Uric Acid and the Development of Hypertension

The Normative Aging Study

Todd S. Perlstein, Olga Gumieniak, Gordon H. Williams, David Sparrow, Pantel S. Vokonas, Michael Gaziano, Scott T. Weiss, Augusto A. Litonjua

Abstract—Experimental evidence supports a causative role for uric acid in the pathogenesis of hypertension. Prospective studies have variably adjusted for relevant confounders and have been of relatively limited duration. We prospectively examined the relationship between uric acid level and the development of hypertension in the Normative Aging Study, a longitudinal cohort of healthy adult men. Of the 2280 initial men in the Normative Aging Study, 2062 had available information for inclusion in the analysis. Cox proportional hazards model was used to examine the relationship between baseline serum uric acid level and the development of hypertension adjusting for age, body mass index, abdominal circumference, smoking, alcohol, plasma triglycerides, total cholesterol, and plasma glucose. A total of 892 men developed hypertension over a mean of 21.5 years of follow-up. Serum uric acid level independently predicted the development of hypertension in age-adjusted (relative risk [RR]: 1.10; 95% CI: 1.06 to 1.15; P<0.001) and multivariable (RR: 1.05; 95% CI: 1.01 to 1.10; P=0.02) models. Among 1277 men at risk for the development of hypertension at the time of their first serum creatinine measurement, 508 (39.8%) developed hypertension over a mean of 10.3±5.5 years of follow-up. Additionally adjusting for calculated glomerular filtration rate in this subset, serum uric acid remained associated with the development of hypertension (RR: 1.06; 95% CI: 1.01 to 1.12; P=0.03). The baseline serum uric acid level is a durable marker of risk for the development of hypertension. The association is independent of elements of the metabolic syndrome, alcohol intake, and renal function. (Hypertension. 2006;48:1031-1036.)

Key Words: uric acid ■ hypertension ■ renal function ■ prospective studies ■ aging

The association of hyperuricemia with hypertension has long been recognized. It remains unresolved whether the association of hyperuricemia with hypertension is solely because of underlying renal and metabolic abnormalities. Decreased renal blood flow and decreased tubular secretion of uric acid have been associated with hyperuricemia in hypertension. Hyperinsulinemia secondary to insulin resistance may also contribute to the association of hyperuricemia with hypertension. Recent observations in experimental hyperuricemia suggest that uric acid may in fact have a pathogenic role in hypertension. Hyperuricemia induces hypertension in experimental animals that corrects with hypouricemic therapy.

Elevated serum uric acid level has been associated with increased risk for developing hypertension. The Normative Aging Study (NAS), a longitudinal study of aging begun in 1963 and with ongoing follow-up, presented a unique opportunity to examine the relationship between serum uric acid level and the development of hypertension. The duration of follow-up, ≤40 years, allowed us to assess the durability of the prospective association of uric acid level with hypertension. The comprehensive data collection allowed adjustment for key potential confounding covariates, such as central adiposity, alcohol intake, metabolic parameters, and, in a subset of study subjects, the serum creatinine level. Previous studies have variably accounted for these confounders. Specifically, some did not adjust for blood pressure, or alcohol intake, and only 1 adjusted for renal function. We, therefore, examined the prospective association of serum uric acid level with the development of hypertension among subjects at risk for the development of hypertension within the NAS cohort, including an analysis of those at risk for the development of hypertension at the time of their first serum creatinine determination. We have included in our multivariable model(s) covariates of the metabolic syndrome, alcohol intake, and renal function.

Methods

Subjects were participants in the NAS, a longitudinal study of aging established by the Veterans Administration in 1961. The study cohort consists of 2280 community-dwelling men from the greater Boston area who were 21 to 80 years of age on enrollment. Volunteers were screened at entry according to specific health criteria and were free of known chronic medical conditions at the

Received June 22, 2006; first decision July 7, 2006; revision accepted September 25, 2006.
From the Divisions of Endocrinology, Diabetes, and Hypertension (T.S.P., O.G., G.H.W.) and Aging (M.G.) and Channing Laboratory (S.T.W., A.A.L.), Department of Medicine, Brigham and Women’s Hospital, Boston, Mass; Veterans Administration Boston Healthcare System (D.S., P.S.V., M.G., A.A.L.), Mass; the Department of Medicine (D.S., P.S.V.), Boston University School of Medicine, Mass; and Harvard Medical School (T.S.P., O.G., G.H.W., S.T.W., A.A.L.), Boston, Mass.
Correspondence to Augusto A. Litonjua, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115. E-mail real@channing.harvard.edu
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Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000248752.08807.4c
Hypertension was defined as follows: (1) a SBP ≥ 160 mm Hg; (2) a DBP ≥ 95 mm Hg; and/or (3) medication therapy for the treatment of hypertension. This definition was chosen to remain consistent with previous analyses in this data set and to reflect clinical practice during most of the period of follow-up. The first study visit at which criteria for the diagnosis of hypertension was met was used as the time of onset of hypertension.

Statistical Methods

Cox proportional hazards model examined the association between the baseline serum uric acid level and the development of hypertension. Ties were handled with the exact method. Hazard ratios are expressed as relative risk. Person-years of follow-up were calculated from the date of enrollment to the date of incident hypertension. Subjects were categorized by serum uric acid (SUA) level as follows: <5.0 mg/dL (<297 μmol/L), 5.0 to 5.4 mg/dL (297 to 322 μmol/L), 5.5 to 5.9 mg/dL (327 to 351 μmol/L), 6.0 to 6.4 mg/dL (357 to 381 μmol/L), 6.5 to 6.9 mg/dL (387 to 410 μmol/L), and ≥7.0 (416 μmol/L). Age-adjusted and multivariable-adjusted analyses were performed, the latter adjusted for age (years), SBP (millimeters of mercury), DBP (millimeters of mercury), body mass index (BMI) (kilograms per squared meter), AC (centimeters), smoking status (no/yes), alcohol intake ≥2 drinks per day (no/yes), fasting glucose (millimoles per liter), total cholesterol (millimoles per liter), and triglycerides (millimoles per liter). SUA satisfied the proportionality assumption. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease Study equation as follows: 186.3 × (serum creatinine) ^ (-1.154 × (age ^ (-0.203)). A dummy variable was created representing median GFR. Analyses were performed with SAS release 8.2 (SAS Institute Inc.).

Results

Of the initial 2280 men, 181 did not have hypertension status available from a follow-up visit, 36 were found to be hypertensive at baseline, and 1 did not have a baseline SUA level. A total of 2062 men (90% of the total) are included in the full data set analysis. Baseline characteristics of the subjects are summarized in Table 1. Also presented in Table 1 are the characteristics of subjects not included in this analysis. These men as a group had a somewhat higher blood pressure, likely attributable to those found to be hypertensive at baseline. The smoking frequency among these men was higher; otherwise, the 2 groups are similar. Associations of baseline characteristics with baseline SUA are presented in Table 2. In this analysis, subjects with higher baseline SUA levels also had higher SBPs and DBPs, greater BMI and AC, and higher triglycerides and total choles-

| Table 1. Baseline Characteristics of Subjects Included in and Excluded From Analyses |
|---------------------------------|------------|------------|-----------------|
| Characteristic                  | Included in Analysis (n=2062) | Excluded From Analysis (n=218) | Crearitine Subset (n=1277) |
| Age, y                          | 41.7±9.2  | 42.2±11.2  | 55.8±7.9        |
| Race, nonwhite                  | 2.3%      | 1.2%       | 2.1%            |
| Current smoker (yes)            | 38.7%     | 49.4%*     | 21.0%           |
| Alcohol ≥2 drink/day (yes)      | 12.6%     | 12.6%      | 25.0%           |
| SBP, mm Hg                      | 123±10.9  | 127±17.6*  | 122±13.4        |
| DBP, mm Hg                      | 77±7.5    | 79±10.2*   | 75±7.9          |
| BMI, kg/m²                      | 25.7±2.8  | 25.6±3.0   | 26.3±3.1        |
| AC, cm                          | 93±8.3    | 93±9.1     | 95±8.8          |
| Fasting glucose, mmol/L         | 5.89±0.59 | 5.95±0.64  | 6.13±1.00       |
| Triglycerides, mmol/L           | 1.37±0.57 | 1.31±0.55  | 1.24±0.73       |
| Uric acid level, μmol/L         | 347±54    | 345±54     | 380±72          |
| Creatinine, μmol/L              | n/a       | n/a        | 106±17          |
| GFR, mL/h                       | n/a       | n/a        | 68.9±13.4       |

Baseline characteristics of the 2062 men included, the 218 men excluded from the analysis, and the 1277 men included in an analysis including baseline serum creatinine level. Expressed as mean and SD for continuous, percentage for discrete variables. Reasons for exclusion: (1) hypertensive at baseline visit (n=36); (2) missing serum uric acid level at baseline (n=1); and (3) hypertension status at follow-up not available (n=181). Group comparisons of those included in and excluded from analysis made by ANOVA or χ² test. n/a indicates not applicable. *P<0.05.

terol. In addition, current smokers had lower baseline SUA levels, whereas subjects who drank ≥2 alcoholic drinks per day had higher levels.

The mean follow-up period was 21.5±10.1 years with a maximum of 40.5 years. A total of 892 men, 43.3% of the study population, developed hypertension. The median survival time free of hypertension was 30.1 years (interquartile range: 19 to 39 years). The mean age at the time of developing hypertension was 61.0±9.9 years. The criteria by

| Table 2. Associations With Baseline SUA Level |
|---------------------------------------------|--------|--------|
| Correlations With Baseline SUA Level        | r      | P Value |
| Age, y                                       | 0.03   | 0.16   |
| SBP, mm Hg                                   | 0.12   | <0.0001|
| DBP, mm Hg                                   | 0.13   | <0.0001|
| BMI, kg/m²                                   | 0.21   | <0.0001|
| AC, cm                                       | 0.24   | <0.0001|
| Fasting glucose, mmol/L                      | −0.03  | 0.13   |
| Triglycerides, mmol/L                        | 0.12   | <0.0001|
| Total cholesterol                            | 0.07   | 0.002  |
| Group mean differences in baseline SUA level | Mean difference, μmol/L | n/a    |
| Current smoker (yes)                         | −8.35  | 0.006  |
| Alcohol ≥2 drinks/day (yes)                  | 15.8   | <0.0001|

Spearman correlation for continuous, group mean difference for discrete variables with comparison by ANOVA.
which subjects met the definition of hypertension are presented in Table 3. Seventy-nine percent of men were treated with medical therapy for hypertension at the time of the study visit in which they met the definition of hypertension.

Adjusting for age, a 1-category increase in SUA level was associated with an increased risk for developing hypertension (relative risk [RR]: 1.10; 95% CI: 1.06 to 1.15; \( P < 0.001 \); Figure 1). In multivariable analysis adjusting for age, SBP, DBP, BMI, AC, smoking, alcohol, triglycerides, total cholesterol, and glucose, SUA remained associated with hypertension (RR for each 1 category increase in SUA: 1.05; 95% CI: 1.01 to 1.10; \( P = 0.02 \); Figure 2).

We explored 2 definitions of hyperuricemia and the risk for hypertension. A population definition of hyperuricemia in men is an SUA greater than 7.0 mg/dL, whereas a physical chemical definition of hyperuricemia is greater than 6.5 mg/dL, as serum is supersaturated for monosodium urate at concentrations above this.\(^{22}\) A SUA level greater than 7.0 mg/dL (416 \( \mu \)mol/L) was associated with a RR for hypertension of 1.36 (95% CI: 1.07 to 1.74) and 1.08 (95% CI: 0.83 to 1.39) in age-adjusted and multivariable-adjusted analyses, respectively. A SUA level greater than 6.5 mg/dL (387 \( \mu \)mol/L) was associated with an RR for hypertension of 1.34 (95% CI: 1.16 to 1.55) and 1.25 (95% CI: 1.08 to 1.45) in age-adjusted and multivariable-adjusted analyses, respectively.

A total of 1277 men were at risk for the development of hypertension at the time of their first creatinine determination. Serum creatinine began to be measured in 1979, 16 years after the initiation of the cohort. The characteristics of these subjects at the time of their first creatinine measurement are summarized in the third column of Table 1. Given the higher range of SUA level in this subset, categories of SUA greater than or equal to 7.0 mg/dL (416 to 440 \( \mu \)mol/L) and greater than or equal to 7.5 mg/dL (446 \( \mu \)mol/L) were added for this analysis. The mean calculated GFR was 68.9 ± 13.4 mL/min. GFR was inversely correlated with the SUA level (\( r = -0.13; P < 0.0001 \)). A total of 508 (39.8%) of these men developed hypertension at a mean of 10.3 ± 5.5 years of follow-up. In age- and log-transformed GFR-adjusted analysis, baseline SUA level was strongly associated with the development of hypertension (\( P = 0.002 \); Figure 3). After additionally adjusting for SBP, DBP, BMI, AC, smoking, alcohol, triglycerides, total cholesterol, and glucose, SUA level remained associated with hypertension (RR for each 1 category increase in SUA: 1.06; 95% CI: 1.01 to 1.12; \( P = 0.03 \); Figure 4). There was no evidence for interaction between median GFR and SUA (\( P = 0.77 \)).

**Discussion**

In a large cohort of community dwelling healthy men, the SUA level independently predicted the development of hypertension over a mean of 21.5 years of follow-up. This association was independent of age, body size, central adiposity, total cholesterol level, triglyceride level, smoking status and alcohol intake, and glucose level. These results demonstrate that the SUA level is a durable marker of risk for hypertension.

The metabolic syndrome is an important potential confounder of the relationship between SUA level and hypertension. Insulin resistance and resultant hyperinsulinemia are believed to be the pathophysiological underpinning of the metabolic syndrome.\(^{5}\) Previous work in the NAS and by others has found that hyperinsulinemia and elements of the metabolic syndrome are associated with the SUA level.\(^{23–25}\) Insulin is known to decrease the renal excretion of uric acid,\(^{4}\) and hyperinsulinemia predicts the development of hypertension.\(^{26}\) We do not have serum insulin levels available at the baseline examination; however, the work of Imazu et al\(^ {12} \) suggests that the relationship between uric acid and the development of hypertension is independent of the insulin level. We were able to control for several elements of the metabolic syndrome, including blood pressure, triglyceride level, glucose level, and central adiposity, but we did not have high-density lipoprotein levels to fully define the presence of...
the metabolic syndrome. Nevertheless, when we adjusted for 4 of the 5 elements of the metabolic syndrome, SUA level remained a significant predictor of hypertension.

We also found that the SUA level predicted the development of hypertension independently of renal function as assessed by estimated GFR. Only 1 previous longitudinal study has accounted for renal function when examining the relationship between uric acid and hypertension. High uric acid levels have been associated with decreased renal perfusion, decreased tubular secretion of uric acid, and activation of the intrarenal renin–angiotensin system. It remains possible that our result is because of residual confounding from underlying renal dysfunction.

There are 2 caveats with our study that may have dampened the relationship between SUA level and hypertension. First, there is known variation in SUA level when measured repeatedly. Because we only used a single determination of SUA level as our exposure, our estimate of the risk for hypertension associated with hyperuricemia is likely lower than the true risk (a bias toward the null hypothesis). This variation likely dilutes our estimate of risk for hypertension conferred by hyperuricemia, because a significant number of subjects are likely misclassified. Second, there is evidence that uric acid may have a causal role in hypertension, the metabolic syndrome, and renal disease. Adjusting for blood pressure, the metabolic syndrome, and renal function may, therefore, remove mechanisms by which uric acid may cause hypertension, that is, overadjustment in our multivariable model. It is possible that our age-adjusted risk estimates more accurately reflect the risk for hypertension conferred by hyperuricemia than do our multivariable-adjusted risk estimates. Future work using other statistical methods, such as a path-analytic approach, may help to resolve this issue.

In a previous report from this cohort, uric acid was not found to be associated with the development of hypertension. The primary aim of that report was to determine predictors of the change in blood pressure over 10 years of follow-up. Of the 1166 men included, only 29 cases of hypertension occurred; therefore, that study had limited power. Also, the multivariable analysis was conducted in a stepwise manner and did not address uric acid specifically. The present analysis had a significantly longer duration of follow-up, was designed specifically to examine the association of uric acid with the development of hypertension, and had 892 cases of hypertension.

Our cohort is limited to men; therefore, caution is necessary when extrapolating these results to women. Other studies have included a significant number of women, suggesting that the relationship between uric acid and risk for hypertension is present in both men and women. Relying on the measurement of the blood pressure at a single visit necessarily was a source of some misclassification. Using a definition of hypertension of $\geq 160/95$ mm Hg likely affords...
specificity, evidenced by the fact that 79% of subjects who developed hypertension were receiving drug therapy for hypertension. Using 160/95 mm Hg, however, is consistent with previous analyses in this study and others. Also, the current definition of hypertension was not established until 1993, 30 years after the initiation of this cohort. The SUA level satisfied the proportional hazards assumption, indicating that the relationship between uric acid and the development of hypertension was constant over the follow-up period. Also, the renal function subset analysis was begun at an examination that occurred in 1979, 16 years after the first baseline examination, and the relationship between uric acid and hypertension held. We additionally performed sensitivity analyses in 2 ways, first by limiting the analyses to only those who met the criteria for hypertension before 1993 and, second, by excluding those who met the hypertension criteria solely based on medication prescription. In age-adjusted analyses, the association of baseline SUA with the development of hypertension was similar to the full cohort: RR for each category increase in SUA at 1.12 and 1.09, respectively, compared with 1.10 for the whole cohort. In multivariable-adjusted analysis, the association of baseline SUA with hypertension again was similar to the whole cohort, with RRs of 1.03 and 1.04 (compared with 1.05). We, therefore, do not suspect that the evolving definition of hypertension was an important source of bias in our study. We did examine the possibility of using a hypertension definition of 140/90 mm Hg and/or drug treatment of hypertension, in accord with the current definition of hypertension established in 1993. Because of members of the cohort meeting this definition at baseline and because of a shorter mean time to developing hypertension, the total person-years of follow-up lessened by 22%. Despite this significant reduction in power, SUA level was associated with hypertension in age-adjusted models (RR: 1.04; 95% CI: 1.01 to 1.08). We submit, however, that the definition of 160/95 mm Hg, although not the current definition of hypertension, is most appropriate for analysis of risk for hypertension in this cohort, for the reasons stated above.

We were interested in whether exposure to hypouricemic therapy before the end of his follow-up period; therefore, we could not pursue this question.

Recent observations suggest that the association between uric acid and hypertension may, in fact, represent causation. Uric acid has proinflammatory effects on vascular smooth muscle cells that seem to be mediated by intracellular redox pathways. Mild hyperuricemia in normal rats induced by the uricase inhibitor oxonic acid results in hypertension, intrarenal vascular disease, and renal injury. Withdrawal of oxonic acid or hypouricemic therapy with either the xanthine oxidase inhibitor allopurinol or the uricosuric agent benzbudarone ameliorates the blood pressure and histological changes. Activation of the renin–angiotensin system and diminution of NO synthase activity contribute to uric acid–mediated hypertension and nephropathy. Human studies have confirmed the association of hyperuricemia with endothelial dysfunction and increased vascular angiotensin II activity. Despite this growing body of evidence, we are not aware of studies that directly test a causative role for uric acid in human hypertension.

Perspectives
The present work extends the observations of others and indicates that the SUA level is a durable independent marker of risk for the development of hypertension. The observation that hyperuricemia is associated with alterations in renal physiology does not disprove that uric acid contributes to the pathogenesis of hypertension. We feel that the observations in experimental hyperuricemia, the ease of measuring the SUA level, the availability of hypouricemic therapy, and the public health consequences of hypertension provide a firm foundation for further study of the relationship between uric acid and hypertension, perhaps with clinical trials of hypouricemic therapy in the prevention and/or treatment of hypertension.

Sources of Funding
O.G. and T.S.P. were in part supported by the National Institutes of Health training grant T32 HL007609 and National Institutes of Health K30 grant HL04095. The Normative Aging Study is supported by the Cooperative Studies Program/ERIC of the US Department of Veterans Affairs and is a component of the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC).
Disclosures

None.

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Hypertension. 2006;48:1031-1036; originally published online October 23, 2006;
doi: 10.1161/01.HYP.0000248752.08807.4c
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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