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Cross-sectional and longitudinal associations between serum uric acid and endothelial function in subjects with treated hypertension☆

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ABSTRACT

Objectives: The endothelial dysfunction-arterial stiffness-atherosclerosis continuum plays an important pathophysiological role in hypertension. The aim of this study was to investigate the cross-sectional association between serum uric acid (SUA) and vascular markers related to this continuum, and to assess the longitudinal association between SUA and endothelial function that represents the initial step of the continuum.
Methods: We evaluated the baseline associations between SUA levels and vascular markers that included flow-mediated vasodilatation (FMD), brachial-ankle pulse wave velocity (baPWV), and common carotid artery intima-media thickness (CCA-IMT) in 648 subjects receiving antihypertensive treatment. The longitudinal association between baseline SUA levels and FMD measured at 1.5 and 3 yr of follow-up was also investigated.
Results: At baseline, modest, but significant correlations were observed between SUA and FMD in females ($r = -0.171$), baPWV in males with SUA >368.78 μmol/L ($r = -0.122$) and in females with a SUA level ≤ 362.83 μmol/L ($r = 0.217$), mean CCA-IMT in females with a SUA level ≤ 333.09 μmol/L ($r = 0.139$), and max CCA-IMT in females with SUA level ≤ 333.09 μmol/L ($r = 0.138$). A longitudinal association between SUA and FMD was less observed in males. In females, the baseline SUA was associated significantly with FMD values at 1.5 yr ($r = -0.211$), and SUA levels >237.92 μmol/L were associated significantly and independently with FMD values at 3 yr ($r = -0.166$).
Conclusions: Lower SUA levels were associated with better vascular markers of the continuum, especially in females. Furthermore, we observed a longitudinal association between SUA and endothelial function, suggesting SUA level may be a potential marker of the continuum in hypertension.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Vascular endothelial dysfunction is the initial step in the development of atherosclerosis and plays a pivotal role in systemic organ damage involving the vessels, heart, and kidney, subsequently leading to a worsening in prognosis [1–4]. During the development of atherosclerosis, endothelial dysfunction also plays a pathogenic role in the progression of arterial stiffness and carotid intima-media thickness (IMT) [5, 6]. Recently, Tomiyama et al. [7] proposed that a triad continuum consisting of endothelial dysfunction, arterial stiffness, and atherosclerosis may play an important role in the progression of atherosclerotic vascular damages in patients with hypertension, and suggested that these vascular functional parameters may be critical markers of the continuous steps of atherosclerosis. Accordingly, it is clinically important to assess these three factors that affect the continuum.

Serum uric acid (SUA) level is considered to be a major determinant of cardiometabolic disorders, including hypertension [8, 9]. Several studies have also shown that elevated levels of SUA are associated with endothelial dysfunction [10–13], arterial stiffness [14, 15], and carotid atherosclerosis [16, 17], all of which are independent predictors of morbidity and mortality. In addition, an increasing body of evidence has demonstrated that elevated SUA levels in patients with hypertension are associated with an increased risk of cardiovascular disease (CVD) and are therefore considered as a residual risk of CVD [8, 18–20]. On the other hand, some studies demonstrated that the relationship between SUA levels and CVD showed a J/U-shaped trend, although the precise mechanism of this relationship remains unclear [8, 21]. It is not fully understood whether or not lower levels of SUA are clinically beneficial on the atherosclerotic continuum. However, to date there is limited information on the cross-sectional and longitudinal associations between SUA levels and the continuum. The current study therefore had the aim of evaluate the relationships between SUA levels and the continuum, and to examine whether there were protective thresholds of SUA levels on physiological and morphological vascular markers of the continuum. The study also assessed the longitudinal effect of SUA levels on endothelial function in patients with hypertension.

2. Methods

2.1. Study design

This sub-study was performed using the data from the B-arm of the FMD-J multicenter prospective observational study, which has the aim of establishing the usefulness of flow-mediated vasodilatation (FMD) in Japanese patients with hypertension receiving primary prevention (UMIN000012951). The detailed protocol of the study has been published previously [22, 23]. Briefly, after assessment of eligibility and obtaining informed consent, blood samples were collected and vascular tests, including FMD, carotid IMT, and brachial-ankle pulse wave velocity (baPWV) were measured. After completion of all the tests and web-based registration, the tests were followed-up at 1.5 and 3 yr. The sub-study first evaluated the cross-sectional relationships between SUA levels and physiological and morphological vascular tests at baseline. Second, we analyzed the longitudinal association between baseline SUA levels and FMD values at 1.5 and 3 yr. The study protocol conformed to the principles of the Declaration of Helsinki and was approved by the local institutional review boards and independent ethics committees at each institution. Written informed consent was obtained from all of the study participants before participation in the study.

2.2. Subjects

Patients with hypertension were eligible for the study if they met the following criteria: 1) aged 20–75 yr, 2) had been receiving medical follow-up for at least 6 months, and 3) had well-controlled blood pressure (BP) levels with treatment (i.e., BP <150/90 mm Hg). The exclusion criteria were as follows: 1) history of coronary artery disease, stroke, and aortic disease, 2) severe valvular heart disease, 3) severe arrhythmia, 4) left ventricular systolic dysfunction, 5) malignancy, 6) receiving steroids, nonsteroidal anti-inflammatory drugs, or immunosuppressants, 7) serum creatinine level > 221 μmol/L, and 8) serious liver dysfunction. A total of 966 patients were enrolled from June 2010 to October 2015 at 17 institutions in Japan.

2.3. Measurement of FMD

A detailed protocol for measurement of FMD has been published previously [7, 22, 23]. Briefly, FMD measurements were performed according to the appropriate physical condition of the patients in an appropriate testing room. A commercially available ultrasound instrument equipped with an online computer-assisted semiautomatic analysis software was used to measure FMD (EF, Unex Co. Ltd., Nagoya). Baseline longitudinal images of the right brachial artery were recorded and then for 3 min after cuff deflation following supra-systolic compression of the right forearm for 5 min (50 mm Hg over systolic BP). The diastolic diameter of the artery was measured semi-automatically and changes in the diameter tracked automatically to calculate the FMD value. The FMD assessment was conducted at each participant institution in a blinded manner.

2.4. Measurement of brachial-ankle PWV and carotid IMT

See Online supplement.

2.5. Laboratory data

Blood samples for laboratory measurement of total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), plasma glucose, creatinine, and SUA level were obtained from the subjects in the fasting state on the day of the baseline, 1.5 and 3 yr FMD measurements. Non-HDL-C was determined as total cholesterol minus HDL-C. The estimated glomerular filtration rate (eGFR) was calculated using the equation for Japanese people [24].

2.6. Statistical analysis

The results were presented as mean ± SD or n (%). Differences in the baseline clinical characteristics between males and females were examined using the *t*-test for continuous variables and the chi-square test for categorical variables. Continuous variables were compared using analysis of variance for quartile groups. The relationship between SUA levels and vascular tests was determined by Pearson's correlation coefficient analysis, while inflection points were assessed by the SPLINE model approach [25]. A linear regression model was constructed to identify factors associated with endothelial dysfunction. A generalized linear mixed effect model was used to test longitudinal changes in the clinical variables. $P < 0.05$ was considered to be statistically significant. All the analyses were carried out using Software environment for statistical computing R version 3.4.3.

3. Results

3.1. Baseline patients' characteristics

The baseline characteristics of the 966 patients are summarized in Table S1. Mean and maximum IMT of the common carotid artery (mean/max CCA-IMT) was not measured in 15.9% of patients in the primary analysis, while <16% of patients who did not have all three variables measured and/or had unclear FMD images were excluded from the analyses (Fig. S1). A total of 648 patients (males 387, females 261) were included in the primary baseline analysis (Table 1 and Table S2). No patient had a history of CVD.

The mean values of triglyceride were higher and total cholesterol and HDL-C lower in males compared to those in females. The mean values of SUA level in overall were 342.62 ± 82.41 μmol/L (5.76 ± 1.39 mg/dL) [males 372.40 ± 76.84 μmol/L (6.26 ± 1.29 mg/dL), females 298.47 ± 69.72 μmol/L (5.02 ± 1.17 mg/dL), $P < 0.001$]. When stratified into quartiles of SUA, lower levels were associated with lower body mass index, diastolic BP and glucose, higher eGFR, and better lipid profiles (Table S3). However, when divided further according to gender, a sex-related difference in the association between SUA levels and some variables was observed (Tables S4 and S5).

3.2. Relationships between SUA and vascular markers at baseline

As shown in Table 1, mean FMD values were lower in males than in females (4.52 ± 2.61% vs. 5.35 ± 3.05%, $P < 0.001$). There was a modest, but significant correlation between FMD and SUA levels in overall and females, but not in males (Fig. S2). A significant relationship between SUA level and baPWV was found only in females ($r = 0.137$, $P = 0.026$), whereas no significant linear trend was found for the association between categorized SUA levels and mean/max CCA-IMT.

The SPLINE model (Fig. 1) showed that the optimal SUA level in the overall that identified an inflection value that changed the slope to a statistically significant reverse association between FMD and SUA level was <327.14 μmol/L (5.5 mg/dL). In males, an inflection value of SUA level of 458.00 μmol/L (7.7 mg/dL) was also observed, while no significant

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