Hyperuricemia is significantly associated with increased vascular stiffness in asymptomatic healthy Korean women

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Hyperuricemia is significantly associated with increased vascular stiffness in asymptomatic healthy Korean women

Directed by Professor Hyeong Cheon Park

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Abstract

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Purpose: Increased serum uric acid is a known risk factor for cardiovascular disease. Brachial–ankle pulse wave velocity (baPWV) is a simple index of arterial stiffness, while the coronary artery calcium score (CACS) derived from multidetector computed tomography is a good marker of coronary atherosclerosis. Patients with coronary artery stenosis have significantly elevated baPWV values. Therefore, we investigated the relationship between serum uric acid level and baPWV in asymptomatic subjects, taking into account confounding factors, including CACS.

Materials and Methods: Of 4894 patients who underwent baPWV measurement and coronary computed tomography angiography as part of a general health examination at Gangnam Severance Hospital from July 2006 through September 2013, 2720 healthy subjects were enrolled in this evaluation after exclusion of confounding factors. Serum uric acid level was divided into quartiles for men and women separately: men, Q1: 1.9–5.2, Q2: 5.21–5.9, Q3: 5.91–6.7, Q4: 6.71–12.1

mg/dL; women, Q1: 2.0–3.8, Q2: 3.81–4.3, Q3: 4.31–4.9, Q4: 4.91–8.7 mg/dL. High baPWV was defined as ≥1400 cm/s.

Results: The mean concentration of serum uric acid was found to be significantly lower in women than in men (4.37±0.91 vs. 5.94±1.15 mg/dL, $p<0.001$). Serum uric acid was significantly elevated in subjects with a high baPWV. After adjustment for age, systolic blood pressure, body mass index, estimated glomerular filtration rate, fasting blood sugar, high- and low-density lipoprotein cholesterol, smoking habits and CACS, serum uric acid was found to be related with high baPWV in women (OR=1.266, 95% CI 1.060–1.512; $p=0.009$). In multivariate logistic regression analysis, Q4 of serum uric acid was independently associated with high baPWV in women (OR=1.71, 95% CI 1.089–2.697; $p<0.05$). After adjustment for traditional cardiovascular risk factors and other confounding factors including CACS, serum uric acid was independently associated with baPWV in women by multiple linear regression analysis (β=10.167, 95% CI 0.654–19.680; $p=0.036$). Subgroup analyses showed that, in Korean women of median postmenopausal age (>50 years), the highest quartile of serum uric acid was associated with high baPWV, after adjustments for other risk factors (OR compared with lowest quartile=1.806, 95% CI=1.065–3.063; $p=0.028$).

Conclusion: Serum uric acid is associated with aggravation of arterial stiffness in healthy Korean women, but not in men.

Key words: arterial stiffness, brachial–ankle pulse wave velocity, serum uric acid, sex

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I. INTRODUCTION

Elevated serum uric acid levels are a common finding in patients with hypertension, metabolic syndrome, and renal disease.[1,2] Studies in populations of patients at high risk for cardiovascular disease (CVD) have shown an association between high serum uric acid levels and CVD.[3] Furthermore, some studies have shown that, even in healthy populations, high serum uric acid levels were significantly associated with increased arterial stiffness.[4] Interestingly, a sex-dependent association has been suggested between higher serum uric acid level and the risk of adverse cardiovascular (CV) events in healthy subjects.[5]

Arterial stiffness is an independent risk factor for CV events. Measurement of brachial–ankle pulse wave velocity (baPWV) is a noninvasive and simple method for determining arterial stiffness.[6] Several studies have shown that baPWV is associated with CVD and is an independent predictor of CV morbidity and mortality.[7,8]

The coronary artery calcium score (CACS) is a good marker of coronary atherosclerosis and CV events, and several hospitals in Korea include multidetector computed tomography (MDCT) screening for cardiac disease in general health evaluation programs. Taking this into account, together with the fact that baPWV values are significantly higher in patients with coronary artery disease than in those without, we performed a general health examination including baPWV and MDCT.[8]

Although some studies have demonstrated a relationship between serum uric acid level and arterial stiffness, they did not exclude confounding factors, such as hypertension, diabetes mellitus, chronic kidney disease, gout, coronary artery disease, and medications.[9-11] Therefore, our study aimed to determine the relationship between serum uric acid level and baPWV in healthy subjects, taking into account the confounding factors, including CACS.

II. MATERIALS AND METHODS

1. Study population

This was a cross-sectional retrospective single-center study. We consecutively collected data for 4894 patients who underwent baPWV and coronary computed tomography angiography as part of a general health examination at Gangnam Severance Hospital, South Korea, from July 2006 through September 2013. The Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, approved the study protocol (IRB no. 3-2015-0128).

2. Measurement of clinical variables and confounding variables

We reviewed the patients' medical records, including history of hypertension, diabetes mellitus, and smoking status. Height, body weight, and blood pressure were measured during hospital visits. Blood samples were obtained on the day of the MDCT scan, after a fasting period of at least 12 h, and the following laboratory parameters were determined: hemoglobin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, uric acid, fasting blood sugar, cholesterol, triglyceride, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol. Kidney function was determined based on estimated glomerular filtration rate (eGFR), which was calculated using the formula developed and validated in the Modification of Diet in Renal Disease (MDRD) study[12] as follows: eGFR = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ (× 0.742, if female).

Urine protein was determined by the result of a single urine dipstick semiquantitative analysis as absent, trace, 1+, 2+, 3+, or 4+. Results recorded as absent or trace were defined as the absence of proteinuria. Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of height (square meters). Smoking habit was classified as current smoker or non-smoker; non-smokers included patients who had never smoked and ex-smokers.

3. PWV measurement

The baPWV was measured using a volume plethysmography device (VP-1000; form PWV/ABI, Colin Co., Komaki, Japan) after subjects had rested for at least 5 min. This automated device records the phonocardiogram, electrocardiogram, volume pulse form, and arterial blood pressure at the left and right brachial arteries and ankles. The baPWV was calculated using time-phase analysis between the right brachial artery pressure and the volume waveform at both ankles. The distance between the brachium and the ankle was calculated automatically according to the subject's height. After measurement of the right and left baPWV, we used the mean baPWV as a marker of arterial stiffness. The validity, reliability, and reproducibility of this equipment were demonstrated according to previous study methods.[13] High baPWV was defined as a value ≥1400 cm/s.[7]

4. Multi-detector computed tomography (MDCT)

Subjects were scanned with a cardiac MDCT system (Philips Brilliance 64; Philips Medical Systems, Best, The Netherlands) with a 3 mm slice thickness and 1.5 mm reconstruction interval. With the patient in the supine position, cardiac MDCT was performed in the craniocaudal direction within a single breath-hold at end-inspiratory suspension. Patients with an initial heart rate >66 beats/min before cardiac MDCT examination received a β-blocker (25 mg atenolol; Tenormin, Hyundai, Seoul, Korea) unless β-adrenergic blocking agents were contraindicated. Iodinated contrast agent

(Optiray 350; Tyco Healthcare, Kantata, Canada), at a dose of 2.0 mL/kg not exceeding a total of 100 mL, was administered using a two-phase injection protocol for the arterial and delayed phases of the CT images. Quantitative calcium scores were calculated according to the method previously described by Agatston et al.[14]

5. Exclusion criteria

Our study only included participants between the ages of 20 and 80 years. To eliminate the influence of confounding variables, subjects with a history of hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, or gout, and those taking medications such as allopurinol, febuxostat, colchicine, probenecid, and benzbromarone were excluded. In addition, subjects were excluded if they had evidence of chronic kidney disease (CKD). The definition of CKD was based on the presence of kidney damage (dipstick proteinuria of 1+, 2+, 3+, or 4+), decreased kidney function (eGFR<60 mL/min/1.73 m^2), or diffuse renal disease on abdominal ultrasound. Furthermore, subjects with systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, CACS ≥100, or glycosylated hemoglobin (HbA1c) ≥6.5% were excluded. Finally, 2720 subjects (1477 men, 1243 women) were included in this study (Figure 1).

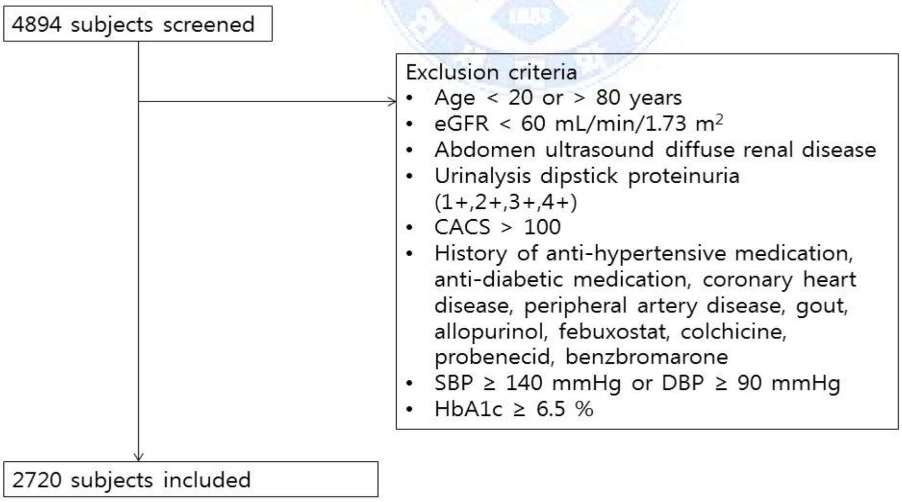

Figure 1. Study design

6. Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 20; Chicago, IL, USA). The data are expressed as mean±standard deviation (SD) for continuous variables or as percentages for categorical variables. Differences between continuous variables were analyzed using the independent *t*-test and the chi-squared test was used to compare categorical variables. Univariate logistic regression analyses were used to derive relationships between high baPWV and clinical variables. To identify independent factors predicting high baPWV, we used multivariate logistic regression analysis to determine odds ratios (OR) and 95% confidence intervals (CI). Serum uric acid levels were divided into sex-specific quartiles. The mean baPWV of each quartile was analyzed using ANCOVA (analysis of covariance), taking confounding factors into account. A single linear regression analysis was also performed to determine the relationship between changes in baPWV and clinical values. Multivariate linear regression analysis was performed using serum uric acid level as independent risk factor with baPWV as dependent factor. A p-value <0.05 was considered statistically significant.

III. RESULTS

The average age of the study population was 50.7±8.9 years (men, 50.4±8.7 years; women, 50.9±9.1 years) and 54.3% of the participants were male. The mean concentration of serum uric acid was 5.2±1.3 mg/dL and was found to be significantly lower in women (4.37±0.91 mg/dL) than in men (5.94±1.15 mg/dL, $p<0.001$). Table 1 shows a comparison of baseline clinical characteristics between subjects divided according to sex. Apart from age, all the other parameters—proportion of current smokers, SBP, DBP, BMI, eGFR, hemoglobin, BUN, creatinine, fasting plasma glucose, serum uric acid, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, CACS, and mean baPWV differed between men and women. Given the difference in their mean serum uric acid concentrations, we performed the rest of the analysis separately for men and women.

Table 1. Clinical characteristics of study population by gender

Clinical variables	Total		
	Men (n=1477)	Women (n=1243)	*p* value
Age (years)	50.36 ± 8.70	50.99 ± 9.13	0.066
Smoking n (%)	289 (19.6)	34 (2.7)	<0.001
SBP (mmHg)	121.15 ± 10.39	115.48 ± 12.20	<0.001
DBP (mmHg)	76.58 ± 7.05	71.62 ± 8.29	<0.001
BMI (kg/m²)	24.30 ± 2.74	22.01 ± 2.68	<0.001
eGFR (ml/min/1.73m²)	92.51 ± 21.24	98.02 ± 28.45	<0.001
Hemoglobin (g/dL)	15.18 ± 1.05	13.03 ± 1.06	<0.001
Blood urea nitrogen (mg/dL)	14.05 ± 3.17	13.20 ± 3.36	<0.001
Creatinine (mg/dL)	0.96 ± 0.16	0.72 ±0.15	<0.001
Fasting plasma glucose (mg/dL)	95.86 ± 13.47	89.60 ± 10.36	<0.001
Uric acid (mg/dL)	5.94 ±1.15	4.37 ± 0.91	<0.001
Total cholesterol (mg/dL)	192.41 ± 34.17	197.14 ± 34.63	<0.001
Triglyceride (mg/dL)	131.35 ± 79.96	85.61 ± 43.01	<0.001
HDL-cholesterol (mg/dL)	46.39 ± 10.86	56.79 ± 12.82	<0.001
LDL-cholesterol(mg/dL)	120.18 ± 32.16	123.13 ± 32.61	0.018
CACS	6.16 ± 17.42	4.15 ± 23.46	0.013
Mean baPWV (cm/s)	1333.6 ± 157.3	1301.0 ± 191.7	<0.001

Note : Data are means ± standard deviation and number (percentage) of subjects.

Abbrevations : SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; CACS, coronary artery calcium score; baPWV, brachial ankle pulse wave velocity

The percentage of subjects with high baPWV (≥1400 cm/s) was 26.6% (n=723). The clinical characteristics of men and women according to normal and high baPWV are shown in Table 2. There were significant differences in age, SBP, DBP, BMI, eGFR, and CACS between the normal and high baPWV groups for both sexes. However, fasting plasma glucose, uric acid, total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol differed significantly between subjects with normal baPWV and those with high baPWV only in women, but not in men.

Table 2. Comparison of clinical characteristics between normal baPWV subjects and high baPWV subjects by gender

Clinical variables	Men (n=1477)			Women (n= 1243)		
	baPWV<1400 (cm/s) (n=1053)	baPWV≥1400 (cm/s) (n=424)	*p* value	baPWV<1400 (cm/s) (n=944)	baPWV≥1400 (cm/s) (n=299)	*p* value
Age (years)	48.9 ± 8.2	54.1 ± 8.9	<0.001	48.9 ± 8.5	57.6 ± 7.9	<0.001
Smoking n (%)	186 (17.7)	103 (24.3)	<0.001	26 (2.8)	8 (2.7)	0.161
SBP (mmHg)	119.8 ± 10.6	124.6 ± 8.9	<0.001	113.0 ±11.8	123.2 ± 10.1	<0.001
DBP (mmHg)	75.5 ± 7.1	79.2 ± 6.3	<0.001	70.0 ± 8.1	76.6 ± 6.9	<0.001
BMI (kg/m^2)	24.5 ± 2.8	23.8 ± 2.5	<0.001	21.8 ± 2.6	22.6 ± 2.8	<0.001
eGFR (ml/min/1.73m^2)	93.3 ± 21.7	90.4 ± 19.8	0.017	99.2 ± 28.3	94.3 ± 28.8	0.010
Fasting plasma glucose (mg/dL)	95.5 ± 12.5	96.7 ± 15.6	0.149	88.6 ± 9.7	92.8 ± 11.7	<0.001
Uric acid (mg/dL)	6.0 ± 1.1	5.9 ± 1.2	0.157	4.3 ± 0.9	4.6 ± 1.0	<0.001
Total cholesterol (mg/dL)	192.5 ± 33.8	192.3 ± 35.2	0.940	194.9 ± 33.5	204.2 ± 37.2	<0.001
Triglyceride (mg/dL)	132.0 ± 83.2	130.0 ± 71.4	0.637	81.5 ± 39.3	98.6 ± 51.2	<0.001
HDL-cholesterol (mg/dL)	46.2 ± 10.6	47.0 ± 11.5	0.167	57.7 ± 12.7	53.9 ± 12.7	<0.001
LDL-cholesterol (mg/dL)	120.5 ± 31.5	119.3 ± 33.7	0.508	120.6 ± 31.2	130.9 ± 35.5	<0.001
Mean PWV (cm/s)	1259.0±89.6	1519.0±134.7	<0.001	1219.6±111.0	1557.8±164.1	<0.001
CACS	5.1 ± 15.3	8.9 ± 21.5	<0.001	1.9 ± 14.2	11.3 ± 40.0	<0.001

Note : Data are means ± standard deviation and number (percentage) of subjects.

Abbrevations : SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; CACS, coronary artery calcium score; baPWV, brachial ankle pulse wave velocity

Table 3 shows the univariate logistic regression related to the risk of high baPWV. In women, age, SBP, DBP, BMI, eGFR, fasting blood sugar, uric acid, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, and CACS correlated significantly with high baPWV by univariate logistic analysis. An increase of 1 mg/dL in uric acid level was associated with a significant increase in the risk of high baPWV (OR=1.473, 95% CI 1.28–1.70; p <0.001). After adjusting for age, SBP, BMI, eGFR, fasting blood sugar, HDL-cholesterol, LDL-cholesterol, smoking habits and CACS, serum uric acid was positively associated with high baPWV in women (OR=1.266, 95% CI 1.060–1.512; p=0.009). However, in men, whereas age, smoking, SBP, DBP, BMI, eGFR, and CACS correlated significantly with high baPWV, serum uric acid level was not independently associated with high baPWV (p=0.157).

Table 3. Univariate logistic regression analysis with beweteen clinical variables and high baPWV

Clinical variables	Men		Women	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.078 (1.062-1.078)	<0.001	1.144 (1.121-1.168)	<0.001
Smoking	1.496 (1.139-1.965)	0.004	0.942 (0.435-2.167)	0.971
SBP	1.049 (1.037-1.062)	<0.001	1.083 (1.069-1.097)	<0.001
DBP	1.085 (1.065-1.105)	<0.001	1.120 (1.098-1.142)	<0.001
BMI	0.912 (0.873-0.952)	<0.001	1.109 (1.057-1.163)	<0.001
eGFR	0.993 (0.987-0.999)	0.017	0.994 (0.989-0.998)	0.011
FBS	1.007 (0.998-1.015)	0.114	1.039 (1.026-1.053)	<0.001
Uric acid	0.932 (0.845-1.028)	0.157	1.473 (1.276-1.700)	<0.001
Total cholesterol	1.000 (0.997-1.003)	0.940	1.008 (1.004-1.011)	<0.001
Triglyceride	1.000 (0.998-1.001)	0.637	1.01 (1.005-1.011)	<0.001
HDL-cholesterol	1.007 (0.997-1.018)	0.167	0.979 (0.965-0.987)	<0.001
LDL-cholesterol	0.999 (0.995-1.002)	0.508	1.010 (1.006-1.014)	<0.001
CACS	1.012 (1.006-1.018)	<0.001	1.018 (1.010-1.026)	<0.001

Abbrevations : SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; CACS, coronary artery calcium score

Serum uric acid levels were divided into sex-specific quartiles as follows: in men, Q1: 1.9–5.2, Q2: 5.21–5.9, Q3: 5.91–6.7, Q4: 6.71–12.1 mg/dL; in women, Q1: 2.0–3.8, Q2: 3.81–4.3, Q3: 4.31–4.9, Q4:4.91–8.7 mg/dL. Figure 2 shows a comparison of mean baPWV level among participants in each quartile of serum uric acid value according to sex. The baPWV in women in the highest quartile of uric acid (Q4) level was significantly higher compared to those in the lowest quartile (Q1), whereas no such significant association was seen in men (Figure 2).

The odds ratios for high baPWV were 1.497 (Q3) and 2.33 (Q4) in women (Table 4). The results of multivariate adjusted logistic regression analysis are summarized in Table 5. After adjusting for age, SBP, BMI, eGFR, fasting blood sugar, HDL-cholesterol, LDL-cholesterol, smoking habits, and CACS, compared with the lowest quartile of uric acid level, only the highest quartile in women was associated with a higher risk of high baPWV (OR=1.714, 95% CI 1.089-2.697; *p*=0.020), whereas in men, serum uric acid level was not independently associated with high baPWV (*p*=1.087).

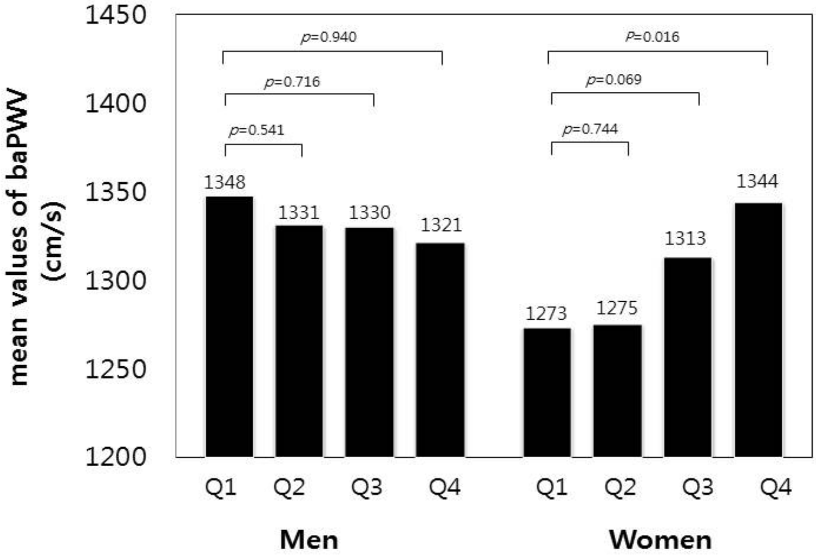

Figure 2. Mean values of baPWV according to the serum uric acid quartile by gender.
Comparison of baPWV among subject with serum uric acid quartiles by gender, based on ANCOVA with adjustment for age, SBP, DBP, FBS, BMI, LDL-cholesterol and HDL-cholesterol

Men, Q1: 1.9-5.2, Q2: 5.21-5.9, Q3: 5.91-6.7, Q4: 6.71-12.1 mg/dL
Women, Q1: 2.0-3.8, Q2: 3.81-4.3, Q3: 4.31-4.9, Q4: 4.91-8.7 mg/dL

Table 4. Univariate logistic regression analysis between different quartiles of uric acid and high baPWV

Uric acid quartiles	Men (n=1477)		Women (n=1243)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Q2 vs. Q1	0.862 (0.629-1.182)	0.358	1.221 (0.820-1.818)	0.326
Q3 vs. Q1	0.929 (0.684-1.261)	0.635	1.497 (1.037-2.160)	0.031
Q4 vs. Q1	0.830 (0.599-1.151)	0.264	2.330 (1.615-3.362)	<0.001

Men; Q1: 1.9-5.2, Q2: 5.21-5.9, Q3: 5.91-6.7, Q4: 6.71-12.1 mg/dL Women; Q1: 2.0-3.8, Q2: 3.81-4.3, Q3: 4.31-4.9, Q4:4.91-8.7 mg/dL

Table 5. Multivariate logistic regression analysis between different quartiles of uric acid and high baPWV

Uric acid quartiles	Men (n=1477)		Women (n=1243)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Q2 vs. Q1	0.947 (0.671, 1.338)	0.947	1.285 (0.801-2.061)	0.298
Q3 vs. Q1	1.181 (0.840, 1.660)	1.181	1.265 (0.817-1.961)	0.292
Q4 vs. Q1	1.087 (0.753, 1.570)	1.087	1.714 (1.089-2.697)	0.020

Adjusted for age, SBP, BMI, eGFR, FBS, HDL-cholesterol, LDL-cholesterol, current smoker, CACS.

Men; Q1: 1.9-5.2, Q2: 5.21-5.9, Q3: 5.91-6.7, Q4: 6.71-12.1 mg/dL Women; Q1: 2.0-3.8, Q2: 3.81-4.3, Q3: 4.31-4.9, Q4:4.91-8.7 mg/dL

Table 6. Univariate linear regression analysis between baPWV and clinical variables

Variable	Men (n=1477)		Women (n=1243)	
	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Age	6.435 (5.571, 7.298)	<0.001	11.146 (10.156, 12.136)	<0.001
SBP	3.848 (3.100, 4.596)	<0.001	6.953 (6.169, 7.738)	<0.001
DBP	6.453 (5.362, 7.545)	<0.001	9.652 (8.482, 10.823)	<0.001
BMI	-7.245 (-10.152, -4.339)	<0.001	12.775 (8.857, 16.693)	<0.001
Somking	19.057 (-1.162, 39.277)	0.065	-52.115 (-117.460, 13.230)	0.118
eGFR	-0.715 (-1.091, -0.338)	<0.001	-0.688 (-1.061, -0.315)	<0.001
FBS	0.758 (0.162, -1.353)	0.013	4.635 (3.638, 5.633)	<0.001
Uric acid	-6.593 (-13.555,0.370)	0.063	31.149 (19.508,42.790)	<0.001
Total cholesterol	0.055 (-0.180, 0.290)	0.647	0.948 (0.644, 1.251)	<0.001
Triglyceride	-0.016 (-0.116, 0.085)	0.762	0.902 (0.659, 1.145)	<0.001
HDL-cholesterol	0.644 (-0.095, 1.384)	0.088	-2.030 (-2.856, -1.204)	<0.001
LDL-cholesterol	-0.038 (-0.289, 0.212)	0.765	1.123 (0.801, 1.445)	<0.001
CACS	1.244 (0.787, 1.701)	<0.001	1.963 (1.522, 2.405)	<0.001

Abbrevations : SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; CACS, coronary artery calcium score

Table 6 shows the coefficients of correlation in linear regression analysis between baPWV and other clinical variables in both men and women. This analysis showed that age, blood pressure, smoking habit, eGFR, fasting blood sugar, and CACS were related to baPWV in men. In women, blood pressure and parameters reflecting either atherosclerotic risk factors or metabolic disorder, with the exception of smoking habits, correlated with baPWV. Multiple linear regression analysis showed that, after adjustment for age, SBP, BMI, smoking, eGFR, fasting blood sugar, HDL-cholesterol, LDL-cholesterol, CACS, and serum uric acid were independently associated with baPWV only in women (Table 7).

Table 7. Multiple linear regression analysis between baPWV and clinical variables

Variable	Men (n=1477)		Women (n=1243)	
	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Age	5.736 (4.861, 6.611)	<0.001	8.297 (7.281, 9.313)	<0.001
SBP	4.525 (3.814, 5.235)	<0.001	5.259 (1.519, 5.999)	<0.001
BMI	-9.684 (-12.523, -6.845)	<0.001	-7.125 (-10.630,-3.619)	<0.001
Smoking	13.047 (-0.080, 26.715)	0.051	-22.143 (-62.749, 18.464)	0.285
eGFR	-0.641 (-0.979, -0.303)	<0.001	-0.501 (-0.793, -0.209)	0.001
FBS	0.295 (-0.248, 0.839)	0.286	1.291 (0.444, 2.138)	0.003
Uric acid	1.946 (-4.455, 8.347)	0.551	10.167 (0.654,19.680)	0.036
HDL-cholesterol	0.164 (-0.516, 0.845)	0.636	-0.700 (-1.368, -0.032)	0.040
LDL-cholesterol	-0.065 (-0.290, 0.160	0.571	0.171 (-0.659, 1.376)	0.208
CACS	0.394 (-0.032, 0.820)	0.070	1.018 (0.659, 1.376)	<0.001

Abbrevations : SBP, systolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; CACS, coronary artery calcium score

Male: R^2=0.229, adjusted R^2=0.224, p<0.001; female: R^2=0.415, adjusted R^2=0.411, p<0.001

Since the median age of Korean women at menopause is 50 years,[15] we divided the women into those less or older than 50 years of age. Fifty-eight point four percent of women were older than 50 (n=726). In women aged >50 years, compared with the lowest quartile of serum uric acid, the highest quartile was associated with high baPWV after adjustment for other risk factors (OR=1.806, 95% CI=1.065–3.063; *p*=0.028). However, for women aged below 50 years the quartiles of serum uric acid level were not related to high baPWV (Table 8).

Table 8. Multivariate logistic regression analysis between different quartiles of uric acid and high baPWV in women by post-menopausal age

Uric acid quartiles	Age < 50 (n=517)		Age ≥ 50 (n=726)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Q2 vs. Q1	1.548 (0.635-3.772)	0.336	1.179 (0.669-2.076)	0.569
Q3 vs. Q1	0.912 (0.358-2.320)	0.846	1.465 (0.877-2.447)	0.145
Q4 vs. Q1	1.943 (0.763-4.951)	0.164	1.806 (1.065-3.063)	0.028

Adjusted for age, SBP, BMI, eGFR, FBS, HDL-cholesterol, LDL-cholesterol, current smoker, CACS.

Women; Q1: 2.0-3.8, Q2: 3.81-4.3, Q3: 4.31-4.9, Q4:4.91-8.7 mg/dL

IV. DISCUSSION

Our study found that increased serum uric acid is associated with high baPWV in healthy Korean women. Multivariate logistic analysis showed that the risk of high baPWV in the highest quartile of uric acid was significantly greater compared to the lowest quartile (OR=1.71, 95% CI 1.809–2.697; p=0.020). Further, after adjusting for confounding factors, serum uric acid level was linearly and significantly related with baPWV in women, but not in men (β=10.167, 95% CI 0.654–19.680; p=0.036).

Several studies have found a relationship between uric acid level and baPWV in healthy subjects. Chen et al.[10] showed that uric acid was positively associated with aortic stiffness and pressure in Chinese men, but their study failed to exclude confounding factors and included subjects with hypertension or diabetes mellitus, as well as those taking medication. Shin et al.[16] reported a significant relationship between uric acid level and arterial stiffness in men, but this relationship was not found in women. They explained that this sex-related difference in results was due to the relatively small number of women enrolled (n=234). Rather, their results are weak and faulty. Fang et al.[5] demonstrated that a high-normal serum uric acid level or greater is related with increased arterial stiffness in healthy women, after adjustment for confounding variables, whereas the relationship between higher uric acid and increased arterial stiffness was not significant in men. Barbieri et al.[17] showed that high uric acid levels are associated with severe coronary artery disease only in women. Their findings were similar to ours, and this sex-linked difference was also found in other studies, such as the Chicago Heart Association Detection Project,[18] NHANES I,[19] post hoc analysis of the LIFE trials,[20] and SHHEC study.[21] The SHHEC study demonstrated that uric acid level was more strongly associated with mortality in women than in men.[21] Along similar lines, a higher internal carotid artery resistive index[22] and an increased risk of silent brain infarction[23] have been reported in women, but not in men. The fact that this association between serum uric acid level and cardiovascular risk factors is closer in women than in men may be related to estrogen effects in women. Although elevated serum uric acid in men frequently begins at puberty, hyperuricemia is usually delayed until after menopause in women. Estrogen in premenopausal women increases renal clearance of uric acid because of inhibition of renal proximal tubular urate reabsorption by organic anion transporters.[24] Thus, women are more susceptible to serum uric acid-associated vascular injury than are men. Further, in cases of elevated serum uric acid, the disease course contributing to the uric acid elevation is more serious in women than in men. However, the precise mechanism of this association remains to be elucidated.

Several possible mechanisms have been proposed via which uric acid could affect arterial stiffness. First, serum uric acid may promote vascular smooth muscle proliferation, cause oxidation of LDL,[25] upregulate the expression of platelet-derived growth factor,[26] and stimulate the inflammatory pathways.[27,28] In addition, uric acid may exacerbate the progression of arterial stiffness by production of reactive oxygen species via the xanthine oxidase pathway.[29] Another possible reason is that hyperuricemia may cause endothelial dysfunction by impairing the generation of nitric oxide in vascular endothelial cells.[30]

Although we could not evaluate the menopause status in each individual, we knew that the median Korean menopausal age is 50 years.[15] In women over the age of 50, compared with the lowest quartile of serum uric acid, the highest quartile was associated with high baPWV, after adjustments for other risk factors (OR=1.806, 95% CI=1.065–3.063; p=0.028). As previous studies demonstrated,[31-33] our results suggest that menopause status is an important factor influencing arterial stiffness in healthy female subjects. Furthermore, Park et al.[32] demonstrated that serum uric acid is independently associated with vascular stiffness in Korean postmenopausal women. Yu et al.[33] reported that hyperuricemia was associated with left ventricular hypertrophy only in postmenopausal women in the general population, but not in premenopausal women. One previous study observed that the incidence of CVD in women increased with age, especially in postmenopausal women.[34] Our data are consistent with those of the previous studies,[32-34] as we found that serum uric acid was an essential independent factor related with arterial stiffness in postmenopausal women. There is a lesser rise in uric acid in postmenopausal women treated with hormone replacement therapy and some studies demonstrated that estrogen has beneficial effects on arterial stiffness.[35,36] Regarding the mechanism of hyperuricemia in postmenopausal women, it has been suggested that endogenous estradiol could play a specific protective role against CVD, resulting in the weak relationship between hyperuricemia and high baPWV in premenopausal women. Endogenous ovarian hormones, such as estradiol, exert an antioxidant effect on atherosclerosis, but this effect of estrogen disappears after menopause.[37] Further investigation is required to establish a possible mechanism for this phenomenon.

It is well known that baPWV increases with age,[31,38] hypertension,[39] diabetes,[40] and CKD.[41-43] Therefore, we excluded these confounding factors that cause increased baPWV. We adopted a study design that controlled for renal function, past medical history (hypertension, diabetes), and medications (uric acid-lowering agents). In addition, the assessment of renal abnormalities was based on the detection of proteinuria, the MDRD equation, and ultrasound renal imaging findings. Since proteinuria is an early and sensitive marker of kidney damage, we used proteinuria detected by dipstick urinalysis as a marker of kidney damage. We paid careful attention to the definition of healthy subjects by excluding those with proteinuria of 1+ or more on dipstick urine analysis.

In this study, the CACS was measured in all subjects using cardiac MDCT. It has been shown that patients with significant coronary artery stenosis have significantly high baPWV.[44] It has been proposed that a CACS of over 100 indicates the presence of atherosclerosis,[45] so we excluded subjects with CACS>100. In our study, baPWV showed a graded increase according to the CACS value in both sexes. Therefore, we considered CACS as a confounding factor. After adjustment for traditional confounding factors as well as for CACS, serum uric acid was independently associated with arterial stiffness.

We defined high baPWV as a level ≥1400 cm/s. As our study was focused on healthy subjects, a baPWV≥1400 cm/s was taken as an indicator of increased arterial stiffness.[7] This cutoff value corresponds to a moderate Framingham risk score and represents the threshold at which the risk for incident hypertension also increases in normotensive individuals. In addition, this value is considered a moderate-risk threshold at which lifestyle modification is recommended.

In our study, age and increased blood pressure were independently associated with increased arterial stiffness, and these results are compatible with former assessments.[9,16,31] Our study showed that hyperglycemia was associated with a higher risk of high baPWV in women, but not in men, and this result is consistent with previous findings of a greater association between insulin resistance and arterial stiffness in women than men.[35,46] Previous studies[32,47,48] demonstrated that the insulin resistance index and homeostatic model assessment of insulin resistance (HOMA-IR) was correlated with serum uric acid level.

Our results showed that current smoking was significantly associated with increased arterial stiffness in men, but not in women. This lack of association between smoking habits and increased arterial stiffness in women might have been due to the small number of women categorized as smokers (n=34).

There is no universally accepted definition of hyperuricemia. Nevertheless, the reference range of serum uric acid is based on its variation among healthy individuals: frank hyperuricemia is defined as >6 mg/dL in women and >7 mg/dL in men.[49] The relationship between uric acid and CVD is observed not only with definite hyperuricemia, but also with a high-normal serum uric acid level range (>5.2 to 5.5 mg/dL) in healthy individuals.[5,16,32] In our study, according to the odds ratio linking serum uric acid with high baPWV, arterial stiffness may be occurring above the fourth quartile (4.91–8.7 mg/dL) group in women. In women, serum uric acid above the threshold of 4.91 mg/dL belongs to the normal range for this substance. However, Akkineni et al.[50] recently reported that treatment of asymptomatic hyperuricemia with allopurinol prevented vascular events in adults. Their study model predicts that treating asymptomatic hyperuricemia with allopurinol is most effective in preventing vascular events at a serum uric acid level above 7.0 mg/dL in men and 5.0 mg/dL in women. Therefore, the cutoff range of serum uric acid used in our study was reasonable.

This study had several limitations. First, as it was cross-sectional we could not demonstrate a causal relationship between serum uric acid level and increased arterial stiffness. Second, we cannot exclude the possibility that our findings were influenced by dietary intake of uric acid supplements and an insufficient history of medications. Certain dietary habits,[51] meat or seafood intake, and alcohol consumption are associated with a higher prevalence of hyperuricemia.[52] In addition, our database did not include information on the patients' history of diuretic or statin use. Third, proteinuria was evaluated with the dipstick method in this study. This method can only semiquantify the degree of proteinuria and cannot detect microalbuminuria. However, this process has been used widely in general health examination screening, and its usability and reliability have been verified.[53] Fourth, we used baPWV instead of carotid–femoral PWV (cfPWV). The prognostic value of baPWV is lower than that of cfPWV. However, recent studies have shown that baPWV is associated with both central and peripheral PWVs,[54] and is useful as a surrogate marker for various cardiovascular risk factors, as well as for cfPWV.[6,13,55,56] In addition, as previously stated, baPWV is easy to measure and is suitable for routine clinical use in healthy subjects. Finally, the study subjects were confined to the Korean population and any extrapolation of our results to the general population should be viewed with caution.

V. CONCLUSION

We found that serum uric acid is associated with increased arterial stiffness in healthy Korean women, but not men. The related mechanisms and possible causal effect of serum uric acid on arterial stiffness warrant further research.

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ABSTRACT (IN KOREAN)

무증상의 한국 여성에서 고요산혈증이 혈관 경직도에 미치는 영향

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최아란

최근 건강검진 목적으로 일반 혈액생화학 검사뿐 아니라 비 침습적인 방법인 상완 발목 맥파 속도를 이용한 혈관 경직도, 관상동맥 혈관촬영 CT를 이용한 관상 동맥 석회화가 포함되기도 한다. 혈청 요산과 심혈관계질환에 대해서는 많은 논문에서 그 연관성에 대해 입증하고 있으며 최근 일부 연구에는 무증상의 환자에서도 그 연관성에 대하여 보고하고 있다. 본 논문은 무증상의 건강검진을 받은 성인을 대상으로 혈청 요산 수치와 혈관 경직도의 관련성에 대해 연구하고자 하였다. 발목 맥박 파 전파속도에 영향을 줄 수 있는 다양한 임상변수들과 관상동맥 석회화 수치가 높을수록 발목 맥박 파 전파속도도 높은 점을 감안하여 이를 혼란 변수로 포함시켰다. 요산 수치는 남성과 여성에서 통계학적으로 차이가 보여 남성과 여성으로 분리하였으며 요산수치를 각각 4사분위로 구분하였다. 다양한 인자를 보정한 이후에도 이분형 회귀분석 및 선형회귀 분석에서 혈청 요산 수치는 혈관 경직도와 의미 있는 상관관계를 가지고 있음을 확인하였다. 이러한 요산과 혈관 경직도의 관계는 여성에서 뚜렷하게 나타났지만 남성에서는 연관성이 없었다. 또한 한국 여성의 폐경기 나이 중앙값을 기준으로 하였을 때 폐경기 여성에서 요산

수치가 혈관 경직도에 통계학적으로 영향을 주는 것으로 나타났다. 본 연구는 무증상의 여성 건강 검진 환자에서 혈청 요산이 혈관 경직도와 연관성이 있다는 것을 보고 하였다.

핵심 되는 말: 동맥 경직, 맥박 파 전파 속도, 요산, 성별