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Association between serum uric acid and arterial stiffness in a low-risk, middle-aged, large Korean population

A cross-sectional study

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Abstract

We investigated the association between serum uric acid (SUA) and brachial ankle pulse wave velocity (baPWV) in an apparently healthy population. We performed a cross-sectional study on middle-aged Koreans who completed a yearly health-screening program between January and December 2014. Subjects with coronary artery disease, diabetes, or hypertension were excluded. Linear regression analyses were used to study the relationship between SUA and baPWV. Multiple adjustments were made for variables based on clinical or statistical significance. Of 66,917 study participants (38,170 men and 28,747 women), the mean age was 39.4 ± 6.7 years and the average SUA level was 5.23 ± 1.4 mg/dL. SUA values were higher in men than in women (6.1 ± 1.2 mg/dL vs. 4.1 ± 0.8 mg/dL). SUA was linearly associated with baPWV in women and in men ($P < .001$, respectively). Multiple regression analyses remained significant for women with a positive association with baPWV across SUA quintiles in a dose–response manner ($P < .001$) while no longer for men with a J-shaped association between SUA quintiles and baPWV. When SUA modeled continuously, baPWV rose by 12.413 cm/s in women ($P < .001$) and by 6.588 cm/s in men ($P < .001$) for each 1 mg/dL increase of SUA. In a low-risk, middle-aged, large Korean population, higher SUA levels could have an unfavorable impact on arterial stiffness as measured by baPWV, and this association was stronger in women than in men.

Abbreviations: baPWV = brachial ankle pulse wave velocity, BMI = body mass index, cfPWV = carotid-femoral pulse wave velocity, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, PWV = pulse wave velocity, ROS = reactive oxygen species, SD = standard deviation, SUA = serum uric acid, TG = triglycerides, XO = xanthine oxidase.

Keywords: general population, pulse wave velocity, uric acid, vascular stiffness

1. Introduction

Arterial stiffness is an indicator of future cardiovascular and cerebrovascular events not only in patients with high baseline risk but also in general population.[1–3] Brachial-ankle pulse wave velocity (baPWV) has been widely used to screen for atherosclerotic vascular damage during health check-ups instead of carotid-femoral pulse wave velocity (cfPWV).[4,5] Because the measurement of baPWV is easier, less time-consuming, and less stressful for subjects than that of cfPWV, many cohort studies have been performed using this more simplified device.[1] Moreover, baPWV was proved to be an index with favorable correlation with aortic pulse wave velocity (PWV) and similar intraobserver and interobserver variability for cfPWV.[6,7]

A high serum uric acid (SUA) level is a known risk factor for cardiovascular disease.[8,9] Epidemiologic studies have also found an association between high SUA level and arterial stiffness in patients with various disorders such as diabetes, hypertension, and chronic kidney disease.[10–13] However, there are few reports in apparently healthy populations regarding this association.[14–16] Accordingly, despite the accumulating body of evidence which links hyperuricemia with arterial stiffness in patients with various comorbidities, continuing doubt remains as to whether hyperuricemia can be truly considered an independent risk factor of arterial stiffness in apparently healthy screening examinees. Considering these findings, we hypothesized that higher SUA would correlate with increased PWV as a subclinical marker of arterial disease. Thus, we evaluated the association between SUA and arterial stiffness as evaluated by baPWV in a low-risk, middle-aged, large Korean population in the setting of health screening.

2. Methods

2.1. Subjects

We recruited 115,641 subjects (age range 19–88 years) who participated in the health check-up program between January

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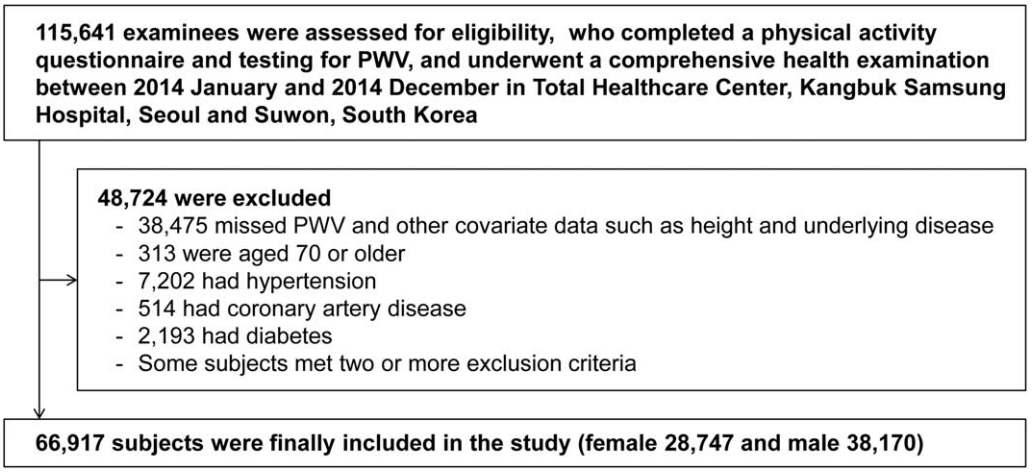

Figure 1. Selection of subjects. PWV = pulse wave velocity.

and December 2014 at the Total Healthcare Centre, Kangbuk Samsung Hospital, Seoul, South Korea. As shown in Fig. 1, a total of 66,917 participants (male, 57%) were eligible for this cross-sectional study. The Institutional Review Board of Kangbuk Samsung Hospital approved this study (KBSMC 2017-01-022) and waived the requirement for informed consent because a de-identified database was used to analyze data retrospectively. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.2. Measurements

A self-administered questionnaire was used to obtain following information: age (years), smoking status (current smoker, ex-smoker, or never smoked) with quantity (pack-years), alcohol consumption (g/wk), and medical history. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). After 12 hours of fasting, serum glucose, aspartate aminotransferase, alanine aminotransferase, triglycerides (TG), total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), uric acid, calcium, phosphorus, creatinine, C-reactive protein (CRP), and homocysteine were measured. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[17] Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III as the presence of 3 or more of the following criteria: waist circumference: ≥90 cm in men and ≥80 cm in women; TG ≥150 mg/dL; HDL-C <40 mg/dL in men and <50 mg/dL in women; blood pressure ≥130/85 mm Hg or antihypertensive medications; and fasting blood glucose ≥110 mg/dL or antidiabetic medications.[18] Anthropometric measurements and laboratory tests were described elsewhere.[19,20] During study periods, range of the coefficients of variation for quality control specimens of low and high concentrations were 0.8% to 2.6% in low level and 0.7% to 1.9% in high level for total cholesterol, 0.9% to 3.5% and 0.9% to 2.5% for HDL-C, 0.8% to 2.8% and 0.7% to 2.0% for TG, 1.2% to 3.3% and 0.9% to 2.6% for LDL-C, 1.0% to 2.4% and 0.8% to 1.6% for glucose, 0.9% to 2.1% and 0.7% to 1.5% for SUA, 1.9% to 4.9% and 0.8% to 1.5% for creatinine, 1.1% to 3.2% and 1.1% to 3.9% for CRP, and 1.6% to 3.8% and 1.0% to 2.5% for homocysteine, respectively.

2.3. Brachial-ankle PWV

The subject was examined in the supine position after at least 5 minutes of bed rest. baPWV was measured using an automatic waveform analyzer (VP-1000; Omron Healthcare, Kyoto, Japan) as previously described in detail.[21] Mean baPWVs from the left and right sides were used for analysis. The high validity, and interobserver and intraobserver reproducibility of this noninvasive baPWV measurement were documented in previous studies.[6,22]

2.4. Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables as means ± standard deviation (SD) or medians and interquartile ranges. The normality was assessed both visually and through the Kolmogorov–Smirnov test during data exploration. Parametric tests were engaged to data satisfying the assumption of normal distribution; unless, nonparametric tests were applied. The correlation coefficient r was measured to assess the relationship between 2 variables. Analyses were done in a gender-specific manner. SUA levels were categorized into quintiles. To determine independent associations of SUV with PWV, a multiple linear regression analysis with an enter method was carried out, in which PWV served as the dependent variable and SUV quintile served as the independent variable; model 1 was adjusted for age, sex, smoking pack-years, alcohol intake, systolic BP, diastolic BP, and BMI; model 2 was adjusted for LDL-C, HDL-C, TG, glucose, CRP, and homocysteine levels, eGFR, and metabolic syndrome in addition to the variables in model 1. To determine linear risk trends, the number of categories was used as a continuous variable and P for trend was tested on each model. All statistical analyses were performed using IBM SPSS Statistics 19.0 (IBM, Armonk, NY), and a P value $< .05$ was considered statistically significant.

3. Results

3.1. Characteristics of study subjects

The characteristics of the eligible subjects are summarized in Table 1. Mean age (± SD) was 39.4 (± 6.7) years and 57.0% of subjects were male. The average SUA level was 5.2 ± 1.4 mg/dL, and the prevalence of hyperuricemia (male > 7 mg/dL, female > 6.0 mg/dL was 21.2% and 2.1%, respectively). Among all

Table 1

Baseline characteristics of total study subjects by quintile (n = 66,917).

	Uric acid, mg/dL					
	Q1 (≤4.00)	Q2 (4.01–4.80)	Q3 (4.81–5.70)	Q4 (5.71–6.60)	Q5 (>6.60)	*P* for trend
Number of participants	15,696	13,069	13,904	12,851	11,397	<.001
Age,* y	38.90 ± 6.03	39.14 ± 6.77	39.93 ± 7.19	39.70 ± 6.80	39.11 ± 6.60	<.001
Systolic BP,* mm Hg (n = 66,910)	107.52 ± 11.42	109.50 ± 11.82	113.56 ± 11.70	116.21 ± 11.02	118.16 ± 10.90	<.001
Diastolic BP,* mm Hg (n = 66,911)	67.27 ± 8.13	68.85 ± 8.52	72.19 ± 8.60	74.28 ± 8.17	75.59 ± 8.07	<.001
BMI,* kg/m^2	21.45 ± 2.61	22.17 ± 2.84	23.32 ± 2.87	24.26 ± 2.80	25.20 ± 2.92	<.001
Ever-smoker, %	1592 (10.2)	2730 (21.0)	6703 (48.3)	8024 (62.5)	7560 (67.4)	<.001
Smoking pack-years†,‡ (n = 66,434)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–8.0)	3.0 (0.0–10.0)	4.0 (0.0–10.0)	<.001
Alcohol intake amount,† g/d (n = 51,346)	2.0 (0.0–6.0)	3.0 (0.0–9.0)	7.0 (2.0–18.0)	11.0 (5.0–23.0)	11.0 (6.0–23.0)	<.001
Metabolic syndrome, %	920 (5.9)	1065 (8.1)	1650 (11.9)	2055 (16.0)	2681 (23.5)	<.001
Total cholesterol,* mg/dL	185.03 ± 31.76	189.45 ± 31.58	195.53 ± 32.80	201.55 ± 33.32	208.13 ± 35.13	<.001
LDL-C,* mg/dL	105.20 ± 27.71	110.57 ± 28.13	118.70 ± 29.86	125.50 ± 29.91	130.90 ± 31.37	<.001
HDL-C,* mg/dL	63.08 ± 13.68	60.76 ± 14.00	55.69 ± 13.31	52.39 ± 12.24	50.10 ± 11.42	<.001
Triglycerides,* mg/dL (n = 66,916)	82.68 ± 44.52	91.37 ± 51.12	112.76 ± 68.07	131.06 ± 79.13	156.66 ± 103.89	<.001
Glucose,* mg/dL	90.11 ± 10.74	90.97 ± 10.07	92.51 ± 10.65	93.62 ± 10.06	94.33 ± 9.63	<.001
Estimated GFR,* mL/min per 1.73 m^2	118.82 ± 30.00	109.49 ± 26.09	102.19 ± 23.00	97.14 ± 21.77	92.59 ± 20.38	<.001
Uric acid,* mg/dL	3.44 ± 0.48	4.44 ± 0.23	5.30 ± 0.26	6.18 ± 0.26	7.46 ± 0.74	<.001
CRP,† mg/L (n = 59,541)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<.001
Homocysteine,* μmol/L (n = 38,121)	10.68 ± 5.15	10.77 ± 5.40	10.95 ± 4.79	11.17 ± 4.59	11.53 ± 4.95	<.001
Pulse wave velocity,* cm/s	1197.95 ± 141.05	1229.97 ± 155.09	1286.54 ± 154.87	1317.56 ± 145.20	1333.40 ± 158.83	<.001

Ever-smokers include ex-smokers and current smokers. Data are expressed as *mean (standard deviation), †median (interquartile range), or percentage. *P* value denotes the comparison between females and males.
BMI = body mass index, BP = blood pressure, CRP = C-reactive protein, GFR = glomerular filtration rate, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol.
‡ Among 66,434 participants with a plausible record for smoking pack-years.

subjects, the mean PWV was 1268.7 ± 159.4 cm/s. Those in the higher quintiles of uric acid tended to have lower eGFR and HDL-C and higher TG, fasting blood glucose, BP, homocysteine, and BMI. In addition, they tended to drink more alcoholic beverages. Only 4.7% of women ever experienced smoking so the pack-years of smoking were converged on near zero. Similarly, the distribution of CRP was naturally skewed in this apparently healthy population, but their distribution was differed significantly between women and men.

Baseline characteristics of study participants in relation to SUA level according to gender are presented in Tables 2 and 3. Mean PWV also differed between genders (1323.3 ± 148.1 cm/s vs. 1196.0 ± 144.1 cm/s for men and women, respectively) justifying a gender-specific analysis. In female subjects, a higher SUA quintile was associated with a greater likelihood of metabolic syndrome. In addition, SUA level was positively associated with the levels of systolic blood pressure, diastolic blood pressure, TC, LDL-C, TG, glucose, homocysteine, and PWV and negatively associated with estimated GFR and HDL-C in females (Table 2). The variables associated with SUA in females showed similar trends in male subjects, except smoking status (Table 3). As shown in Fig. S1, http://links.lww.com/MD/C443, there was a

Table 2

Baseline characteristics of female study participants by quintile (n = 28,747).

	Uric acid, mg/dL					
	Q1 (≤3.40)	Q2 (3.41–3.90)	Q3 (3.91–4.30)	Q4 (4.31–4.80)	Q5 (>4.80)	*P* for trend
Number of participants	14,221	9590	3987	801	148	<.001
Age,* y	38.62 ± 5.77	38.28 ± 6.18	38.30 ± 6.62	38.54 ± 7.22	38.46 ± 6.08	<.001
Systolic BP,* mm Hg (n = 28,742)	106.65 ± 11.13	107.43 ± 11.50	108.02 ± 12.04	110.58 ± 12.31	113.16 ± 14.20	<.001
Diastolic BP,* mm Hg (n = 28,742)	66.57 ± 7.77	67.14 ± 8.01	67.75 ± 8.43	69.05 ± 8.60	70.85 ± 9.32	<.001
BMI,* kg/m^2	21.22 ± 2.48	21.76 ± 2.79	22.61 ± 3.32	23.72 ± 3.73	25.33 ± 4.79	<.001
Ever-smoker, %	625 (4.5)	446 (4.7)	209 (5.3)	57 (7.2)	14 (9.5)	.001
Smoking pack-years† (n = 28,531)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.001
Alcohol intake amount,‡ g/d (n = 17,488)	1.0 (0.0–3.0)	1.0 (0.0–5.0)	2.0 (0.0–5.0)	2.0 (0.0–7.0)	1.0 (0.0–5.25)	<.001
Metabolic syndrome, %	734 (5.2)	744 (7.8)	473 (11.9)	148 (18.5)	43 (29.1)	<.001
Total cholesterol,* mg/dL	183.94 ± 31.37	188.12 ± 31.20	193.49 ± 33.16	201.58 ± 36.51	209.76 ± 41.99	<.001
LDL-C,* mg/dL	103.73 ± 27.03	108.01 ± 27.34	113.52 ± 30.13	121.35 ± 33.12	128.34 ± 38.64	<.001
HDL-C,* mg/dL	64.00 ± 13.49	62.92 ± 13.92	61.23 ± 14.24	59.93 ± 15.47	57.61 ± 15.83	<.001
Triglycerides,* mg/dL (n = 28,746)	79.01 ± 40.01	84.11 ± 43.83	93.92 ± 55.32	106.33 ± 73.06	133.26 ± 110.06	<.001
Glucose,* mg/dL	89.56 ± 9.54	89.84 ± 8.45	90.16 ± 9.14	90.98 ± 10.97	91.36 ± 13.46	<.001
Estimated GFR,* mL/min per 1.73 m^2	120.46 ± 30.20	111.85 ± 27.08	107.95 ± 27.18	105.01 ± 28.35	100.57 ± 32.71	<.001
Uric acid,* mg/dL	3.44 ± 0.47	4.41 ± 0.22	5.20 ± 0.24	6.05 ± 0.23	7.24 ± 0.70	<.001
CRP,‡ mg/L (n = 25,408)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<.001
Homocysteine,* μmol/L (n = 570)	8.21 ± 4.48	8.35 ± 1.85	8.65 ± 2.12	9.54 ± 1.50	10.33 ± 2.58	<.001
Pulse wave velocity,* cm/s	1185.21 ± 134.54	1199.50 ± 149.34	1214.55 ± 156.69	1240.80 ± 153.92	1271.76 ± 149.61	<.001

Ever-smokers include ex-smokers and current smokers. Data are expressed as *mean (standard deviation), ‡median (interquartile range), or percentage.
BMI = body mass index, BP = blood pressure, CRP = C-reactive protein, GFR = glomerular filtration rate, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol.
† Among 17,488 participants with a plausible record for smoking pack-years.

Table 3

Baseline characteristics of male study participants by quintile (n = 38,170).

	Uric acid, mg/dL					
	Q1 (≤5.10)	Q2 (5.11–5.80)	Q3 (5.81–6.30)	Q4 (6.31–7.00)	Q5 (>7.00)	*P* for trend
Number of participants	1475	3479	9917	12,050	11,249	<.001
Age,* y	41.56 ± 7.62	41.50 ± 7.70	40.59 ± 7.31	39.79 ± 6.77	39.12 ± 6.59	<.001
Systolic BP,* mm Hg (n = 38,168)	115.96 ± 10.79	115.22 ± 10.75	115.79 ± 10.78	116.59 ± 10.83	118.22 ± 10.83	<.001
Diastolic BP,* mm Hg (n = 38,169)	74.02 ± 8.39	73.57 ± 8.07	73.98 ± 8.01	74.63 ± 8.02	75.65 ± 8.03	<.001
BMI,* kg/m^2	23.64 ± 2.80	23.29 ± 2.68	23.61 ± 2.61	24.30 ± 2.73	25.20 ± 2.89	<.001
Ever-smoker, %	967 (65.6)	2284 (65.7)	6494 (65.5)	7967 (66.2)	7546 (67.1)	.453
Smoking pack-years† (n = 37,903)	4.0 (0.0–10.0)	4.0 (0.0–10.0)	4.0 (0.0–10.0)	4.0 (0.0–10.0)	4.0 (0.0–10.0)	.638
Alcohol intake amount,‡ g/d (n = 33,858)	11.0 (5.0–23.0)	10.0 (3.0–23.0)	11.0 (5.0–23.0)	11.0 (5.0–23.0)	11.0 (6.0–23.0)	<.001
Metabolic syndrome, %	186 (12.6)	321 (9.2)	1177 (11.9)	1907 (15.8)	2638 (23.5)	<.001
Total cholesterol,* mg/dL	195.54 ± 33.59	193.10 ± 32.30	196.34 ± 32.62	201.54 ± 33.11	208.10 ± 35.03	<.001
LDL-C,* mg/dL	119.40 ± 30.01	117.63 ± 29.04	120.78 ± 29.50	125.77 ± 29.67	130.94 ± 31.26	<.001
HDL-C,* mg/dL	54.25 ± 12.37	54.80 ± 12.39	53.46 ± 12.23	51.89 ± 11.82	50.00 ± 11.32	<.001
Triglycerides,* mg/dL	118.04 ± 65.28	111.37 ± 63.05	120.34 ± 71.18	132.70 ± 79.24	156.97 ± 103.77	<.001
Glucose,* mg/dL	95.36 ± 17.87	94.09 ± 13.06	93.45 ± 11.06	93.80 ± 9.97	94.37 ± 9.56	<.001
Estimated GFR,* mL/min per 1.73 m^2	102.95 ± 22.31	102.97 ± 21.84	99.88 ± 20.63	96.62 ± 21.16	92.49 ± 20.15	<.001
Uric acid,* mg/dL	3.49 ± 0.54	4.53 ± 0.22	5.35 ± 0.25	6.19 ± 0.25	7.46 ± 0.74	<.001
CRP,‡ mg/L (n = 34,133)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<.001
Homocysteine,* μmol/L (n = 37,551)	11.08 ± 5.14	10.92 ± 5.50	10.97 ± 7.80	11.17 ± 4.60	11.53 ± 4.96	<.001
Pulse wave velocity,* cm/s	1320.81 ± 143.31	1313.96 ± 138.83	1315.48 ± 144.36	1322.66 ± 146.16	1334.21 ± 158.80	<.001

Ever-smokers include ex-smokers and current smokers. Data are expressed as *mean (standard deviation), ‡median (interquartile range), or percentage.

BMI = body mass index, BP = blood pressure, CRP = C-reactive protein, GFR = glomerular filtration rate, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol.

† Among 33,858 participants with a plausible record for smoking pack-years.

clear positive linear association between SUA quintile and PWV in all subjects and females. By contrast, data analysis revealed a J-shaped association between PWV and SUA quintile among males.

3.2. Association between SUA and arterial stiffness

A graded association with baPWV and increase in SUA quintile was observed in all study participants (*P* for trend < .001 in all models) (Table 4). Subjects in the highest quintile of SUA had a significantly higher baPWV compared with those in lower quintiles. The analysis was conducted separately in men and women to evaluate whether gender influenced the association between SUA level and PWV (Table 5). In the analysis of female subjects, a similar trend of graded association was shown between baPWV and increase in SUA quintile (*P* for trend < .001 in all models). The higher was the quintile of SUA, the higher was the baPWV in female subjects. Because the baPWV of male subjects was found to have a "J-shaped" relationship with SUA quintile, the second quintile group was used as a reference in the regression analysis. A significant dose–response relationship between baPWV and SUA quintile was found in Q3, Q4, and Q5 despite of unavailable statistical assessment of the trend.

When SUA introduced as a continuous scale in regression models, association results were somewhat attenuated but remained significant. Successively adjusted for more variables in women and men, baPWV was higher by 12.41 and 6.58 cm/s, respectively, with an increase of 1 mg/dL in SUA (*P* < .001, respectively).

4. Discussion

This retrospective, cross-sectional study investigated an association between PWV and SUA level in a low-risk, large population of middle-aged Korean subjects undergoing yearly health screening. A linear positive association between SUA quintiles

Table 4

Relationship between serum uric acid and pulse wave velocity in total study participants.

	Age- and sex-adjusted model			Multivariate model 1			Multivariate model 2		
Uric acid	Coefficient	SE	*P*	Coefficient	SE	*P*	Coefficient	SE	*P*
Quintiles, mg/dL									
Q1 (≤4.00)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (4.01–4.80)	14.443	1.693	<.001	11.893	2.011	<.001	11.519	2.002	<.001
Q3 (4.81–5.70)	24.386	1.923	<.001	18.870	2.212	<.001	18.194	2.213	<.001
Q4 (5.71–6.60)	35.607	2.164	<.001	27.073	2.414	<.001	24.730	2.432	<.001
Q5 (>6.60)	50.258	2.262	<.001	36.639	2.527	<.001	31.024	2.584	<.001
P for trend	<.001			<.001			<.001		
Per 1 mg/dL increase	12.680	0.520	<.001	9.381	0.572	<.001	6.624	0.701	<.001

Multivariable model 1 was adjusted for age, sex, smoking pack-years, alcohol intake, systolic BP, diastolic BP, and BMI; multivariable model 2 was adjusted for levels of LDL-C, HDL-C, triglyceride, and glucose, estimated glomerular filtration rate, CRP, homocysteine, and metabolic syndrome, in addition to variables in model 1.

BMI = body mass index, BP = blood pressure, CRP = C-reactive protein, GFR = glomerular filtration rate, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, SE = standard error.

Table 5

Linear regression models examining the relationship between SUA and baPWV in women and men.

	Women				Men			
	Model 1		Model 2		Model 1		Model 2	
Uric acid	β	*P*	β	*P*	β	*P*	β	*P*
Quintiles*								
Q1	Reference	Reference	Reference	Reference	6.641	.138	1.802	.698
Q2	13.640	<.001	13.139	<.001	Reference	Reference	Reference	Reference
Q3	26.167	<.001	22.884	<.001	4.046	.155	3.310	.262
Q4	40.700	<.001	34.570	<.001	14.021	<.001	11.728	<.001
Q5	43.488	.003	32.128	.027	25.407	<.001	18.999	<.001
P for trend	<.001		<.001		UA		UA	
Per 1 mg/dL increase	13.995	<.001	12.413	<.001	8.336	<.001	6.588	<.001

Model 1 was adjusted for age, sex, smoking pack-years, alcohol intake, systolic BP, diastolic BP, and BMI; model 2 was adjusted for levels of LDL-C, HDL-C, triglyceride, and glucose, estimated GFR, CRP, homocysteine, and metabolic syndrome, in addition to variables in model 1.

baPWV = brachial ankle pulse wave velocity, BMI = body mass index, BP = blood pressure, CRP = C-reactive protein, GFR = glomerular filtration rate, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, SUA = serum uric acid, UA = unavailable.

* SUA quintiles of women were ≤3.40 in Q1, 3.41–3.90 in Q2, 3.91–4.30 in Q3, 4.31–4.80 in Q4, and >4.80 in Q5; SUA quintiles of men were ≤5.10 in Q1, 5.11–5.80 in Q2, 5.81–6.30 in Q3, 6.31–7.00 in Q4, and >7.00 in Q5.

and baPWV was shown in multiple regression analyses in women while a J-shaped association in men. Taken together, these findings suggest that higher SUA levels could have an unfavorable impact on arterial stiffness even in low-risk populations.

Most previous studies have evaluated the utility of SUA as a risk factor for arterial stiffness in patients at high risk (diabetes, hypertension, and chronic kidney disease), as well as among various ethnic groups.[10–13,23] Nevertheless, there are unclear and conflicting results in apparently healthy populations. In cross-sectional data from 982 Japanese health examinees, a positive association between SUA and baPWV independent of traditional risk factors was found.[24] In this study, however, 30% of all participants were taking antihyperlipidemic, antidiabetic, and antihypertensive drugs, some of which could have affected SUA level because of their uricosuric effect. These may interfere with evaluating the true impact of SUA on PWV. In another study of 1276 Koreans who underwent a health check-up, uric acid level was not significantly associated with heart-femoral or brachial-ankle PWV in either men or women.[25] Furthermore, in a study of 619 Italians who were not taking antihypertensive, antidiabetic, lipid-lowering, or uric acid-lowering drugs, a significant association between SUA and cfPWV was found in a univariate analysis, but the trend became nonsignificant when adjusted.[14] Gender differences were often observed regarding the relationship between SUA and PWV. In a study of 2704 healthy Koreans, SUA was positively associated with baPWV in women, but not in men.[16] On the other hand, SUA was linearly associated with cfPWV in men, but not in women among 3588 healthy Brazilians.[26]

In this vein of ambiguity, we found the positive impact of SUA on baPWV after extensive adjustment for potential confounders. There was a slight gender difference when separately analyzed; the positive association between SUV and baPWV was uniformly observed but more prominent in women than in men. Unlike other studies,[2,11–13,15,16] our data showed a stronger and genuine effect of SUA on arterial stiffness in a relatively young and large Korean population, where the mean age of participants was 39.4 years old and none had cardiovascular risk factors. Meanwhile, this impact on baPWV was shown not only in hyperuricemic level but also found within the reference range of SUA. Among Koreans, the reported reference level of SUA was 5.37 ± 1.106 mg/dL in men and 3.87 ± 0.745 mg/dL in women,[27] which seems to be slightly lower compared to those of other Asian countries.[28,29] Those discrepancies may come from nutritional status and other physical conditions. Thus, our results may not be generalizable to other ethnic groups with different demographics. Nonetheless, our study suggests that, even in a low-risk, relatively young population, SUA contributes to arterial stiffness, and regular monitoring of SUA and urate lowering therapy, if needed, may be actively considered to reduce the risk of subclinical atherosclerosis represented by arterial stiffness. These hypotheses need to be confirmed in an interventional, prospective study, of which design based on the different life style and daily life behavior is required to elucidate the precise causal effect of SUA on arterial stiffness in an apparently healthy population.

Precise mechanisms of SUA involved in arterial stiffness have yet to be elucidated but possible explanation could be inferred from some studies. Uric acid reportedly induces expression of CRP in vascular endothelial and smooth muscle cells, which stimulate cell proliferation.[30] In addition, uric acid may induce endothelial dysfunction by decreased nitric oxide production in vascular endothelial cells.[31] Major reactive oxygen species (ROS) modulating vascular contractility are generated by xanthine oxidase (XO), which is involved in catalyzing uric acid. Considering the lower SUA levels of women in fertile years than those of men owing to uricosuric effect of estrogen, the same SUA level in both genders could reflect a higher activity of XO in women than in men.[31–33] Given that the mean age of our female participants was 38.5 years, this higher XO activity might bring ROS activation, leading to the stronger relationship between SUA and PWV in women rather than in men. Meanwhile, our data showed a J-shaped association of SUA quintile with PWV in male subjects. An increased PWV in the lowest quintile group compared to the second quintile group is the most unexpected outcome of the study. Considering that uric acid acts as a major antioxidant in human plasma with possible benefit of antiatherosclerotic effects,[34] it is complicated to speculate the impact on the degree of arterial stiffness in male subjects with a lower SUA level. Nevertheless, the antioxidant properties of SUA remain to be a subject of intense scrutiny.

Alternate mechanism could be related to the inflammatory properties of SUA, which directly causes arteriosclerosis. Nod-like receptor family protein 3 (NLRP3) inflammasome is

activated by urate crystal engulfed macrophages.[35] Via this pathway urate-stimulated human macrophages secret interleukin-1β, and it causes inflammation and collagen production, leading to the development of arteriosclerosis. Another explanation could be the expression of urate transporter on human blood vessels, which move urate via glucose transporter 9 and voltage-driven urate efflux transporter 1, causing inflammation in vasculature.[36]

The present study was strengthened by the large sample size, which provided excellent statistical power, and extensive exclusion and adjustment of potential confounders. There were also some limitations. First, the cross-sectional design constrained the analysis to the assessment of association only so the causality needs to be proven in further study. Second, we collected data based on a self-administered questionnaire, which might be subject to recall bias regarding smoking and drinking habits, and restrain further analysis covering medications. Third, we used baPWV instead of cfPWV as a surrogate marker of subclinical atherosclerosis. baPWV and cfPWV, as indices of arterial stiffness, have a similar extent of associations with cardiovascular disease risk factors and clinical events.[4,5,34] Fourth, subjects in this study were highly educated, young and middle-aged Korean adults who regularly attended health screening exams, most often as part of work-related health check-up programs. Although it makes a generalization difficult to other groups, our results are less likely to be influenced by the presence of comorbidities and the use of multiple medications that concerns old ages. Lastly, the risk of our normal range of SUA needs to be elucidated as a true danger for arterial stiffness in Korean. If so, it may arouse reconsideration to the reference range of SUA. Actually, there was a discussion to suggest a change of threshold value of SUA, regarding the silent deposition of urate crystal in chronic hyperuricemic status.[37] Thus, our results could be another evidence of pathophysiological role of SUA in human disease.

In conclusion, the present study demonstrated the SUA was positively associated with arterial stiffness as measured by baPWV in a low-risk, middle-aged, large Korean population undergoing yearly health screening. This was observed not only in hyperuricemia but also within a reference range. It may infer that a strategy for aiming at modulating the SUA levels has clinical implications for the prevention and treatment of arterial stiffness with subsequent cardiovascular events. The pathophysiological role of uric acid remained to be enlightened.

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Author contributions

All authors critically reviewed and edited the manuscript and approved the final version. Jiwon Hwang and Jung Hye Hwang have contributed equally to this work. Joong Kyong Ahn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Jiwon Hwang, Jung Hye Hwang, Sun Mi Chung, Min-Jung Kwon, and Joong Kyong Ahn were responsible for study concept and design, acquisition, analysis or interpretation of the data, drafting of the manuscript, and study supervision.

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