Relations of Serum Uric Acid to Longitudinal Blood Pressure Tracking and Hypertension Incidence


Abstract—Serum uric acid (UA) has been implicated in the pathogenesis of hypertension. We investigated the relationship of serum UA to hypertension incidence and blood pressure (BP) progression in 3329 Framingham Study participants (mean age 48.7 years; 55.6% women) free of hypertension, myocardial infarction, heart failure, renal failure, or gout. At follow-up 4 years from baseline, 458 persons (13.8%) had developed hypertension, and 1201 persons (36.1%) had experienced progression to a higher BP stage. Age- and sex-adjusted rates of hypertension incidence increased progressively from 9.8% for the lowest quartile to 15.6% for the top quartile of serum UA; BP progression rates increased from 32.8% (lowest quartile) to 39.6% (top quartile). In multivariable analyses adjusting for age, sex, body mass index, diabetes, smoking, alcohol intake, serum creatinine, proteinuria, glomerular filtration rate, baseline BP, and interim weight change, a 1 SD higher serum UA was associated with an odds ratio (OR) of 1.17 (95% confidence interval [CI], 1.02 to 1.33) for developing hypertension, and an OR of 1.11 (95% CI, 1.01 to 1.23) for BP progression. In analyses of a subsample of 3157 individuals not on antihypertensive treatment at the follow-up examination, serum UA was positively associated with changes in systolic (P=0.02) and diastolic pressure 4 years later (P=0.04). In summary, serum UA level was an independent predictor of hypertension incidence and longitudinal BP progression at short-term follow-up in our community-based sample. (Hypertension. 2005;45:28-33.)

Key Words: uric acid • blood pressure • epidemiology

Serum uric acid (UA) levels have been associated with an increased risk of cardiovascular disease events in some studies but not all studies. Serum UA has also been reported to predict vascular events in hypertensives. More recently, researchers have drawn attention to a putative role of UA in the pathogenesis of high blood pressure (BP) and renal disease.

Considerable experimental evidence supports a causal role for UA in development of hypertension. Mild hyperuricemia in rats leads to elevated BP, which can be prevented by UA-lowering treatment. In animal models, hyperuricemia may predispose to hypertension by several mechanisms such as inflammatory and vascular changes in the renal microcirculation, activation of the renin-angiotensin system, and endothelial dysfunction.

Clinical data also corroborate a possible pathogenetic role for UA in systemic hypertension. Cross-sectional studies have consistently noted that more than a quarter of patients with untreated hypertension have elevated serum UA. Serum UA levels have also been associated cross-sectionally with BP and longitudinally with hypertension incidence and future increases in BP. However, some previous reports were limited by modest sample sizes, exclusively male samples, case-control design, varying definitions of hypertension, and by failure to adjust for key confounders of the relationship such as serum creatinine, alcohol consumption, baseline BP, and weight gain at follow-up. Accordingly, we examined the relationship of serum UA to longitudinal BP tracking in a large community-based sample of nonhypertensive individuals.

Methods

Study Sample

The design and selection criteria of the original Framingham Heart Study and the Framingham Offspring Study have been described previously. Participants were eligible for inclusion in the present study if they attended original cohort examination 13 (1972 to 1976; n=3133) or offspring cohort examination 2 (1979 to 1982; n=3863), and a follow-up examination 4 years later.

Subjects were excluded from the present investigation for the following reasons: prevalent hypertension at baseline, as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) and the World Health Organization–International Society of Hypertension (WHO-ISH), (ie, systolic BP ≥140 mm Hg, diastolic...
BP ≥90 mm Hg, or use of antihypertensive medication (n=2486)); history of recognized myocardial infarction (n=147), heart failure (n=38), or gout (n=55); nonattendance or missing BP information at the baseline or the follow-up examinations (n=514); atrial fibrillation (n=14); serum creatinine >2.0 mg/dL (n=7); use of >2 g of salicylates per day (n=64); use of diuretics (n=143); or missing covariates at baseline examination (n=199). Because serum creatinine was not available at original cohort examination 13, values available at examination 15 were used for exclusions. After exclusions, 3329 individuals (mean age 48.7 years; 55.6% women) remained eligible. All participants gave informed consent. The Boston Medical Center institutional review board approved the study.

Baseline Examinations
Participants underwent a standardized medical history and physical examination, anthropometric measurements, laboratory tests, and a 12-lead ECG. Using a mercury column sphygmomanometer and a standardized protocol, a physician measured systolic and diastolic BP twice in the left arm of seated subjects who had been resting for ≥5 minutes. The mean of 2 readings was used for classification of BP according to JNC VI criteria into optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), or high-normal BP (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg) at the baseline examination.31 Diabetes was defined according to current American Diabetes Association guidelines.32 A panel of 3 physicians determined prevalence of cardiovascular diseases using published criteria.33

Serum UA was measured with an autoanalyzer using a phosphotungstic acid reagent.34 Proteinuria was measured with a urine dipstick test and graded as none, trace, or more.

Outcome Measures
At follow-up 4 years from baseline, participants underwent routine assessment of their BP using the same standardized protocol, and their BP was reclassified according to JNC VI criteria.28 The outcomes examined were incidence of hypertension and progression of BP as defined by an increase of BP by ≥1 JNC VI stage.31

Statistical Analysis
UA was normally distributed in both sexes, with values being higher in men compared with women. To determine appropriateness of pooling data from 2 different cohorts, sex-specific regressions were run, with UA as the dependent variable and clinical and laboratory variables (age, body mass index [BMI], systolic and diastolic BP, smoking, diabetes, alcohol consumption, serum creatinine) and examination cycle as covariates. In these multivariable analyses, examination cycle was not a predictor of serum UA. Therefore, data from the 2 cohorts were pooled.

Multiple logistic regression was used to investigate the relationship between serum UA levels and BP outcomes (incident hypertension and BP progression by ≥1 JNC VI category) at follow-up 4 years from baseline. Serum UA was analyzed as a continuous variable and as sex-specific quartiles. Because no effect modification by sex was noted, all analyses were for pooled sexes, with sex as a covariate. The following regression models incorporating UA were examined.

A. Unadjusted (crude);
B. Adjusted for age and sex; and
C. Adjusted for age, sex, baseline BMI, diabetes, smoking, alcohol intake, serum creatinine, glomerular filtration rate (log-transformed continuous variable) and proteinuria (dichotomous variable, none versus trace or more), baseline systolic and diastolic BP and BP category, and baseline use of cardiac medication for indications other than hypertension, as well as interim percent change in weight.

These covariates have been reported to influence BP tracking previously.31 Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation as follows: 186.3×serum creatinine $^{-1.154}\times$age $^{-0.203}\times$0.742 for women.35 Serum creatinine values were indirectly calibrated to the laboratory that developed the MDRD equation using methods described previously.33 For original cohort examination 13, serum creatinine from examination 15 was used as a covariate. We also examined models incorporating cohort status as a covariate. We investigated differences in the relationship of serum UA to BP outcomes according to baseline age and BMI by fitting appropriate interaction terms in multivariable models.

Additional Analyses
To assess the contribution of renal variables to the association of UA and BP tracking, analyses were repeated excluding variables related to renal function (glomerular filtration rate and proteinuria) from model C. Further, to exclude residual confounding by mild degrees of renal impairment, the relationship of UA to BP tracking was examined in a subset of 872 individuals who had optimal BP at baseline, no proteinuria, and a glomerular filtration rate of ≥90 mL/1.73 m$^2$ per minute.

We also examined the relationship of serum UA to changes in systolic and diastolic BP 4 years later in a subgroup of 3157 individuals (95% of sample) who were not on antihypertensive medications at the follow-up examination. Linear regression models were constructed with change in systolic and diastolic BP as dependent variables and UA as a continuous predictor variable (separate models for systolic and diastolic pressure; covariates as in model C).

We performed secondary analyses relating UA to hypertension incidence in which ascertainment of incidence of hypertension was made at routine examinations every 4 years for a duration of 12 years after the baseline examination. We also investigated the association of remote serum UA levels (average of values at examinations 1 through 4 of the original cohort) and 4-year hypertension incidence (between examinations 13 and 15) among 734 participants of the original cohort who met all inclusion criteria at examination 13. All analyses were performed using SAS (SAS Institute, Inc, NC).34 and a 2-sided $P$ value <0.05 was considered statistically significant.

Results
Baseline characteristics of participants are shown in Table 1. In our middle-aged sample, 47% of individuals had optimal
TABLE 2. Baseline Sex-Specific Serum UA Quartiles and 4-Year Incidence of BP Outcomes

<table>
<thead>
<tr>
<th>UA Quartile*</th>
<th>Men</th>
<th>Women</th>
<th>No. at Risk†</th>
<th>% Subjects Developing Hypertension</th>
<th>% Subjects With Increase by ≥1 BP Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td></td>
<td>Age- and Sex-Adjusted‡</td>
<td>Crude</td>
</tr>
<tr>
<td>Q1</td>
<td>255 (83–286)</td>
<td>181 (65–208)</td>
<td>839</td>
<td>10.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Q2</td>
<td>309 (291–327)</td>
<td>229 (214–244)</td>
<td>832</td>
<td>12.4</td>
<td>12.1</td>
</tr>
<tr>
<td>Q3</td>
<td>356 (333–381)</td>
<td>267 (250–286)</td>
<td>874</td>
<td>14.3</td>
<td>12.7</td>
</tr>
<tr>
<td>Q4</td>
<td>429 (387–571)</td>
<td>332 (291–523)</td>
<td>784</td>
<td>18.1</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*Mean ages for individuals in the UA quartiles (Q1–Q4) are as follows: 47.9, 46.7, 49.4, and 51.1 years.
†Percent males in the UA quartiles are 41%, 45%, 48%, and 44%.
‡Values are age- and sex-adjusted proportions using logistic regression (sample mean age 48.7 years; 44.4% males).

Incidence of Hypertension
At follow-up 4 years from baseline, 458 persons (13.8%; 51% women) developed hypertension. Crude and age- and sex-adjusted rates of progression to hypertension were similar in men and women and are presented by baseline sex-specific serum UA quartile (Table 2). Age- and sex-adjusted rates of hypertension incidence increased progressively from the lowest to the top quartile. The results of multivariable analyses are shown in Table 3. A 1 SD increase in serum UA was associated with 17% to 29% increased odds of developing hypertension (P<0.05 in all 3 models). The multivariable-adjusted odds ratio (OR) of developing hypertension with an SD increment in UA was comparable to that associated with a 5-year age increment. There was a statistically significant trend for increasing incidence of hypertension across serum UA quartiles in unadjusted and age- and sex-adjusted models that became borderline significant in multivariable models (Table 3).

Upward Tracking of BP
At follow-up, 1201 persons (36.1%; 54% women) experienced an increase in BP to a higher JNC VI stage. Rates of BP progression were similar in men and women. Age- and sex-adjusted rates of BP progression increased from the lowest to the top quartile (Table 2). In multivariable analyses (Table 3), an SD increase in serum UA was associated with 11% to 15% increased odds of BP progression (P<0.05 in all models). BP progression increased across serum UA quartiles in all models evaluated.

Additional Analyses
Incorporation of examination cohort (offspring versus original cohort) as a covariate did not alter any of the results. None of the investigated interaction terms were significant (all P values exceeded 0.35 for both BP outcomes). In analyses evaluating changes in BP, systolic BP increased by a mean of 3.6 mm Hg (SD 11.5), whereas diastolic BP increased by a mean of 1.2 mm Hg (SD 7.5) among study participants not on antihypertensive medications at follow-up. Increments in systolic BP rose from a mean of 3.4 mm Hg for the bottom quartile to 4.3 mm Hg for the top quartile of UA. Increments in diastolic BP also increased from a mean of 1.0 mm Hg in the lowest quartile to 1.5 mm Hg in the uppermost quartile. In multivariable analyses, an SD increment in UA was associated with an increase in systolic BP of 0.6 mm Hg (P=0.02) and an increase in diastolic pressure of 0.3 mm Hg (P=0.04).

In secondary analyses evaluating models not incorporating renal function variables, results were similar to the primary multivariable-adjusted model (data not shown). Of the 872 individuals who had optimal BP at baseline, no proteinuria, and a glomerular filtration rate of ≥90 mL/1.73 m² per minute at baseline, 30 individuals (3.4%) developed hypertension and 288 (33%) experienced progression of BP by ≥1 stages at follow-up 4 years from baseline. We had very limited statistical power to evaluate incidence of hypertension; an SD increment in UA (69 μmol/L for this subgroup) was associated with a nonsignificant 18% increased odds of hypertension (OR, 1.18; 95% confidence interval [CI], 0.74 to 1.87). We had greater statistical power to evaluate progression of BP; an SD increment in UA was associated with a 27% increased odds of experiencing BP progression (OR, 1.27; 95% CI, 1.03 to 1.56).

In secondary analyses extending follow-up to 12 years from baseline, 1145 individuals (34.4%) developed hypertension. Serum UA was associated with increased risk of hypertension in age- and sex-adjusted models (OR per SD increment, 1.22; 95% CI, 1.12 to 1.33; OR per quartile increment, 1.18; 95% CI, 1.10 to 1.26) but not in multivariable models (OR per SD increment, 1.07; 95% CI, 0.96 to 1.19; P=0.22; OR per quartile increment, 1.06; 95% CI, 0.98 to 1.15; P=0.13; covariates as in model C).

We investigated the relationship of remote serum UA (average of values at examinations 1 through 4) and BP outcomes between examinations 13 and 15. Remote mean UA levels were lower (247±56 μmol/L) compared with examination 13. In multivariable models adjusting for covariates at examination 13, a borderline significant association of remote UA with incidence of hypertension was noted (OR per SD increment, 1.25; 95% CI, 0.94 to 1.65; P=0.13; for trend across quartiles, 1.21, 95% CI, 0.99 to 1.47; P=0.06). A remote UA level in the top quartile (>316 μmol/L in men and >249 μmol/L in women) was associated with a statistically significant increased risk of hypertension (multivariable-adjusted OR, 1.89; 95% CI, 1.03 to 3.48; P=0.04) compared...
with the lowest quartile (<225 μmol/L in men and <193 μmol/L in women).

Discussion

Principal Findings
Serum UA was positively associated with longitudinal BP tracking at short-term follow-up (4 years) in our large community-based sample. Associations were consistent for analyses relating UA to hypertension incidence and to BP progression. Results of models using UA as a continuous variable were consistent with analyses examining trend across quartiles, although the association was of borderline statistical significance in the latter models, partly because of lesser statistical power. Analyses of longitudinal changes in systolic and diastolic BP in individuals not on antihypertensive agents at follow-up corroborated the results of primary analyses. In the subgroup of individuals with optimal BP and normal kidney function at baseline, we observed an association of UA with BP progression. In secondary analyses extending follow-up to 12 years, the association of serum UA with hypertension incidence became statistically nonsignificant.

Comparison With the Published Literature
Our findings relating UA to hypertension incidence at short-term follow-up confirm several previous reports.18–22 However, the strength of the association was modest in our study (a 10% to 15% increased odds of hypertension incidence and BP progression per SD increment in UA) compared with previous reports. For example, in the Olivetti Study,18 a 1 mg/dL (59.3 μmol/L) increment in serum UA was associated with an OR of 1.23 for hypertension incidence during 12 years of follow-up. In another study of Utah pedigrees, an SD (69 μmol/L) increment in UA was associated with an OR of 1.44 for developing diastolic hypertension over 7 years. A strong association was also noted in the Kaiser Permanente Multiphasic Health Checkup cohort19 using a case-control design. Only 1 previous study examined the relationship of UA to longitudinal increases in BP. Masuo et al23 reported that a 1.0 mg/dL higher serum UA at baseline (1 SD = 1.5 mg/dL in that study) was associated with a 27.5 mm Hg higher systolic and 15.2 mm Hg higher diastolic BP 5 years later, which appears to be a much larger effect than that observed in our study. Several reasons may account for the more modest effect of UA on hypertension incidence and BP tracking during a 4-year period in our sample. Our participants were on average a decade older than in previous studies, and it is conceivable that effects of UA may be more evident at a younger age.17 Additionally, we adjusted for a comprehensive panel of key confounders, some of which were not accounted for in previous studies. Adjustment for confounders may partly account for the attenuation of effect of UA in multivariable models. Notwithstanding the differences from previous studies, the overall results demonstrating an association of UA with short-term BP tracking corroborates previous studies.18–23  

In secondary analyses, the association of UA with hypertension incidence became statistically nonsignificant during a 12-year follow-up period. These findings differ from those reported by the Olivetti Study18 for a similar duration of follow-up. Participants in that study were on average a decade younger than our sample.18 There are several potential explanations for the attenuation of the relationship of UA and hypertension with increasing duration of follow-up in our study. First, the effect of a single estimate of UA may decrease over time.35 Second, the higher background rate of hypertension incidence with increasing age may have contributed to a reduction in the ORs for UA. Third, the effect of UA may be greater at a younger age.17 Additionally, we adjusted for a comprehensive panel of key confounders, some of which were not accounted for in previous studies. Adjustment for confounders may partly account for the attenuation of effect of UA in multivariable models. Notwithstanding the differences from previous studies, the overall results demonstrating an association of UA with short-term BP tracking corroborates previous studies.18–23  

UA and Hypertension: Underlying Mechanisms
In experimental studies, hyperuricemia results in renal vascular inflammation (through stimulation of nuclear transcription factors and release of proinflammatory cytokines),10 a preglomerular arteriopathy (attributable to increased vascular smooth cell proliferation via increased expression of

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Model</th>
<th>OR (95% CI) for Developing BP Stage</th>
<th>OR (95% CI) for Increase by ≥1 BP Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum UA as a continuous variable</td>
<td>A. crude</td>
<td>1.29 (1.17–1.42)</td>
<td>1.15 (1.07–1.23)</td>
</tr>
<tr>
<td>Per 1 SD increase in serum UA</td>
<td>B. age- and sex-adjusted</td>
<td>1.26 (1.12–1.41)</td>
<td>1.14 (1.04–1.24)</td>
</tr>
<tr>
<td></td>
<td>C. multivariable*</td>
<td>1.17 (1.02–1.33)</td>
<td>1.11 (1.01–1.23)</td>
</tr>
<tr>
<td>Serum UA as a categorical variable</td>
<td>Trend across serum UA quartiles</td>
<td>A. crude</td>
<td>1.23 (1.13–1.35)</td>
</tr>
<tr>
<td></td>
<td>B. age- and sex-adjusted</td>
<td>1.18 (1.08–1.29)</td>
<td>1.11 (1.04–1.18)</td>
</tr>
<tr>
<td></td>
<td>C. multivariable*</td>
<td>1.10 (0.99–1.22)</td>
<td>1.09 (1.01–1.17)</td>
</tr>
</tbody>
</table>

*Models adjusted for age, sex, BMI, diabetes, interim weight change, smoking, alcohol intake, serum creatinine, (glomerular filtration rate), proteinuria, baseline systolic and diastolic BP and BP category, and baseline use of cardiac medication for indications other than hypertension.
mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor), and tubulointerstitial inflammation and fibrosis. These renal changes result in activation of the renin-angiotensin system. Increased intrarenal vasoconstriction ensues with a reduction in single nephron glomerular filtration, decreased sodium filtration, and a rightward shift in the pressure–natriuresis relationship. Eventually, a salt-sensitive form of hypertension sets in. Indeed, it has been hypothesized that a uricase gene mutation in humans in the Miocene era led to relative hyperuricemia and an increased BP response to sodium. Additional contributory mechanisms include increased juxtaglomerular renin production and reduced neuronal NO synthase in the macula densa. A possible role for insulin resistance as a common precursor of hyperuricemia and hypertension has also been proposed. Additionally, it is possible that UA is an indicator of subtle renal dysfunction that, in turn, promotes hypertension. Our data cannot prove causality or invoke a particular mechanism. Our observations are of biological importance and of major concern for hypertension management.

Strengths and Limitations
The large community-based sample, standardized assessment of BP, and the adjustment for numerous potential confounders strengthen our investigation. It is important to acknowledge the relative merits and weaknesses associated with the use of serum UA measures from examination 13 of the original cohort (primary analyses) and from the earlier examinations (secondary analyses). Analyses of UA values from examination 13 reflect a more contemporary time period when BP measurements were more standardized and data on several confounders were available. The limitations of using serum UA from examination 13 include the single determination of UA, the exclusion of participants at highest risk because of hypertension at baseline, and the greater importance of other mechanisms of hypertension such as loss of arterial compliance in an older cohort. Analyses using remote serum UA values from examinations 1 through 4 are strengthened by the availability of multiple observations (a mean of 4 serum UA values was used) and the measurements at a younger age; a relative weakness is the lack of data on several key confounders. Other potential limitations of our study include the predominantly white ethnicity of the Framingham sample that limits generalizability of our results.

Perspectives
Baseline serum UA level was an independent predictor of hypertension incidence and longitudinal BP progression during short-term follow-up in our large community-based sample of nonhypertensive individuals. Given the modest effect sizes observed in our analyses, it may be argued that these findings have limited clinical significance. Indeed, serum UA levels are unlikely to be good screening tools to aid the risk stratification of individuals at risk of developing hypertension. Nonetheless, our observations are of biological importance because they support the notion that UA plays a role in the pathogenesis of hypertension. Additionally, the effect size of UA, although modest, was comparable to that of 5 years of aging and was observed after 4 years of follow-up in a relatively healthy normotensive sample free of gout (excluding a considerable proportion of people with higher UA levels) and after adjustment for several key confounders. Further studies are warranted to confirm these observations and to elucidate whether the relationship observed between UA and incident hypertension at short-term follow-up is causal.

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