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URIC ACID IS A STRONG RISK MARKER FOR DEVELOPING HYPERTENSION FROM PREHYPERTENSION

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ABSTRACT

Prehypertension frequently progresses to hypertension, a condition associated with high morbidity and mortality from cardiovascular diseases and stroke. However, the risk factors for developing hypertension from prehypertension remain poorly understood. We conducted a retrospective study using the data from 2008 to 2017 prehypertensive Indian adults (52.1±11.0 years, 1040 men) found to be prehypertensive in 2008 and reexamined in 2017. We calculated the cumulative incidences of hypertension over 09years, examined risk factors and calculated odds ratios (ORs) for developing hypertension after adjustments for age, sex, body mass index, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, chronic kidney disease, and serum uric acid levels. The additional analysis evaluated whether serum uric acid (hyperuricemia) constituted an independent risk factor for developing hypertension. The cumulative incidence of hypertension from prehypertension over 9 years was 25.3%. There were no significant differences between women and men (24.4% versus 26.0%; *P*=0.28). The cumulative incidence of hypertension in subjects with hyperuricemia (n=363) was significantly higher than those without hyperuricemia (n=1279; 30.7% versus 24.0%; *P*<0.001). After multivariable adjustments, the risk factors for developing hypertension from prehypertension were age (OR, 1.023; *P*<0.001), female sex (OR, 1.595; *P*<0.001), higher body mass index (OR, 1.051; *P*<0.001), higher baseline systolic (OR, 1.072; *P*<0.001) and diastolic blood pressure (OR, 1.085; *P*<0.001), and higher serum uric acid (OR, 1.149; *P*<0.001). Increased serum uric acid is a strong risk marker for developing hypertension from prehypertension. Further studies are needed to determine whether treatment of hyperuricemia in prehypertensive subjects could impede the onset of hypertension.

INTRODUCTION

Hyperuricemia (elevated serum uric acid) has emerged as one of the strongest risk factors for the development of prehypertension[1,2] primary hypertension,[2,3] and resistant hypertension[4] Experimentally raising uric acid in rats also causes hypertension[5] Moreover, pilot clinical studies suggest lowering serum uric acid has been reported to lower blood pressure in hypertensive and prehypertensive children and adults in several studies although this has not been observed universally[13] This, coupled with associations of uric acid with insulin resistance/diabetes mellitus, stroke, heart disease, and chronic kidney disease, has led to interest in uric acid as a potentially modifiable cardiovascular risk factor[14,15] If hyperuricemia has a contributory role in cardiovascular disease, then it may make sense to reduce serum uric acid as a means to prevent the development of hypertension and cardiovascular disease. In this regard, a trial to lower serum uric acid in normotensive subjects may require a large sample size because the rate of progression to hypertension over a 9-year period is relatively low. However, if hyperuricemia remains a risk factor in prehypertensive subjects for the development of hypertension, then it may be possible to perform a study with sufficient power because the risk for developing hypertension is substantially higher. We therefore performed a study in a large population with prehypertension to determine the risk for developing

hypertension after 9 years, with an especial focus on the role of uric acid. Our study suggests that prehypertensive subjects with an elevated serum uric acid are especially at risk for developing hypertension and therefore may be an ideal target population to determine whether urate-lowering therapy can prevent the development of hypertension.

METHODS

Study Design and Study Subjects

This study is a large-scale, retrospective, single-center cohort study in India. The database was from Dept of Medicine, UP University of Medical Sciences, India(DEPT MED UPUMS INDIA)subjects who underwent annual medical examinations in 2008 and were reevaluated 9 years later. When the subjects had >1 annual examination, we only used the first examination of that year to avoid double counts. Every subject had the same workup, including medical history, routine physical examination, and blood and urine tests collected in this database.[16,19]

In the present studies, we included subjects between ages 30 and 80years old in 2008 whose data were available in both 2004 and 2017. Subjects <30 years old were excluded because of their modest risk for hypertension and cardiovascular diseases, whereas subjects aged ≥80 years old have a substantial risk for death over 9-year follow-up. Of the 6600 subjects, only 60 subjects were <30 years old and 5 subjects were ≥80 years old in 2008. Subjects (6600) were enrolled at the first step, 1300 subjects with hypertension (652 subjects on medication for hypertension) at the baseline were excluded. Finally, we analyzed 3444 subjects with normotensive (blood pressure<120/80 mm Hg; age, 47.7±10.3 years old; 37.1% men) and 1792 prehypertensive subjects (age, 52.1±11.0 years old; 58.1% men) in 2008 separately.

We evaluated the cumulative incidence of hypertension from normal blood pressure and prehypertension over 9years. Moreover, we evaluated risk factors for developing hypertension from prehypertension over 9 years and calculated odds ratios (ORs). The distribution of serum uric acid levels differed between men and women, and these analyses were also stratified by sex. We also divided the study population into quartiles according to the serum uric acid levels by sex and compared the risk of developing hypertension from prehypertension between each quartile. Additionally, we compared cumulative incidence of hypertension from prehypertension over 9 years between hyperuricemia and normouricemia after excluding subjects with hypouricemia (serum uric acid levels <3 mg/dL) or diabetes mellitus because hypouricemia sometimes become a risk for hypertension and diabetes mellitus causes decreasing serum uric acid by excretion of urine uric acid. Moreover, to exclude the sampling bias, we also conducted a subanalysis using propensity score–matching model to check that hyperuricemia becomes a risk for developing hypertension from prehypertension.

Definition of Terms: Hypertension, Prehypertension, Diabetes Mellitus, Dyslipidemia, Chronic Kidney Disease, and Hyperuricemia

Hypertension is defined as a condition when subjects are on current antihypertensive medication or on systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg[20,21] Blood pressure readings were obtained using an automatic brachial sphygmomanometer which was upper arm blood pressure measuring and had passed validation. Two blood pressure examinations were taken after the participants were seated and rested quietly for >5 minutes with their feet on the ground and their back supported. The mean systolic and diastolic blood pressure of each of the subjects were calculated from the recorded measurements. Prehypertension is defined as a condition when subjects have a systolic blood pressure between 120 and 139 mm Hg or a diastolic blood pressure between 80 and 89 mm Hg.[21,22]

Diabetes mellitus is defined as current diabetes mellitus on medication use or HbA1c (National Glycohemoglobin Standardization Program) ≥6.5%, according to International Expert Committee.[23] Dyslipidemia is defined as current medication use for dyslipidemia or low-density lipoprotein cholesterol ≥130 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men and<50mg/dl in women and triglyceride ≥150 mg/dL, according to Inernational Atherosclerosis Society guidelines[24]

Chronic kidney disease is defined as estimated glomerular filtration rate (eGFR) <60 mL·min·1.73 m^2. We calculated eGFR using the Japanese GFR equation: eGFR (mL·min·1.73 m^2)=194×serum creatinine$^{-1.094}$×age$^{-0.287}$ (×0.739 if woman).[25] Hyperuricemia is defined as serum uric acid level >7.0 mg/dL in men and ≥6.0 mg/dL in women.[23,26–30]

Statistical Analysis

The statistically significant level was set at probability P<0.05 (2 sided). Data are expressed as mean±SD or as percent frequency unless otherwise specified. Comparisons between 2 groups were performed with Student *t* tests for normally distributed variables and χ^2 analyses for categorical data. The risk factors for developing hypertension from normal blood pressure or prehypertension in the period of over 9 years were evaluated both by crude models and by multivariable logistic regression models with adjustments for age, sex, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, body mass index (BMI), diabetes mellitus, dyslipidemia, chronic kidney disease, and serum uric acid (or hyperuricemia), and ORs were analyzed in each group. All analyses were stratified by sex. The cumulative incidences of hypertension from normal blood pressure

or prehypertension over 9 years were compared between the subjects with and without hyperuricemia. When we analyzed the quartile of serum uric acid levels, the lowest quartile served as the reference group. When we conducted a propensity-matching analysis, we divided the study subjects into between with and without hyperuricemia at the baseline with adjustments of age, BMI, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, and chronic kidney disease at the baseline by propensity score–matching model. We checked the main outcome of the development of hypertension from prehypertension over 9 years. All the statistical analyses were performed using the SPSS Statistics software.

RESULTS

Demographics of This Study Subjects

Table 1 shows the demographics for men and women with normal blood pressure and prehypertension. Compared to men with normal blood pressure, women were younger, had a lower BMI, lower systolic and diastolic blood pressure, faster pulse rate, low prevalence of smoking and drinking habits, diabetes mellitus, dyslipidemia, hyperuricemia, chronic kidney disease, lower white blood cell counts, hemoglobin, eGFR, C-reactive protein, and serum uric acid levels (Table 1). In contrast, women with prehypertension were older than men, but the other tendencies are similar compared with normal blood pressure group (Table 1).

Table 1: Demographics of Study Subjects With Prehypertension in 2008.

	Total	Women	Men	*P* Value
Normal blood pressure				
No. of subjects	3444	2165	1278	
Age	47.7±10.3	46.8±9.9	49.2±10.8	<0.001
Height, cm	162.7±8.2	158.1±5.5	170.5±5.9	<0.001
Weight, kg	57.0±10.5	51.3±6.6	69.7±8.5	<0.001
Body mass index, kg/m^2	21.4±2.7	20.5±2.4	22.9±2.5	<0.001
Systolic BP, mm Hg	105.6±8.8	104.0±9.0	108.3±7.6	<0.001
Diastolic BP, mm Hg	66.0±6.5	64.7±6.6	68.3±5.7	<0.001
Pulse rate, bpm	71.9±9.5	73.4±9.6	69.3±8.9	<0.001
Smoking	35.1%	18.3%	63.4%	<0.001
Drinking habits	39.2%	27.9%	58.4%	<0.001
Diabetes mellitus	2.3%	0.9%	4.6%	<0.001
Dyslipidemia	28.9%	20.7%	42.7%	<0.001
Hyperuricemia	11.4%	4.4%	23.2%	<0.001
Chronic kidney disease	2.0%	1.5%	2.9%	<0.001
White blood cell, μL^{-1}	5062±1376	4831±1207	5454±1666	<0.001
Hemoglobin, g/dL	13.3±1.3	12.6±1.0	14.5±0.9	<0.001
Total protein, g/dL	7.08±0.35	7.09±0.36	7.08±0.34	0.24
eGFR, mL·min·1.73 m^2	87.6±15.2	89.6±15.4	84.2±14.3	<0.001
C-reactive protein, mg/dL	0.13±0.21	0.12±0.18	0.15±0.25	<0.001
Serum uric acid, mg/dL	5.00±1.32	4.35±0.88	6.10±1.19	<0.001
Prehypertension				
No. of subjects	3584	1503	2081	
Age	52.1±11.0	53.0±10.5	51.5±11.3	<0.001
Height, cm	164.4±8.9	156.6±5.4	170.0±6.2	<0.001
Weight, kg	63.3±12.0	54.3±8.3	69.8±9.8	<0.001
Body mass index, kg/m^2	23.3±3.1	22.1±3.1	24.1±2.8	<0.001
Systolic BP, mm Hg	127.7±5.8	127.4±5.7	127.9±5.8	0.007
Diastolic BP, mm Hg	79.3±5.2	78.4±5.3	79.9±5.1	<0.001
Pulse rate, bpm	74.8±10.8	78.1±11.1	72.4±10.0	<0.001
Smoking	40.8%	13.6%	60.5%	<0.001
Drinking habits	45.5%	23.9%	61.1%	<0.001
Diabetes mellitus	4.4%	2.7%	5.5%	<0.001
Dyslipidemia	47.5%	41.7%	51.7%	<0.001
Hyperuricemia	20.3%	8.7%	28.6%	<0.001
Chronic kidney disease	3.5%	2.6%	4.2%	0.008
White blood cell, μL^{-1}	5298±1373	4987±1244	5522±1418	<0.001
Hemoglobin, g/dL	13.9±1.3	12.9±1.1	14.7±1.0	<0.001
Total protein, g/dL	7.21±0.35	7.09±0.36	7.17±0.34	<0.001
eGFR, mL·min·1.73 m^2	85.1±15.6	86.9±15.6	83.8±15.5	<0.001
C-reactive protein, mg/dL	0.16±0.32	0.14±0.27	0.17±0.35	0.019

Serum uric acid, mg/dL	5.59±1.39	4.63±0.95	6.29±1.23	<0.001

Specifically, we evaluated 3444 normotensive Indian adults (30–80 years old) whose records were available and determined the cumulative incidence of hypertension over a 9-year period. Among this population, the cumulative incidence of hypertension was 2.9%, with a higher incidence in men than women (3.8% versus 2.4%; *P*=0.002). Subjects with hyperuricemia (n=392) had significantly higher cumulative incidence of hypertension than those without hyperuricemia (5.6% versus 2.6%; *P*<0.001). After stratification by sex, the higher cumulative incidence of hypertension in normotensive subjects with hyperuricemia was observed both in women (6.9% versus 2.2%; *P*<0.001) and men (5.2% versus 3.3%; *P*=0.036). The threshold level (defined as higher incidence of hypertension than the mean) of serum uric acid for developing hypertension from normal blood pressure was> 7.0 mg/dL in men and >6.0 mg/dL in women. The overall relative risk for hyperuricemia for developing hypertension was 2.27, which is in alignment with prior studies.

A, Normal blood pressure. The cumulative incidence of hypertension over 9 y and the number of subjects (n) were 5.6% (n=392) in total with hyperuricemia, 2.6% (n=3052) in total without hyperuricemia, 6.9% (n=95) in women with hyperuricemia, 2.2% (n=2070) in women without hyperuricemia, 5.2% (n=297) in men with hyperuricemia, and 3.3% (n=982) in men without hyperuricemia. **B**, Prehypertension. The cumulative incidence of hypertension over 9 y and the number of subjects (n) were 30.7% (n=363) in total with hyperuricemia, 24.0% (n=1429) in total without hyperuricemia, 38.2% (n=65) in women with hyperuricemia, 23.1% (n=686) in women without hyperuricemia, 29.1% (n=298) in men with hyperuricemia, and 24.8% (n=743) in men without hyperuricemia.

Cumulative Incidences of Hypertension From Prehypertension Over 9 Years

The cumulative incidence of hypertension from prehypertension over 9 years was 25.3%. There were no significant differences in the cumulative incidences of hypertension between women and men (24.4% versus 26.0%; *P*=0.28). The cumulative incidence of hypertension in subjects with hyperuricemia (n=363) was significantly higher than those without hyperuricemia (n=1429 30.7% versus 24.0%; *P*<0.001). After stratification by sex, the higher cumulative incidence of hypertension in prehypertensive subjects with hyperuricemia was evident in both women (38.2% versus 23.1%; *P*<0.001) and men (29.1% versus 24.8%; *P*<0001; Subjects with higher baseline serum uric acid level had higher cumulative incidences of hypertension over 9 years both in women and men except for hypouricemic women (serum uric acid levels <2.0 mg/dL;). For women, the risk for hypertension rose rapidly with serum uric acid levels over 5 mg/dL, with 50% of women with a serum uric acid of 7 mg/dL developing hypertension and nearly 65% of women with a serum uric acid of 8 mg/dL or greater. In contrast, the risk of developing hypertension with increasing serum uric acid levels was less in men, and a level of ≥7 mg/dL carried a risk of about 30% that did not increase significantly at higher levels of serum uric acid. The threshold level of serum uric acid for developing hypertension from prehypertension was 7.0 mg/dL in men and 6.0 mg/dL in women.

Risk Factors for Developing Hypertension From Prehypertension Over 9 Years

We conducted a multivariable logistic regression analyses and calculated ORs for developing hypertension from prehypertension in each group with adjustments for age, sex, BMI, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, chronic kidney disease, and serum uric acid (or hyperuricemia). The risk factors for developing hypertension from prehypertension over 9years were age (OR per 1 year increased, 1.023; 95% CI, 1.015–1.032), female sex (OR versus male sex, 1.595; 95% CI, 1.269–2.005), higher BMI (OR per 1 kg/m^2 increased, 1.051; 95% CI, 1.021–1.081), higher baseline systolic blood pressure (OR per 1 mm Hg increased, 1.072; 95% CI, 1.055–1.089) and diastolic blood pressure (OR per 1 mm Hg increased, 1.085; 95% CI, 1.065–1.106), lower pulse rate (OR per 1 bpm increased, 0.991; 95% CI, 0.983–1.855), and higher serum uric acid (OR per 1 mg/dL increased, 1.149; 95% CI, 1.066–1.238; Table 2). When analyses were separated by sex, the results were similar, except that BMI in women and pulse rate in both women and men did not become risks for developing hypertension from prehypertension (Table 2). Moreover, we conducted subanalyses using eGFR, fasting blood glucose, and HbA1c instead of chronic kidney disease and diabetes mellitus (Table S1). The results gave similar results as our primary analyses (Table 2).

Table 2. Risk Factors for Developing Hypertension From Prehypertension Over 9 Years.

	Crude			Adjusted		
	OR	**95% CI**	***P* Value**	**OR**	**\95% CI**	***P* Value**
Total*						
Age, per 1 y increased	1.024	1.017–1.031	<0.001	1.023	1.015–1.032	<0.001
Female sex vs male sex	0.920	0.789–1.072	0.283	1.595	1.269–2.005	<0.001
Body mass index, per 1 kg/m^2 increased	1.066	1.041–1.092	<0.001	1.051	1.051–1.081	<0.001
Smoking (positive vs negative)	1.200	1.031–1.397	0.019	1.103	0.914–1.330	0.31
Drinking habits (positive vs negative)	1.100	0.946–1.279	0.216	1.075	0.897–1.289	0.43
Baseline systolic BP, per 1 mm Hg increased	1.115	1.100–1.131	<0.001	1.072	1.055–1.089	<0.001
Baseline diastolic BP, per 1 mm Hg increased	1.128	1.109–1.147	<0.001	1.085	1.065–1.106	<0.001
Pulse rate, per 1 bpm increased	0.995	0.998–1.002	0.15	0.991	0.983–0.999	0.030
Diabetes mellitus (positive vs negative)	1.502	1.067–2.114	0.020	1.277	0.878– 1.855	0.20
Dyslipidemia (positive vs negative)	1.098	0.944–1.276	0.22	0.857	0.724–1.014	0.073
Chronic kidney disease (positive vs negative)	1.047	0.699–1.570	0.82	0.700	0.449–1.089	0.114
Serum uric acid, per 1 mg/dL increased	1.125	1.066–1.188	<0.001	1.149	1.066–1.238	<0.001
Hyperuricemia (positive vs negative)	1.406	1.175–1.683	<0.001	1.348	1.101–1.650	0.004
Women†						
Age, per 1 y increased	1.030	1.018–1.042	<0.001	1.028	1.014–1.043	<0.001
Body mass index, per 1 kg/m^2 increased	1.075	1.037–1.115	<0.001	1.041	0.998–1.086	0.064
Smoking (positive vs negative)	1.101	0.785–1.543	0.58	1.039	0.718–1.503	0.84
Drinking habits (positive vs negative)	1.089	0.829–1.431	0.541	1.256	0.918–1.718	0.15
Baseline systolic BP, per 1 mm Hg increased	1.125	1.100–1.149	<0.001	1.080	1.053–1.107	<0.001
Baseline diastolic BP, per 1 mm Hg increased	1.130	1.101–1.160	<0.001	1.085	1.054–1.118	<0.001
Pulse rate, per 1 bpm increased	0.998	0.987–1.008	0.66	0.993	0.981–1.005	0.26
Diabetes mellitus (positive vs negative)	2.026	1.069–3.837	0.030	1.593	0.799–3.176	0.186
Dyslipidemia (positive vs negative)	1.227	0.968–1.556	0.091	0.796	0.602–1.053	0.109
Chronic kidney disease (positive vs negative)	0.671	0.294–1.533	0.344	0.443	0.180–1.089	0.076
Serum uric acid, per 1 mg/dL increased	1.386	1.224–1.569	<0.001	1.242	1.080–1.429	0.002
Hyperuricemia (positive vs negative), ≥6.0 mg/dL	2.054	1.413–2.987	<0.001	1.513	1.003–2.282	0.048
Men†						
Age, per 1 y increased	1.021	1.012–1.030	<0.001	1.02	1.010–1.030	<0.001
Body mass index, per 1 kg/m^2 increased	1.061	1.025–1.098	<0.001	1.056	1.015–1.099	0.007
Smoking (positive vs negative)	1.242	1.013–1.521	0.037	1.133	0.910–1.411	0.27
Drinking habits (positive vs negative)	1.072	0.876–1.311	0.50	1.002	0.804–1.250	0.98
Baseline systolic BP, per 1 mm Hg increased	1.109	1.089–1.129	<0.001	1.068	1.046–1.090	<0.001
Baseline diastolic BP, per 1 mm Hg increased	1.129	1.104–1.154	<0.001	1.085	1.058–1.112	<0.001
Pulse rate, per 1 bpm increased	0.994	0.984–1.004	0.23	0.990	0.979–1.000	0.061
Diabetes mellitus (positive vs negative)	1.318	0.878–1.980	0.18	1.158	0.740–1.812	0.52
Dyslipidemia (positive vs negative)	1.005	0.826–1.223	0.96	0.886	0.714–1.099	0.27
Chronic kidney disease (positive vs negative)	1.224	0.765–1.958	0.40	0.836	0.499–1.401	0.50
Serum uric acid, per 1 mg/dL increased	1.085	1.002–1.176	0.046	1.101	1.006–1.204	0.037
Hyperuricemia (positive vs negative), >7.0 mg/dL	1.245	1.007–1.540	0.043	1.268	1.003–1.602	0.047

BP indicates blood pressure; CI indicates confidence interval; and OR, odds ratio.

*Data adjusted for age, sex, body mass index, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, chronic kidney disease, and serum uric acid (or hyperuricemia).

†Data adjusted for age, body mass index, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, chronic kidney disease, and serum uric acid (or hyperuricemia).

Serum Uric Acid as a Risk Factor for Developing Hypertension From Prehypertension

We calculated each serum uric acid quartile by sex to account for sex differences in serum uric acid levels. In men, subjects in the highest quartile (serum uric acid of ≥7.2 mg/dL) had 1.35-fold (95% CI, 1.023–1.768) higher OR of developing hypertension than those in the lowest quartile (serum uric acid of <5.6 mg/dL). Women in the third quartile (serum uric acid from 4.6–5.2 mg/dL) and the highest quartile (serum uric acid of ≥5.2 mg/dL) had 1.77-fold (95% CI, 1.231–2.556) and 2.40-fold (95% CI, 1.693–3.400) higher ORs of developing hypertension than those in the lowest quartile (serum uric acid of <4.0 mg/dL; Table 3). After adjustment for age, BMI, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, and chronic kidney disease, these ORs were 1.37 (95% CI, 1.008–1.859) in men, 1.66 (95% CI,

1.120–2.462) in the third quartile, and 1.97 (95% CI, 1.338–2.901) in the highest quartile in women compared with the lowest quartile (Table 3).

Table 3: Relative Odds of Developing Hypertension From Prehypertension Over 9Years by Serum Uric Acid Quartile.

	No. of Subjects	Cumulative Incidence, %	Crude			Adjusted*		
			OR	95% CI	*P* Value	OR	95% CI	*P* Value
Women								
First quartile (<4.0 mg/dL)	177	16.7	Reference			Reference		
Second quartile (≥4.0<4.6 mg/dL)	193	21.5	1.370	0.946–1.983	0.096	1.342	0.907–1.998	0.14
Third quartile (≥4.6<5.2 mg/dL)	180	26.2	1.774	1.231–2.556	0.002	1.661	1.120–2.462	0.012
Fourth quartile (≥5.2 mg/dL)	202	32.4	2.399	1.693–3.400	<0.001	1.970	1.338–2.901	<0.001
Men								
First quartile (<5.6 mg/dL)	138	24.4	Reference			Reference		
Second quartile (≥5.6<6.4 mg/dL)	133	25.3	1.050	0.797–1.384	0.73	1.086	0.811–1.454	0.85
Third quartile (≥6.4<7.2 mg/dL)	126	24.4	1.002	0.756–1.328	0.99	0.970	0.715–1.316	0.85
Fourth quartile (≥7.2 mg/dL)		30.2	1.345	1.023–1.768	0.034	1.369	1.008–1.859	0.044

CI indicates confidence interval; and OR, odds ratio.
*Data adjusted for age, body mass index, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, chronic kidney disease, and serum uric acid quartile.

Additionally, we also performed an analysis in which we excluded subjects with severe hypouricemia (who largely have a genetic cause[31,33] and may have increased risk for hypertension[34–36]) and diabetes mellitus (who often have low uric acid because of the effects of glycosuria[37]) because both groups may therefore alter the normal relationship of uric acid with hypertension. This analysis therefore excluded 16 hypouricemic subjects (5men and 11 women, defined as serum uric acid <3.0 mg/dL) and 78 diabetes mellitus subjects (58 men and 22 women, 1 man and 1 woman had both hyperuricemia and diabetes mellitus) from 1792 prehypertensive subjects, leaving 1688 subjects (978 men). The cumulative incidence of hypertension from prehypertension over 9 years in subjects with hyperuricemia was higher than those without hyperuricemia (30.4% versus 23.7%; $P<0.001$). The difference of cumulative incidence of hypertension between hyperuricemia and normouricemia in women (38.4% versus 22.8%; $P<0.001$) is much larger than in men (28.7% versus 24.5%; $P=0.054$).

Propensity Score–Matching Model

We conducted a subanalysis using propensity score–matching model. We divided the study subjects into between with and without hyperuricemia at the baseline with adjustments of age, BMI, smoking and drinking habits, baseline systolic and diastolic blood pressure, pulse rate, diabetes mellitus, dyslipidemia, and chronic kidney disease by propensity score–matching model (Table 4). The results showed that subjects with hyperuricemia had >20% higher incidence of hypertension from prehypertension over 9 years compared with those without hyperuricemia (30.1% versus 25.0%; $P=0.040$).

Table 4. Propensity Score–Matching Model.

	Normouricemia	Hyperuricemia	*P* Value
No. of subjects	344	344	
Age	51.3±11.0	51.6±11.1	0.57
Male sex	80.7%	81.1%	0.84
Height, cm	167.7±8.3	167.7±8.3	0.95
Weight, kg	69.2±11.4	69.2±11.2	0.97
Body mass index, kg/m^2	24.5±3.0	24.5±2.9	0.96
Systolic BP, mm Hg	128.1±5.9	128.1±5.9	0.96
Diastolic BP, mm Hg	79.8±5.2	79.7±5.2	0.94
Pulse rate, bpm	73.5±10.6	73.6±10.5	0.90
Smoking	54.7%	55.8%	0.66

Drinking habits	55.5%	56.4%	0.74
Diabetes mellitus	2.5%	3.1%	0.51
Dyslipidemia	61.5%	61.6%	0.96
Chronic kidney disease	6.1%	5.4%	0.56

Data are presented as mean±SD. The subjects with hyperuricemia had significantly higher cumulative incidence of hypertension from prehypertension over 5 y compared with those without hyperuricemia by $\chi 2$ analyses (30.1% vs 25.0%; P=0.040). BP indicates blood pressure.

DISCUSSION

The primary goal was to identify the major risk factors for developing hypertension in a large healthy Indian prehypertensive population. Higher baseline systolic blood pressure, diastolic blood pressure, increasing BMI, female gender, and age emerged as risk factors, as well as hyperuricemia. Over the 9-year period, ≈25% of the prehypertensive subjects developed hypertension. However, the striking finding was that, among prehypertensive subjects, a high serum uric acid further increased the risk for hypertension. Although in men the presence of hyperuricemia increased the risk to ≈35%, in women the increased risk for hypertension was much higher, with hypertension developing in 1.7-fold in the third serum uric acid quartile and 2.0-fold in the highest quartile compared with the lowest quartile, respectively. These results provide a framework of reference for the design and size of clinical trials aimed to evaluate whether urate-lowering therapies can prevent hypertension in prehypertensive subjects.

There is a report that uric acid is an independent predictor for developing prehypertension[1] However, our study is the first to evaluate whether the progression from prehypertension to hypertension is influenced by serum urate levels. Our primary finding was that, although hyperuricemic normotensive subjects had a >2-fold increased risk for developing hypertension over 5 years (5.6% versus 2.6%, respectively), the risk for developing hypertension in hyperuricemic prehypertensive subjects was much greater, even when compared with normouricemic prehypertensive subjects (30.7 versus 24.0%, respectively). Thus, our study suggests that targeting the prehypertensive hyperuricemic individual may be the ideal group to evaluate the role of urate lowering to prevent hypertension.

After multiple adjustments, the risk factors for developing hypertension from prehypertension continued to include age, female gender, higher BMI, higher baseline systolic and diastolic blood pressure, lower pulse rate, and higher serum uric acid but not smoking and drinking habits, diabetes mellitus, dyslipidemia, or chronic kidney disease. However, after stratification by sex, BMI in women and pulse rate in both women and men did not become risks for developing hypertension from prehypertension. These results suggest the importance of focusing on obesity, serum uric acid levels, and blood pressure as modifiable risk factors to delay or impede the development of hypertension. Unexpectedly, smoking and drinking habits, diabetes mellitus, dyslipidemia, and chronic kidney disease were not independent risk factors for developing hypertension in prehypertensive subjects. These factors are known to carry increased risks of cardiovascular disease but perhaps play an indirect role in the pathogenesis of hypertension in Indian population.

Another interesting finding is the greater risk for the development of hypertension carried by hyperuricemia in prehypertensive women than in prehypertensive men. It has been known for some time that for equivalent levels of serum uric acid, women tend to carry a greater risk for hypertension and kidney disease.[29,38,39] This may relate to differences in expression of urate transporters in nonrenal tissues[40] because SLC2A9, for example, is known to be differentially regulated in male and female mice.[41] Estrogen also decreases serum uric acid levels, and after menopause serum uric acid levels increase in women[34] The other hypothesis is that hyperuricemic women have large urate production with increased xanthine oxidative activity, which generates reactive oxygen products because molecular oxygen is used as an electron acceptor[42] These reactive oxygen products[13,45,46] combine nitric oxide and prevent vasodilation[43] Moreover, uric acid itself stimulates proliferation, angiotensin II production, and oxidative stress through the tissue renin-angiotensin system[44] In the results, hyperuricemic women had more risk for hypertension than hyperuricemic men.

Although early clinical trials of lowering uric acid in subjects has been promising[6,8.10,12], there have been negative studies[13,45,46], and Mendelian genetic studies have also not been able to show a relationship between serum uric acid and hypertension[47,48] However, the negative studies have generally been observed in subjects whose blood pressure is already under treatment, and the genetic studies are often limited by not considering other influencing conditions, such as diet. Moreover, the EURIKA study showed serum uric acid is a risk factor for resistant hypertension[4] Our study in prehypertensive (untreated) subjects underlines the need to design a definitive study to evaluate the role of lowering uric acid in the prevention of hypertension.

Our study has several limitations. First, this study is a retrospective single-center study, which may have introduced selection bias. On the other hand, single-center studies offer the advantage of the similarity of methodology. Second, this longitudinal study lacks time-to-event data, which precluded survival analysis. Third,

our study does not rule out that the effect of uric acid might be confounded by subtle changes in kidney function. Although we could not show chronic kidney disease or eGFR to be an independent risk factor in this study, this may be limited by the few patients with chronic kidney disease, or because including uric acid in the analysis may make kidney function not an independent risk factor because of the potential that they could both be working via the same mechanism. Thus, it remains possible that an elevation of serum uric acid may increase the risk for hypertension in part because a higher serum uric acid is associated with subtle renal dysfunction. Fourth, this study did not account for presence of metabolic syndrome, although we did include various components such as prehypertension, dyslipidemia, and diabetes mellitus. Although we recognized metabolic syndrome could be an important risk factor for hypertension, including these other variables could act as confounders, and hence we avoided performing such an analysis. Fifth, some hypertensive subjects might have white-coat hypertension and some nonhypertensive subjects might have home hypertension because we measured blood pressure only at the center. Ambulatory blood pressure monitoring is the best method for blood pressure evaluation, but it is difficult in practice in the setting of an annual medical examination. Finally, this is an observation study, and intervention studies are needed to clarify whether the treatments for hyperuricemia in prehypertensive subjects are useful to prevent the development of hypertension.

CONCLUSION

Increased serum uric acid is a strong risk marker for developing hypertension from prehypertension. Therefore, serum uric acid may be an important modifiable risk factor in managing patients with prehypertension. Further research and especially clinical trials are needed to evaluate whether uric acid lowering can impede the development of hypertension from prehypertension.

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