Original Article

Involvement of Arterial Stiffness and Inflammation in Hyperuricemia-Related Development of Hypertension

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Abstract—This study analyzed repeated measurement data to clarify the longitudinal associations between hyperuricemia and the risk factors for the development of hypertension (ie, increased arterial stiffness, renal dysfunction, and inflammation), and then examined whether these risk factors show longitudinal associations with the development of hypertension. In 3274 Japanese men without hypertension, the brachial-ankle pulse wave velocity, blood pressure, estimated glomerular filtration rate, and serum uric acid and CRP (C-reactive protein) levels were measured annually over an 8-year period. Of these, 474 subjects developed hypertension by the end of the study period. Mixed model linear regression analysis revealed a significant longitudinal association of hyperuricemia with increase of the brachial-ankle pulse wave velocity (estimate=5.50, P=0.04), decrease of the estimated glomerular filtration rate (estimate=−2.02, P<0.01), and elevation of the CRP (estimate=0.08×10^{-1}, P=0.02). Hyperuricemia at the study baseline was associated with a significant odds ratio for the development of hypertension by the end of the study period. After adjustments for covariates, the brachial-ankle pulse wave velocity (estimate=0.51×10^{-2}, P<0.01) and CRP (estimate=1.91, P=0.03), but not estimated glomerular filtration rate, were found to show independent longitudinal associations with the new onset of hypertension. In Japanese men without hypertension, hyperuricemia may have a longitudinal association with the development of hypertension, and increased arterials stiffness and inflammation may be involved in the risk of development of hypertension associated with hyperuricemia. **(*Hypertension*. 2018;73:00-00. DOI: 10.1161/HYPERTENSIONAHA.118.11390.)**

Key Words: blood pressure ■ hypertension ■ hyperuricemia ■ inflammation ■ risk factors

According to recently reported meta-analyses, hyperuricemia is an independent risk factor for the development of hypertension,[1,2] although the underlying mechanisms have not yet been fully clarified. Hyperuricemia has also been reported to be associated with the early stages of development of some risk factors for hypertension, such as arterial stiffness,[3] renal function decline,[4] and inflammation.[5] Thus, we attempted to verify the possibility of involvement of these risk factors in the risk of development of hypertension associated with hyperuricemia.[6] Although an observational study would be needed for such an objective, conventional observational studies, in which the relevant assessments are conducted at 2 observational points, have the limitation that they exclude the effects of time-varying confounding variables.[7] However, analysis of repeated measures data by mixed model linear (MML) regression analysis and general estimated equation (GEE) analysis may be useful to minimize the effects of time-varying confounders.[7]

In the present prospective observational study conducted in Japanese men without hypertension at the study baseline, we analyzed repeated measures data by MML regression analysis and GEE analysis to clarify the longitudinal associations of hyperuricemia with the above-mentioned risk factors for the development of hypertension, and then to examine the longitudinal associations of these risk factors with the development of hypertension.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for the purpose of reproducing the results or replicating the procedure.

Design and Subjects

The present study was conducted in the same cohort as that used in a previously reported prospective observational study.[8,9] The cohort consisted of employees working at the headquarters of a single large Japanese construction company located in downtown Tokyo. According to the Occupational Health and Safety Law in Japan, it is mandatory for all company employees to undergo annual health checkups. Informed consent for participation in this study was obtained from all of the study participants before their enrollment in this study. The study was

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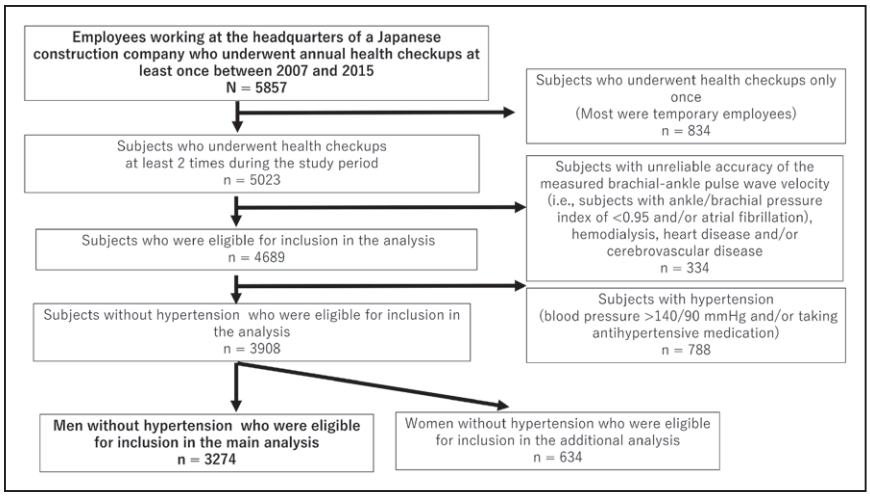

Figure. Flow diagram of the subjects enrolled in the study.

conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University (No. 209 and No. 210 in 2003).

The health checkup data obtained for the years 2007 through 2015 were used for the present study. Of the total of 5857 subjects working at the headquarters of the construction company who had undergone measurement of the brachial-ankle pulse wave velocity (baPWV) at least once, 834 who underwent the measurement only once during the study period (most of these were temporary employees) were excluded. Finally, the data of the remaining 3274 men in whom the blood pressure (BP) was categorized as being in the normal range at the study baseline (ie, <140/90 mm Hg) were included in our analyses (Figure).[8]

BP Measurement

Brachial BP was measured as the mean of 2 measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. Both measurements were performed on the same occasion with the subjects in the seated position after they had rested for at least 5 minutes.

Definition of Hypertension

Systolic BP (SBP) ≥140 mm Hg and diastolic BP (DBP) ≥90 mm Hg and a history of receiving antihypertensive drug therapy at the time of the annual health checkups.

Measurement of the baPWV

The baPWV was measured using a volume-plethysmographic apparatus (Form/ABI, Omron Healthcare Co, Ltd, Kyoto, Japan), as described previously.[8–10] Briefly, occlusion cuffs connected to both the plethysmographic and oscillometric sensors were tied around both the upper arms and lower legs of the subjects lying in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. The measurements were conducted after the subjects had rested for at least 5 minutes in the supine position in an air-conditioned room (maintained at 24°C) designated exclusively for this study. Data of subjects with ABI (ankle brachial pressure index) <0.95 and those with atrial fibrillation were excluded from the analyses.

Laboratory Measurements, Calculation of the Estimated Glomerular Filtration Rate, and Definition of Hyperuricemia

Serum concentrations of uric acid (UA), triglyceride, LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), and creatinine, as well as the plasma glucose concentration and HbA1c (glycohemoglobin A1c) value, were measured using standard enzymatic methods (Falco Biosystems Co Ltd, Tokyo). Serum CRP (C-reactive protein) was measured by the latex-aggregation method (Falco Biosystems Co Ltd, Tokyo).[11] Hyperuricemia was defined as a serum UA level of >7.0 mg/dL, based on a guideline for the management of hyperuricemia and gout.[12]

All the blood samples were obtained in the morning after the patients had fasted overnight. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation[13] for Japanese subjects.

Statistical Analysis

Data are expressed as means±SD unless otherwise indicated. The serum CRP levels were skewed rightward, therefore, the values were log-transformed for the analyses. The minimum value of the serum CRP was set at 0.5 mg/L.[11] Then, the CRP values were multiplied by 10 for the log-transformation (log [CRP×10]), to align all the values in the positive range.

The differences in the measured values between the baseline and final examinations were assessed by the paired *t* test for continuous variables and by McNemar nonparametric test for categorical variables.

To determine the longitudinal associations of the variables with the new onset of hypertension, GEE analyses were performed, and to determine the longitudinal associations among the variables, MML analyses were performed. In the GEE analysis, time was a significant factor for the new onset of hypertension (estimate=0.27; SE=0.01; $P<0.01$). Therefore, in the MML and GEE analyses, the time effect was entered as the interaction term between time (years from the baseline) and each of the explanatory variables.

In MML analyses, β-estimates of the interaction between time and each of the explanatory variables were regarded as the annual changes in each of the outcome variables per unit annual increase of the corresponding explanatory variable. The MML analyses were conducted using 5 different model structures (ie, autoregressive,[1] compound symmetry, diagonal, Toeplitz, and unstructured). Then, we used Akaike information criterion to determine the best model structure. The basic covariates adjusted for were the body mass index, current smoking history, current daily alcohol intake, heart rate, LDL, HDL, triglyceride, HbA1c, creatinine, history of medication use for hypertension, dyslipidemia, diabetes mellitus, and hyperuricemia (not receiving medication=0, receiving medication=1; for each medication), and family history of hypertension.

Logistic regression analysis was performed to identify the variables that were predictive of the development of hypertension. In the adjustment, basic covariates measured at the study baseline (medication use for hypertension was excluded) plus the SBP/DBP at the study baseline were entered simultaneously in the same binary logistic regression analysis models (model A/B). In addition to identification of the significant predictive variables in this adjusted logistic regression analysis, the effects of other predictive variables for the development of hypertension on the association of hyperuricemia with the development of hypertension was assessed by mediation analysis.

In the GEE analyses, β-estimates of the interaction between time and each of the explanatory variables were regarded as the annual rate

of new onset of hypertension per unit annual increase of the corresponding explanatory variable. In the adjustment, the basic covariates for adjustment (excluding the medication use for hypertension), as mentioned above, were entered. The GEE analyses were conducted using 4 different model structures (ie, independent, autoregressive,[1] exchangeable, and unstructured). Then, we used the quasi-likelihood under the independence model criterion to determine the best correlation structure.

All analyses were conducted using the SPSS software (version 24.0; IBM/SPSS Inc, Armonk, NY). $P<0.05$ was considered as indicative of a statistically significant difference in all the statistical tests.

Results

Table 1 shows the clinical characteristics of the men (entire subject population and subjects with/without hyperuricemia at the study baseline) at the start of the study and at the final observation. End of the study period was defined by the last examination of the participants who had undergone at least 2 annual examinations.[8,9] Among the whole study subjects included, 474 (14.5%) developed hypertension (of which 152 were already receiving antihypertensive medication by the end of the study period) by the end of the study period. The mean number of times that the variables were measured was 5.2±2.1×, and the mean duration of follow-up was 6.4±2.5 years. Table 2 summarizes the number of available data for each variable from each annual observation. Although the BP and baPWV increased significantly in the subjects during the study period, unexpectedly, the serum UA levels decreased (Table 1). As compared with the subjects without hyperuricemia, the prevalence rate of a family history of hypertension, body mass index, positive alcohol history, BP, baPWV, triglyceride, serum CRP levels and also the rate of the development

Table 1. Clinical Characteristics of the Male Study Subjects

	Whole Study Subjects		With Hyperuricemia		Without Hyperuricemia	
Parameter	Start	End	Start	End	Start	End
n	3274	3274	732	732	2542	2542
Age, y	42±9	47±9*	42±9	47±9*	42±9	47±9*
BMI, kg/m^2	23.7±2.9	23.9±3.0*	25.0±3.2†	25.1±3.0*†	23.3±3.3	23.5±3.0*
FamHxHBP, %	960 (29.3)		239 (32.7)†		721 (28.4)	
Current smokers, n (%)	1055 (32.2)	843 (26.0)*	232 (31.7)	182 (25.0)*	823 (32.4)	661 (26.0)*
Current drinkers, n (%)	2787 (85.1)	2903 (88.7)*	652 (89.1)†	672 (91.8)*†	2135 (84.0)	2231 (87.8)*
Ethanol, g/d	12.2±10.8	14.2±11.7	14.3±11.2	16.4±12.0	11.5±10.5	13.6±11.5
SBP, mm Hg	120±10	123±12*	122±10†	125±12*†	119±10	122±12*
DBP, mm Hg	72±8	76±10*	74±8†	78±10*†	72±8	75±10*
HBP, %	0	474 (14.5)	0	170 (23.2)†	0	304 (12.0)
baPWV, cm/s	1244±143	1302±187*	1274±154†	1341±192*†	1236±139	1291±184*
LDL, mmol/L	3.06±0.78	3.18±0.77*	3.16±0.85†	3.16±0.81	3.03±0.78	3.18±0.77*
HDL, mmol/L	1.62±0.40	1.59±0.39*	1.56±0.40†	1.53±0.38*†	1.63±0.40	1.60±0.39*
TG, mmol/L	1.35±0.95	1.33±0.91	1.72±1.17†	1.65±1.08*†	1.24±0.84	1.24±0.84
HbA1c, %	5.2±0.5	5.5±0.6*	5.2±0.5	5.6±0.7*	5.2±0.5	5.5±0.6*
UA, μmol/L	365±73	355±72*	460±47†	419±63*†	338±54	337±63
eGFR, mL/min per 1.73 m^2	86±9	83±9*	83±10†	81±10*†	87±8	84±8*
CRP, mg/L	1.0±1.6	1.0±1.5	1.2±1.7†	1.3±2.1†	1.0±1.5	0.9±1.3
Receiving medication for hypertension, %	0	152 (4.6)*	0	62 (8.5)*†	0	90 (3.5)*
Receiving medication for dyslipidemia, %	56 (1.7)	160 (4.9)*	24 (3.3)†	77 (10.5)*†	32 (1.3)	83 (3.3)*
Receiving medication for diabetes mellitus, %	44 (1.3)	90 (2.7)*	6 (0.8)	21 (2.9)*	38 (1.5)	69 (2.7)*
Receiving medication for hyperuricemia, %	112 (3.4)	153 (4.7)*	112 (15.3)†	139 (19.0)*†	0	14 (0.6)*

baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration equation; FamHxHBP, family history of hypertension; final, at the end of the observation period; HbA1c (glycohemoglobin A1c), serum level of glycosylated hemoglobin A1c; HBP, number of subjects with hypertension; HDL, serum high-density lipoprotein cholesterol level; hyperuricemia, serum uric acid level >7.0 mg/dL; LDL, serum low-density lipoprotein cholesterol level; medication, no. (percentage) of subjects receiving medications; SBP, systolic blood pressure; start, at the start of the observation period; TG, serum triglyceride level; and UA, uric acid.

*$P<0.05$ vs at the start of the observation period.

†$P<0.05$ vs subjects without hyperuricemia.

of hypertension during the study period were higher, and the HDL and eGFR were lower, in the subjects with hyperuricemia (Table 1).

MML regression analysis with adjustments revealed significant independent longitudinal associations of hyperuricemia with increase of the baPWV (adjusted for the basic covariates [ie, age, body mass index, current daily alcohol intake, heart rate, LDL, triglyceride, and HbA1c, medication use for hypertension, hyperuricemia, dyslipidemia, and diabetes mellitus, and family history of hypertension] plus mean BP and eGFR), decline of the eGFR (adjusted for the basic covariates plus mean BP and baPWV), and elevation of the serum CRP level (adjusted for the basic covariates plus mean BP, baPWV, and eGFR) during the study period (Table 3).

Without adjustments, binary logistic regression analysis demonstrated that the serum UA levels, baPWV, eGFR, and serum CRP levels had significant odds ratios for the development of hypertension. When basic covariates measured at the study baseline (medication use for hypertension was excluded) plus the SBP/DBP at the study baseline were entered simultaneously in the same binary logistic regression analysis models (model A/B), the serum UA levels and baPWV, but not the eGFR or serum CRP levels, were found to have significant odds ratios for the development of hypertension (Table 4). In addition, hyperuricemia (serum UA level >7.0 mg/dL) also showed a significant odds ratio, even after the adjustments in model A/B (Table 4). As subanalysis, in subjects not receiving medication for hyperuricemia at the study baseline (n=3162), both elevated serum UA levels (model A: odds ratio=1.29; 95% confidence interval (CI)=1.16–1.43; $P<0.01$; model B: odds ratio=1.28; 95% CI=1.15–1.43; $P<0.01$) and hyperuricemia (model A: odds ratio=1.52; 95% CI=1.16–2.01; $P<0.01$; model B: odds ratio=1.49; 95% CI=1.13–1.97; $P<0.01$) were found to show significant odds ratios for the development of hypertension, even after the adjustments.

Among women (n=634), 46 (7.3%) developed hypertension by the end of the study period. However, the serum UA levels did not show a significant odds ratio for the development of hypertension in women, even in the absence of adjustments (odds ratio=1.24; 95% CI=0.89–1.74; $P=0.20$).

When basic covariates measured at the study baseline (medication use for hypertension was excluded) plus the SBP/DBP at the study baseline were entered simultaneously in the same model of mediation analyses (model A/B), the mediation analyses demonstrated that the serum UA levels had a direct effect (model A: effect=0.24; SE=0.05; $P<0.01$; model B: effect=0.23; SE=0.05; $P<0.01$), whereas the baPWV (model A: effect=0.17×10^{-1}; SE=0.07×10^{-1}; $P=0.01$; model B: effect=0.21×10^{-1}; SE=0.08×10^{-1}; $P<0.01$) had an indirect effect, on the risk of development of hypertension.

The GEE analyses conducted in 2 steps to assess the longitudinal associations of clinical variables (UA, baPWV, eGFR, and logCRP) with the new onset of hypertension. Step 1 analysis (conducted for each of the variables individually in the absence of adjustments for covariates) revealed significant longitudinal associations of the serum UA levels, baPWV, eGFR, and logCRP with the new onset of hypertension (Table 5; step 1). Step 2 analysis (each of the variables was entered simultaneously in the same model) with adjustments for basic covariates (excluding medication use for hypertension) revealed a significant longitudinal association of the baPWV and logCRP with the new onset of hypertension (Table 5; step 2). Analysis with entry of the interaction term into the model revealed no significant interaction of the baPWV and logCRP in their longitudinal associations with the new onset of hypertension (estimate=0.69; SE=0.58; $P=0.23$).

Discussion

To the best of our knowledge, the present prospective observational study, in which we analyzed repeatedly measured data over a period of 8 years, is the first to examine the longitudinal associations among hyperuricemia, arterial stiffness, renal function decline, inflammation, and the development of hypertension. Our results revealed that hyperuricemia had significant independent longitudinal associations with an elevation of the baPWV, decline of the eGFR, and elevation of the serum CRP levels. Hyperuricemia was also showed as an independent predictor of the development of hypertension, with an increase of the baPWV playing a mediatory role. Our analyses finally identified high baPWV and elevated serum CRP levels, but not eGFR decline, as showing significant independent longitudinal associations with the development of hypertension.

Hyperuricemia and the Risk of Development of Hypertension

Several prospective studies have demonstrated that hyperuricemia is associated with an elevated risk for cardiovascular disease.[5,6] However, arterial stiffness, renal dysfunction, and inflammation have also been reported to be associated with

Table 2. Number of Available Data for Each Variable at Each Annual Observation

	Annual Observation								
Parameters	Start	2nd AN	3rd AN	4th AN	5th AN	6th AN	7th AN	8th AN	9th AN
UA	3274	2550	2022	2317	1777	1448	1696	1227	879
SBP/DBP	3274	2550	2022	2317	1777	1448	1696	1227	879
baPWV	3274	2543	2015	2303	1772	1443	1686	1224	877
eGFR	3274	2548	2019	2313	1775	1446	1692	1227	879
CRP	3274	2421	1905	2071	1301	432	1693	1224	878

AN indicates annual examination; baPWV, brachial-ankle pulse wave velocity; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; start, start of the study period; SBP, systolic blood pressure; total, all study subjects included in the analysis; and UA, uric acid.

Table 3. Results of Mixed Model Linear Regression Analysis Conducted to Assess the Longitudinal Associations of the Serum UA Levels With the Arterial Stiffness, GFR, and Log-Transformed Serum CRP Levels

Outcome	Explain	Estimate	SE	*P* Value
Crude				
baPWV	UA	12.11	2.69	<0.01
eGFR	UA	−1.93	0.11	<0.01
Log (CRP×10)	UA	0.12×10^{-1}	0.03×10^{-1}	<0.01
Adjusted				
baPWV	UA	5.50	2.60	0.04
eGFR	UA	−2.02	0.13	<0.01
Log (CRP×10)	UA	0.08×10^{1}	0.03×10^{-1}	0.02

Adjusted=basic covariates (age, body mass index, heart rate, serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides, HbA1c [glycohemoglobin A1c], smoking history, drinking history, history of medication for hypertension, dyslipidemia, diabetes mellitus and hyperuricemia [for each of the above: not receiving medication=0, receiving medication=1], and the time [years from the baseline]). For baPWV, basic covariates plus mean blood pressure and eGFR; for eGFR, basic covariates plus mean blood pressure and baPWV; and for log (CRP×10): basic covariates plus mean blood pressure, baPWV, and eGFR. baPWV indicates brachial-ankle pulse wave velocity; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; estimate, β-estimates of the interaction between time and each of the explanatory variables; explain, explanatory variable; outcome, outcome variable; and UA, uric acid.

the risk of development of hypertension.[14–17] Increased arterial stiffness increases the amplitude of the forward pressure wave ejected from the heart and augments the pressure wave reflection from more peripheral sites on the arterial tree.[18,19] These phenomena elevate the BP. Renal dysfunction elevates the BP via several mechanisms such as sodium retention, sympathetic activation, etc.[6,20] Inflammation is also a risk factor for the development of hypertension via several mechanisms.[21]

Conventional observational studies, in which the relevant assessments are conducted at 2 observational points, have the limitation that they exclude the effects of time-varying confounders on the association of the explained variables with the outcome variables.[7] Therefore, to minimize the effects of time-varying confounders, analysis of repeated measures data by MML regression analysis is performed. Although Canepa et al[3] reported a significant longitudinal association of hyperuricemia with the PWV based on the results of MML analysis, MML analysis of repeated measures data to determine the longitudinal association of hyperuricemia with renal function decline or inflammation has not been conducted until now. The analyses in the present study revealed independent longitudinal associations between hyperuricemia and elevation of the baPWV, decline of the eGFR, and elevation of the serum CRP levels. Thus, hyperuricemia seems to show an independent longitudinal association with the worsening of these risk factors for the development of hypertension.

Hyperuricemia and Development of Hypertension

Recent meta-analyses conducted by Grayson et al[1] and Wang et al[2] revealed hyperuricemia as a risk factor for incident hypertension, independent of the traditional risk factors for hypertension. In addition, experimental studies have demonstrated that hyperuricemia contributes to the development of hypertension via activation of the renin-angiotensin system, increased oxidative stress, loss of nitric oxide synthase activity, renal microvascular changes, etc.[6,22,23] However, the mechanisms underlying the risk of hypertension associated with hyperuricemia in clinical settings still remain unclear. Gaffo et al[24] proposed the existence of a causal association of hyperuricemia with cardiovascular disease, both independent and that mediated by other risk factors for cardiovascular disease. Therefore, we considered it possible that hyperuricemia would also show a causal association (ie, both independent and that mediated by other risk factors) with the new onset of hypertension.

In relation to the risk of development of hypertension associated with hyperuricemia, hyperuricemia per se as well as other physiological abnormalities associated with hyperuricemia, such as increased arterial stiffness, may be involved

Table 4. Results of Logistic Regression Analysis Performed to Examine the Predictive Value of the Variables for the New Onset of Hypertension by the End of the Study Period

Parameter	Odds Ratio	95% Confidence Interval	*P* Value
Crude			
UA, per mg/dL increase	1.41	1.30–1.53	<0.01
baPWV, per m/sec increase	1.74	1.63–1.87	<0.01
eGFR, per 10 mL/min per 1.73 m^2 increase	0.67	0.61–0.75	<0.01
CRP, per 0.1 mg/L increase	4.43	2.04–9.59	<0.01
Covariates adjusted for (UA, baPWV, eGFR, and CRP were entered simultaneously in the same model)			
Model A			
UA, per mg/dL increase	1.25	1.13–1.38	<0.01
baPWV, per m/sec increase	1.38	1.27–1.50	<0.01
eGFR, per 10 mL/min per 1.73 m^2 increase	0.64	0.82–1.13	0.64
CRP, per 0.1 mg/L increase	0.97	0.36–2.65	0.97
Model B			
UA, per mg/dL increase	1.24	1.12–1.37	<0.01
baPWV, per m/sec increase	1.48	1.36–1.62	<0.01
eGFR, per 10 mL/min per 1.73 m^2 increase	0.98	0.84–1.16	0.84
CRP, per 0.1 mg/L increase	1.03	0.38–2.79	0.96
Hyperuricemia			
Crude	2.23	1.81–2.75	<0.01
Model A	1.50	1.14–1.97	<0.01
Model B	1.47	1.12–1.94	<0.01

Adjusted=basic covariates (age, body mass index, heart rate, serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides, HbA1c [glycohemoglobin A1c], smoking history, drinking history, history of medication for hypertension, dyslipidemia, diabetes mellitus and hyperuricemia [for each of the above: not receiving medication=0, receiving medication=1], and the time [years from the baseline]) plus systolic blood pressure (Model A) or diastolic blood pressure (Model B) measured at the study baseline. baPWV indicates brachial-ankle pulse wave velocity; CRP, C-reactive protein, eGFR, estimated glomerular filtration rate; and UA, uric acid.

Table 5. Results of Generalized Estimating Equation Analysis to Assess the Longitudinal Associations of Clinical Variables With the New Onset of Hypertension

Outcome	Explain	Estimate	SE	*P* Value
Step 1				
newHypertension	UA	0.24	0.08	<0.01
newHypertension	baPWV	0.60×10^{-2}	0.05×10^{-2}	<0.01
newHypertension	eGFR	-0.40×10^{-1}	0.10×10^{-1}	<0.01
newHypertension	logCRP	3.40	0.37	<0.01
Step 2				
newHypertension	UA	0.03	0.10	0.81
newHypertension	baPWV	0.51×10^{-2}	0.06×10^{-2}	<0.01
newHypertension	eGFR	−0.01	0.01	0.32
newHypertension	logCRP	1.91	0.86	0.03

baPWV indicates brachial-ankle pulse wave velocity; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; newHypertension, new onset of hypertension; step 1, the analyses were conducted for each of the variables (UA, baPWV, eGFR, and logCRP) individually in the absence of adjustments for covariates; step 2, the analysis was conducted under the condition that each of the variables was entered simultaneously in the same model with adjustments for basic covariates (medication use for hypertension was excluded); and UA, uric acid.

in the risk of new onset of hypertension. In the present study, the results of the GEE analysis were as follows: (1) when the serum UA levels, baPWV, eGFR, and log-transformed serum CRP levels were entered individually into the GEE model as explanatory variables, each was found to have a significant independent longitudinal association with the new onset of hypertension; (2) when the above variables were entered simultaneously into the same model, baPWV, and log-transformed serum CRP levels, but not hyperuricemia or renal dysfunction, were identified as significant variables. In addition, although several experimental studies have demonstrated that inflammation plays a key role in the worsening of these physiological risk factors in association with hyperuricemia,[5] in the present study, the GEE analysis failed to demonstrate any significant interaction between the baPWV and logCRP in the risk of new onset of hypertension. Thus, increased arterial stiffness and inflammation, both of which were found to be associated with hyperuricemia, may show independent longitudinal associations with the development of hypertension.

Limitations of the Study

The present study had some limitations as follows: (1) recently Kuwabara et al[25] reported that women with hyperuricemia were at a higher risk of developing hypertension than men with hyperuricemia. In the present study, the number of women in the study population was small (n=634), and the serum UA levels did not show a significant odds ratio for the development of hypertension. Furthermore, racial and sex differences have been reported in the prevalence rate of hyperuricemia and also in the association of hyperuricemia with the development of hypertension.[26,27] Therefore, further studies are needed to confirm the generalizability of the present findings. (2) Recent Mendelian randomization analyses have reported conflicting results in regard to the causal association of hyperuricemia with cardiovascular outcomes, including high BP.[28,29] Thus, we could not clearly conclude from the results of the present study whether hyperuricemia is indeed a causal factor for the development of hypertension; (3) we did not examine the role of oxidative stress in the associations of hyperuricemia with hypertension/physiological abnormalities associated with hypertension[30]; (4) during the study period, the average serum UA levels decreased despite a significant increase of the subjects' body mass index and increase in the prevalence of alcohol drinking; one of the plausible explanations was the number of men receiving medication for hyperuricemia increased from 3.4% to 4.7% during the study period, although we remain unable to fully explain this finding.

Perspectives

Hyperuricemia is thought to be a multifaceted risk factor for the development of cardiovascular disease, including hypertension.[6,25] The results of the present study suggested the existence of longitudinal associations of hyperuricemia with an increase of the arterial stiffness and inflammation, and in turn, these hyperuricemia-related pathophysiological abnormalities were longitudinally associated with the development of hypertension. Thus, hyperuricemia seems to show a multifaceted longitudinal association with the development of hypertension, increased arterial stiffness and inflammation may be involved in the risk of development of hypertension associated with hyperuricemia. Further study is needed to examine whether PWV and serum CRP levels could serve as surrogate markers for reducing the risk of cardiovascular disease, including hypertension, associated with hyperuricemia.

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Disclosures

The sponsor (Omron Health Care Company) assisted in the data formatting (ie, the data of the brachial-ankle pulse wave velocity stored in the hard disc of the equipment used for measurement of the brachial-ankle pulse wave velocity was transferred to an Excel file). Other than this, however, the company played no role in the design or conduct of the study, that is, in the data collection, management, analysis or interpretation of the data, or in the preparation, review or approval of the article. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- In the present study, hyperuricemia was identified as having longitudinal associations with arterial stiffness and inflammation, and all of these factors, in turn, also showed independent longitudinal associations with the development of hypertension. Thus, the present study suggested that increased arterial stiffness and inflammation, but not renal dysfunction, may be involved in the risk of development of hypertension associated with hyperuricemia.

What Is Relevant?

- Hyperuricemia is a risk factor for the development of hypertension and was found to also be associated with other risk factors for the development of hypertension, such as increased arterial stiffness, renal dysfunction, or inflammation. However, no study has been conducted to examine whether these risk factors are involved in the risk of development of hypertension associated with hyperuricemia.

Summary

In 3274 Japanese men without hypertension at the study baseline, hyperuricemia was verified to be a risk factor for the development of hypertension. The study also revealed independent longitudinal associations of hyperuricemia with increased arterial stiffness, renal function decline, and inflammation. In turn, arterial stiffness and inflammation, but not renal function decline, were found to show independent longitudinal associations with the development of hypertension.

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