L)	4.2 ± 0.9	4.3 ± 1.0	0.0199	4.6 ± 1.0	4.5 ± 1.1	0.3667
Triglyceride (mmol/L)	1.6 ± 1.5	2.2 ± 1.7	<.0001	1.6 ± 1.0	1.9 ± 1.0	0.0013
Creatinine (μmol/L)	75.0 ± 13.3	86.2 ± 34.2	<.0001	61.1 ± 22.3	69.1 ± 30.6	0.0005
Urea (mmol/L)	6.1 ± 10.9	6.1 ± 2.9	0.9940	5.9 ± 14.2	5.9 ± 3.0	0.9397
Ca^{2+} (mmol/L)	2.2 ± 0.1	2.2 ± 0.1	0.0701	2.2 ± 0.2	2.3 ± 0.5	0.0493
TPV (mm^3)	608.4 ± 463.7	663.5 ± 471.2	0.1556	486.6 ± 394.0	579.8 ± 438.7	0.0124
LPV (mm^3)	64.9 ± 60.3	64.1 ± 51.9	0.8641	36.7 ± 36.8	41.3 ± 35.1	0.1690
Hypertension			0.0364			<.0001
No	157 (30%)	43 (22%)		123 (29%)	23 (14%)	
Yes	373 (70%)	154 (78%)		295 (71%)	145 (86%)	
Cigarette smoking			0.1526			0.0054
No	221 (42%)	71 (36%)		386 (92%)	165 (98%)	
Yes	309 (58%)	127 (64%)		33 (8%)	3 (2%)	
Family history of CAD			0.3034			0.9794
No	465 (88%)	168 (85%)		357 (85%)	143 (85%)	
Yes	65 (12%)	30 (15%)		62 (15%)	25 (15%)	
Chest pain			0.7066			0.9268
No	144 (41%)	52 (39%)		110 (38%)	45 (37%)	
Yes	210 (59%)	82 (61%)		182 (62%)	76 (63%)	

Data are expressed as the mean ± SD for continuous variables and n (%) for categorical variables. [a]Calculated using Student's t-test for continuous variables and the Chi-squared test for categorical variables. BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TPV: total plaque volume; LPV: low-attenuation plaque volume; CAD: coronary artery disease.