Research Paper

Impact of uric acid on incident hypertension: Sex-specific analysis in different age groups

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A R T I C L E   I N F O

A B S T R A C T

The aim of the present study is to evaluate the association of serum uric acid (UA) levels with the risk of incident hypertension among different age groups in men and women using a single large Japanese general cohort. The present study is based on annual health check-up program in Gunma, Japan. We studied 12,029 participants (mean age, 48 ± 9 years old; 31% women) free of prevalent cardiovascular disease and hypertension at baseline (2009). Hypertension was defined by self-report, hypertensive medication use, or measured BP $> 140/90$ mmHg at each visit. Discrete proportional hazards regression model was used to evaluate the association of UA level at baseline with incident hypertension through 2012 adjusted for age, gender, baseline blood pressure, and other CVD risk factors among different age decade groups in men and women. During follow-up of 3 years, 12% of the cohort (n = 1457) developed hypertension. UA was strongly associated with incident hypertension in the multivariable model in all participants. In age-stratified analysis, participants below 50 years of age in men had the significant association of UA with incident hypertension, whereas participants above 50 years did not. In women, participants above 40 years had the significant association, whereas participants below 40 years did not. The present data suggest that UA level is an independent predictor for incident hypertension among middle aged men below 50 years old and middle aged and the elderly women above 40 years.

1. Introduction

Hypertension is an important public health challenge because of its high frequency and concomitant risks of cardiovascular morbidity and mortality [1]. However, hypertension cases are mainly of essential hypertension, and the etiology of its onset remains unclear [2]. It is important to elucidate the pathophysiological mechanisms underlying hypertension and to discover new approaches for identifying individuals prone to hypertension development.

Serum uric acid (UA) have been proposed as a risk factor for incident hypertension [3–6], as well as cardiovascular disease [7]. Previous studies also have demonstrated the blood pressure is lowered by UA-lowering drugs [8]. However, there have been controversial results especially in the elderly regarding the blood pressure control by UA-lowering drug [9]. Also, attenuation of UA effect on blood pressure with increasing age has been reported [3]. Taken together, the impact of

UA with incident hypertension might differ in different age groups.

There is no study that assesses the effect of UA on incident hypertension among different age groups in both men and women. Thus, the aim of the present study is to assess the prospective association of serum UA levels with the risk of incident hypertension among different age groups in men and women using a single large Japanese general cohort.

2. Method

2.1. Study population

The present study is retrospective observational study based on annual health check-up program in Gunma, Japan. As shown in Fig. 1, we retrospectively screened 24,112 individuals >20 years old who had health check-up program at baseline (2009). Of these participants, we excluded participants who have missing data and those without follow-
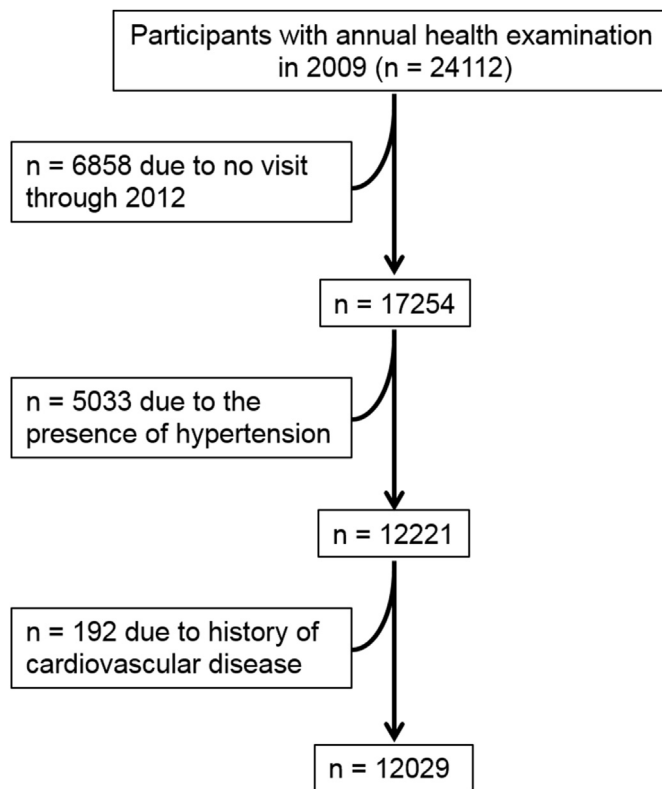

Fig. 1. Flow chart of the study participants.

up visit through 2012. We also excluded participants who had baseline hypertension, defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of any antihypertensive medication, and prevalent cardiovascular disease. Finally, a total of 12,029 participants free of prevalent hypertension and cardiovascular disease were included for the present study.

Compared with excluded participants, included participants were younger and less likely to be less cardiovascular risk factors (data not shown). The institutional ethics review boards of Gunma Chuo Hospital approved this study with waiver of consent.

2.2. Outcomes

We had two follow-up examinations in 2011 and 2012 annually. Resting systolic (SBP) and diastolic blood pressures (DBP) were measured in the seated position using an automated oscillometric sphygmomanometer. We defined incident hypertension as a SBP≥140 mmHg, DBP≥90 mmHg, or use of any antihypertensive medication, or self-reported hypertension during any of the follow-up examinations.

2.3. CVD risk factors assessment

During baseline examination, all participants completed standardized questionnaires to provide information about demographic variables, smoking history, and medication use for hypertension, diabetes, and dyslipidemia. Glucose and lipids were measured after a 12-h fast. Diabetes mellitus was defined as fasting glucose ≥126 mg/dl or use of insulin or oral hypoglycemic medication. Estimated glomerular filtration rate (eGFR) from serum creatinine concentrations using the Chronic Kidney Disease (CKD) Epidemiology Collaboration 2012 equation.

2.4. Statistical analysis

Continuous variables are shown as mean ± SD unless otherwise specified and categorical variables are shown as percentages.

Comparisons between participants with or without incident hypertension were performed using student's t-test and Mann-Whitney U test for normally and non-normally distributed data, respectively. Oneway ANOVA was used for comparison of continuous variables among more than 3 groups. Categorical variables are presented as frequencies and percentages and analyzed using χ^2 tests.

We used discrete proportional hazards (complementary log-log) regression models to estimate hazard ratios (HRs) for baseline serum UA levels with incident hypertension [10]. This model is similar to a Cox proportional hazards model, but is able to account for the time between the discrete time visits because the exact date of the development hypertension is unknown. Thus, this method is suitable for data based on annual check-up program in the present study. We show the HR for a 1 mg/dl increase of UA levels. Cox regression models using sex-specific UA quartile instead of continuous uric acid levels was also performed. We also conducted analyses stratified by age tertile groups (<40 years, 40–49 years, 50–59 years, and >60 years) in men and women. Model 1 adjusted for demographic factors (age, gender, height, and weight) and Model 2 adjusted for conventional cardiovascular risk factors (systolic blood pressure, diabetes mellitus, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and eGFR) adding to Model 1.

A 2-tailed p value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 14.0 (Stata Corp LP, College Station, TX).

3. Results

3.1. Participant characteristics

Demographic and clinical parameters at baseline for participants is presented in Table 1. The study population was 41% female with mean age of 48 ± 9 years. The mean serum UA at baseline was 5.2±1.4 mg/dl (5.9±1.2 for male, and 4.3±0.9 for female). A total of 1457 participants (12%) experienced incident hypertension over an average of 3 years follow-up. Participants with incident hypertension were older and more likely to be male, diabetic, and active smokers, and more likely to have increased body mass index, LDL cholesterol and blood pressures, and decreased HDL compared to participants without events. UA levels were greater in participants with incident hypertension among both gender. Participants with higher UA levels were more likely to have greater cardiovascular risk profile (Supplemental Table 1). Participants in the

Table 1
Baseline characteristics stratified by incident hypertension.

	All participants	no HTN	HTN	p value
	(n = 12029)	(n = 10572)	(n = 1457)	
Age, years	48 (9)	47 (9)	51 (9)	<0.001
Female, %	41	43	27	<0.001
Height, cm	165 (9)	165 (9)	166 (8)	<0.001
Weight, kg	62 (11)	61 (11)	65 (12)	<0.001
BMI, kg m^{-2}	22.6 (3.1)	22.4 (3.0)	23.7 (3.3)	<0.001
Current Smoking, %	33	32	37	<0.001
LDL, mg dl^{-1}	127 (33)	126 (33)	132 (33)	<0.001
HDL, mg dl^{-1}	65 (17)	65 (17)	62 (16)	<0.001
eGFR, ml min^{-1} per 1.73 m^2	84.1 (13.9)	84.3 (13.8)	82.4 (14.2)	<0.001
Fasting Glucose, mg dl^{-1}	93 (18)	92 (16)	98 (26)	<0.001
SBP, mmHg	119 (11)	118 (11)	128 (8)	<0.001
DBP, mmHg	75 (8)	74 (8)	81 (6)	<0.001
Uric acid, mg dl^{-1}	5.2 (1.4)	5.2 (1.3)	5.7 (1.4)	<0.001
Male	5.9 (1.2)	5.9 (1.2)	6.1 (1.3)	<0.001
Female	4.3 (0.9)	4.3 (0.9)	4.6 (1.0)	<0.001

Values are mean (SD) or %. BMI indicates body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; HTN, hypertension.

Table 2
Hazard ratios of the uric acid for incident hypertension.

	no.of events	Unadjusted HR (95% CI)	Model1 HR (95% CI)	Model2 HR (95% CI)
Continuous				
total n = 12029	1457	1.27 (1.23–1.32)*	1.21 (1.15–1.27)*	1.14 (1.09–1.20)*
Categorical				
Q1 (n = 3406)	334	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2 (n = 2869)	295	1.05 (0.90–1.23)	1.05 (0.90–1.23)	0.98 (0.84–1.15)
Q3 (n = 2893)	365	1.30 (1.12–1.51)*	1.33 (1.15–1.54)*	1.21 (1.04–1.41)†
Q4 (n = 2861)	463	1.72 (1.50–1.98)*	1.74 (1.51–2.00)*	1.44 (1.25–1.67)*

Hazard ratios are indicated per 1 mg/dl increase for continuous uric acid level, and each quartile compared to lowest quartile. Adjustment was performed for the following risk factors: model 1 = adjusted for age, gender, height, and weight; model 2 = model 1 + systolic blood pressure, diabetes, smoking, LDL cholesterol, HDL cholesterol, and eGFR.
Q1 indicates lower quartile for uric acid; Q4, highest quartile; HR, hazard ratio; other abbreviation as in Table 1.
*p < 0.001, †p < 0.05.

higher age group had higher blood pressure. In men, older participants had lower serum UA, whereas older women had higher UA, compared to younger participants (Supplemental Table 2).

3.2. Relationship of uric acid with incident hypertension

Discrete proportional hazards models for all participants are presented in Table 2. In univariate analysis, UA was associated with incident hypertension in all participants. This association of UA with incident hypertension was maintained after adjusting for CVD risk factors (HR, 1.14; 95% CI, 1.09 to 1.20; p < 0.001; per 1 mg/dl increase for UA). Hazard ratio for highest sex-specific quartile group for UA was 1.44 (95% CI; 1.25–1.67) compared with lowest quartile. Similar results were obtained in models using diastolic blood pressure, or both systolic and diastolic blood pressure instead of systolic blood pressure (data not shown). In sex-stratified analysis, HR of women in association of UA with incident hypertension had trend to be higher that of men (HR 1.23 for women, 1.10 for men in multivariable models), but there was no significant interaction of UA with sex in its association with incident hypertension using multiplicative interaction terms (p = 0.08, Table 3)

3.3. Age stratified analysis in men and women

In analyses stratified by baseline age category, we observed that the significant association of UA with incident hypertension among participants below 50 years of age in men, whereas not among participants above 50 years, in multivariable models, respectively (Table 3). In women, there was significant association of UA with incident hypertension among participants above 40 years), whereas not among participants below 40 years (Table 3). In the models using diastolic blood pressure, or both systolic and diastolic blood pressure instead of systolic blood pressure, the associations in 40–50 years in men and above 60 years old in men maintained, whereas the associations in below 40 years in men and below 60 years in women were absent (data not shown).

4. Discussion

The present study evaluates the association of serum UA levels with incident hypertension at short-term (3 years) follow up in a large Japanese general population, using discrete proportional hazards regression models based on annual health check-up data. UA was a significant predictor for incident hypertension independent of other risk factors including baseline blood pressure in the overall population. When we evaluated this association of serum UA with incident hypertension according to different age groups (<40, 40–49, 50–59, ≥60 years), it was only significant in the non-elderly population under 50 years old for men, whereas it was significant in the middle age and the elderly population above 40 years old for women.

The relationship between serum UA and incident hypertension has been explored extensively at short term and long term in different ethnicity [3,6,11,12]. We found that serum UA was associated with incident hypertension at short-term follow-up (3 years) in the Japanese population. The strength of the association was modest in our study (a 14% increased hazard ratios of hypertension incidence 1 mg/dl increment in UA) in the multivariable model and consistent with previous reports from Framingham study that is similar to participants characteristics (mean age 48.7 years old) and follow-up period (4 years). Several mechanisms between serum UA and hypertension have been noted. In experimental studies, hyperuricemia induces renal vascular in renal vasoconstriction through a reduction in nitric oxide, with activation of renin-angiotensin system [13,14].

The present study demonstrated that sex specific association of serum UA with incident hypertension in different age groups: in men, higher serum UA was associated with incident hypertension only in participants with under 50 years of age, not in those with above 50 years, whereas women, that association was significant in participants with over 40 years of age. In regards to men, the results in the present study are consistent with the previous study that showed the positive relationship of UA with blood pressure only in the non-elderly in cross-sectional analysis [15]. There are several potential explanations for the attenuation of the relationship of UA with hypertension in the elderly men. Previous studies showed that the effects of serum UA might be more evident at a younger age [3,16]. Higher background rate of the hypertension incidence with increasing age

Table 3
Age stratified analysis for the association of UA with incident hypertension in men and women.

	n	no. of incident hypertension	HR	95%CI		p
Male						
Total	7,112	1,057	1.1	1.04	1.17	<0.001
age subgroups						
<40 years	1,769	148	1.14	0.98	1.32	0.084
40-50 years	2,654	378	1.17	1.07	1.28	0.001
50-60 years	1,881	360	1.07	0.96	1.19	0.201
≥60 years	808	171	1.03	0.9	1.18	0.686
Female						
Total	4,917	400	1.23	1.1	1.38	<0.001
age subgroups						
<40 years	937	31	1.05	0.66	1.67	0.66
40-50 years	1,902	130	1.29	1.07	1.56	0.009
50-60 years	1,436	148	1.21	1	1.47	0.053
≥60 years	642	91	1.34	1.04	1.73	0.023

Hazard ratios are indicated per 1 mg/dl increase for uric acid level. Adjustment was performed for the following risk factors: model 1 = adjusted for age, gender, height, and weight; model 2 = model 1 + systolic blood pressure, diabetes, smoking, LDL cholesterol, HDL cholesterol, and eGFR.
Q1 indicates lower quartile for uric acid; Q4, highest quartile; HR, hazard ratio; other abbreviation as in Table 1.

or other risk factors might have contributed to a reduction in the relationship of UA with hypertension [3].

Several previous studies demonstrated that the cardiovascular risk in women increases in postmenopause period [17–19], because estrogen has protective effects on vessel function through nitric oxide release and an antiproliferative effect on smooth muscle cells [17]. These estrogen's effect might lessen the impact of UA on blood pressure progression, and reduction of these estrogen's effect around postmenopause period might be the one of the reason for the significant association of serum UA with incident hypertension in women after middle age in the present study.

Our study has limitations. The definition for incident hypertension is based on annual physical examination visit. Because annual health examination is in part dependent of own health consciousness in each participants, the participants at baseline represent a relatively healthy sample who take care of their health. Thus, generalization of the study results is limited by selection and survival bias. Second, we cannot exclude the possibility that participants took lower uric acid medication because we only evaluated the medication for hypertension, diabetes, and dyslipidemia in the present study. The strength of our study is a large sample size and repeated measures of cardiovascular risk factors including uric acid.

5. Conclusion

In the present study based on annual health check-up, higher uric acid is independently associated with greater risk of incident hypertension in the Japanese general population. The present study also confirmed the sex-specific effect on the relationship of serum uric acid levels with incident hypertension in different age groups; baseline serum uric acid level could be an independent predictor among middle aged men below 50 years and middle aged and the elderly women above 40 years. It is important to detect the age/gender groups which would obtain maximal benefit from the treatment of hyperuricemia for the prevention and treatment of hypertension. Future prospective studies and clinical trials are needed to determine whether uric acid is a potential screening and therapeutic target.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2019.100009.

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