Plasma Uric Acid Level and Risk for Incident Hypertension Among Men

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Several studies have found that uric acid (UA) level is associated with an increased risk for hypertension, but the association could be confounded by metabolic factors that were not included in these previous studies. UA level and risk for incident hypertension was examined prospectively among men who participated in the Health Professionals’ Follow-up Study. From among men without hypertension at the time blood was collected, 750 participants who developed hypertension during the subsequent 8 yr and 750 age-matched controls were selected. In addition to adjustment for standard hypertension risk factors and renal function, adjustments controlled for fasting insulin, triglyceride, and cholesterol levels. The mean age of participants was 61 yr, and mean plasma UA level was 6.0 mg/dl (SD 1.25 mg/dl). The multivariable relative risk (RR) for a 1-SD increase in UA was 1.02 (95% confidence interval [CI] 0.87 to 1.18); the RR comparing the highest with lowest quartile of UA was 1.08 (95% CI 0.71 to 1.63). The multivariable RR associated with a 1-SD increase in UA was 1.38 (95% CI 1.05 to 1.81) for men aged <60 yr and 0.90 (95% CI 0.74 to 1.10) for men ≥60 yr (P = 0.04 for interaction). However, further adjustment for fasting insulin, triglyceride, and cholesterol levels attenuated the results (RR for men <60 yr 1.24; 95% CI 0.93 to 1.66). In conclusion, no independent association between UA level and risk for incident hypertension was found among older men.

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Expanding animal and human literature supports a role for plasma uric acid (UA) level in the development of hypertension (1). A rat model of mild hyperuricemia that was developed by Johnson and colleagues (2–4) demonstrated activation of the renin-angiotensin system (RAS) and endothelial dysfunction with preglomerular vascular disease. Nine prospective observational studies have reported that UA is associated with incident hypertension or an increase in BP (5–13). These observational studies have varied in population composition as well as statistical method, with some not controlling for potentially important confounding factors, such as body mass index (BMI) (5,7), renal function (5,7–11,13), and certain metabolic derangements such as insulin resistance or dyslipidemia (5–8,12,13). Common to each of these nine prospective studies, however, is the relatively young age of the participants; the mean age of each population was 50 yr, whereas two thirds of the hypertension disease burden lies among older individuals (14). We performed a prospective nested case-control study of 1454 male participants of the Health Professionals’ Follow-up Study (HPFS) to examine the independent association between plasma UA and risk for incident hypertension among older men aged 47 to 81 yr and to explore effect modification by age.

Materials and Methods

Study Sample

The HPFS is an ongoing prospective cohort study of 59,529 male health professionals that began in 1986 and has been described in detail elsewhere (15). Follow-up of participants was >90% through 2004. In 1993, 18,025 men contributed blood samples that were stored in liquid nitrogen (<130°C). We conducted a nested case-control study among men with available blood samples and without prevalent hypertension in 1994 (approximately 1 yr after blood samples were collected). Only men whose BMI in 1994 was <30 kg/m² and whose blood sample was drawn after fasting for ≥8 h were considered. The BMI restriction was imposed because BMI is a strong predictor of UA level (16,17) and is a powerful predictor of hypertension and because the association between UA and hypertension may be modified by BMI (11). Fasting status was imposed to evaluate possible confounding by fasting insulin, triglycerides, and cholesterol. We then randomly selected 750 men who developed a new diagnosis of hypertension from 1994 to 2002 and 750 age-matched controls by risk-set sampling (18). Because risk-set sampling allows that a control may be selected as a case in a subsequent time period, 713 controls were unique individuals and 37 were selected later as a case and matched to a new control. Risk-set sampling is
commonly used for prospective, nested, case-control studies, and the resulting odds ratio that is derived from logistic regression directly estimates the relative risk (RR) (18). After the exclusion of nine men with missing UA information, the total study sample consisted of 1454 unique individuals with 745 matched case-control pairs. The institutional review board at Brigham and Women’s Hospital reviewed and approved this study.

Ascertainment of UA

UA concentration was determined by oxidation with the specific enzyme uricase to form allantoin and H₂O₂ (Roche Diagnostics, Indianapolis, IN) at Boston Children’s Hospital Laboratory (Nader Rifai, director). The coefficient of variation for this assay using quality control specimens was 2.7%.

Ascertainment of Hypertension

In biennial mailed questionnaires, we asked participants to report whether a clinician had made a new diagnosis of hypertension during the preceding 2 yr. Self-reported hypertension was shown to be highly reliable in HPFS (19). Among a subset of men who reported hypertension, 100% had the diagnosis confirmed by medical record review. In addition, self-reported hypertension was highly predictive of subsequent cardiovascular events (19). A participant was considered to have prevalent hypertension and thus excluded if he reported this diagnosis on any questionnaire up to and including the 1994 questionnaire. Therefore, cases included only individuals who first reported hypertension on subsequent questionnaires (1996 to 2002).

Ascertainment of Covariates

Age, BMI (weight in kilograms divided by height in meters squared), smoking status, physical activity, and alcohol intake were ascertained from the 1994 questionnaire. Baseline BP was ascertained from the 1992 questionnaire, when participants reported their usual BP in categories, and were assigned the median of the chosen category. Change in weight was calculated as the difference between the weight in 1994 and the subsequent weight when case or control status was defined. Questionnaire-derived information about these covariates was validated previously, with correlations of 0.97 for weight compared with direct measurement, 0.79 for physical activity compared with physical activity diaries, and 0.90 for alcohol compared with multiple averaged dietary records (15,20,21). Family history of hypertension was available on the 1990 questionnaire.

In addition to UA, blood samples were assayed in the same laboratory for creatinine using a modified Jaffe method, insulin using a RIA, triglycerides by a standardized enzymatic assay, and cholesterol by a standard esterase-oxidase method. The coefficients of variation for these measurements were 4.0, 4.6, 3.6, and 2.7% respectively. Estimated GFR (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation: 186 × creatinine⁻¹.154 × age⁻⁰.²⁰³ × 1.212 (if black) (22).

Statistical Analyses

UA was normally distributed and was examined as a continuous variable in the principal analyses to calculate the RR for hypertension for a 1-SD (1.25 mg/dl) increment. In other analyses, we examined UA in quartiles and by clinically defined hyperuricemia (>7.0 mg/dl) (23–25). To determine differences in baseline characteristics among UA quartiles, we log-transformed continuous variables and used one-way ANOVA; for categorical variables (smoking status and family history of hypertension), we used χ² tests for trend.

We analyzed the association between UA and hypertension using conditional logistic regression conditioning on the matching factor (age). Multivariable models were adjusted for BMI, alcohol consumption, change in weight, eGFR, physical activity, smoking status, race, family history of hypertension, and baseline systolic and diastolic BP. For all RR, we calculated 95% confidence intervals (CI).

The men in our sample were considerably older than the populations studied by others; we therefore investigated whether the association between UA and hypertension varied by age (<60 and ≥60 yr). Because Nakashima et al. (11) found a stronger association among those with lower BMI, we also examined possible interaction between UA and BMI (<25 and ≥25 kg/m²). Effect modification was analyzed by creating appropriate interaction terms between UA level and either age or BMI.

Finally, because higher UA levels are correlated with other metabolic abnormalities such as insulin resistance (16,17,26–31), higher triglyceride levels (16,28,29,31,32), and higher BMI, some have argued that UA is a component of the metabolic syndrome (16,29). Its association with hypertension therefore may be confounded by other metabolic abnormalities (33). In an attempt to examine the independent association between UA and hypertension, we further adjusted our analyses for fasting insulin, triglyceride, and total cholesterol levels. All statistical analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

The mean plasma UA was 6.0 mg/dl (range 2.4 to 11.5), and the SD was 1.25 mg/dl. The mean age of the population at baseline was 61 yr (range 47 to 81), and the mean BMI was 25.0 kg/m² (range 16.4 to 29.9). The characteristics and laboratory values of the controls at baseline are shown in Table 1, stratified by quartile of plasma UA. With increasing quartile of UA, we observed higher BMI and increasing levels of plasma creatinine (and decreasing eGFR), fasting insulin, triglycerides, and total cholesterol.

Overall Analysis

The crude RR of incident hypertension for each 1-SD increment in plasma UA was 1.02 (95% CI 0.92 to 1.13), and the multivariable-adjusted RR was 1.02 (95% CI 0.87 to 1.18; Table 2). The multivariable RR for men in the highest compared with lowest quartile of plasma UA was 1.08 (95% CI 0.71 to 1.63) and was 0.93 (95% CI 0.64 to 1.33) for hyperuricemic men compared with those without hyperuricemia. Because diastolic BP may be a negative confounder in this population of older men, we also performed multivariable analyses without adjusting for diastolic BP; the results essentially were unchanged.

Effect Modification

The multivariable RR of incident hypertension for each 1-SD increment in plasma UA varied according to age group (P = 0.04 for interaction; Table 3). Plasma UA level was associated positively and significantly with risk for incident hypertension among the men who were younger than 60 yr (RR 1.38; 95% CI 1.04 to 1.81) but not associated among men who were ≥60 yr of age (RR 0.90; 95% CI 0.74 to 1.10).

In the quartile analysis, there was a trend toward a positive association between UA and risk for hypertension among the younger but not the older men. Comparing participants in the
Table 1. Baseline characteristics and laboratory values according to quartile of plasma UA among controls (n = 745)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile of Plasma UA (mg/dl; Median [Range])</th>
<th>P (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.6 (2.4 to 5.1)</td>
<td>5.5 (5.2 to 5.9)</td>
</tr>
<tr>
<td>Age (yr; median [IQR])</td>
<td>61 (53 to 68)</td>
<td>61 (53 to 68)</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2}; median [IQR])</td>
<td>23.8 (22.2 to 25.1)</td>
<td>24.7 (23.0 to 26.5)</td>
</tr>
<tr>
<td>Physical activity (MET; median [IQR])</td>
<td>28.5 (13.6 to 52.0)</td>
<td>27.3 (11.6 to 54.0)</td>
</tr>
<tr>
<td>Alcohol intake (g/d; median [IQR])</td>
<td>3.4 (0 to 12.4)</td>
<td>5.9 (0 to 14.8)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Family history of hypertension (%)</td>
<td>34.4</td>
<td>34.6</td>
</tr>
<tr>
<td>Creatinine (mg/dl; median [IQR])</td>
<td>0.96 (0.88 to 1.07)</td>
<td>0.99 (0.92 to 1.05)</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m\textsuperscript{2}; median [IQR])</td>
<td>63.6 (55.4 to 70.1)</td>
<td>61.0 (56.3 to 67.3)</td>
</tr>
<tr>
<td>Fasting Insulin (IU/ml; median [IQR])</td>
<td>5.0 (3.4 to 7.4)</td>
<td>6.0 (3.6 to 9.1)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl; median [IQR])</td>
<td>95 (71 to 142)</td>
<td>110 (77 to 163)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl; median [IQR])</td>
<td>200 (178 to 230)</td>
<td>208 (194 to 230)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Study sample restricted to body mass index (BMI) <30 kg/m\textsuperscript{2}. eGFR, estimated glomerular filtration rate; IQR, interquartile range; METS, metabolic equivalents; UA, uric acid.

Discussion

Plasma UA was not associated with an increased risk for incident hypertension among older men. Although we observed a significant association in the subgroup of men who were <60 yr of age, this association was attenuated and no longer significant after further controlling for fasting insulin, triglycerides, and total cholesterol.

The most notable difference between our study and previous ones is the age of the populations. Age is critically important given that approximately two thirds of the hypertension disease burden in men lies with older individuals (14). Whereas the mean age of men in our sample was 61 yr, the next oldest cohorts were that of Hunt et al. (7) (mean age 50 yr) and Sundstrom et al. (12) (mean age 48.7 yr) (12). The possible effect of age on the UA–hypertension association was suggested previously in the discussion by Sundstrom et al. (12); they noted a 13% increase in risk for each 1.0 mg/dl increment in UA (mean age 48.7 yr), compared with a 20% increase per 1.0 mg/dl in Taniguchi et al. (9) (mean age 41 yr) and a 23% increase per 1.0 mg/dl in Josaa et al. (8) (mean age 36 yr). The findings from our study are consistent with the lack of a relation between UA and hypertension in older individuals.

A rat model of mild hyperuricemia that was developed by Johnson and colleagues demonstrates UA-dependent BP elevation and offers a biologic mechanism whereby UA could lead to similar BP elevations in humans. First, renal vasoconstriction occurs by inhibition of the nitric oxide pathway and by activation of the RAS; the resulting elevation of BP was reversible by

Table 2. RR of incident hypertension per 1 SD and according to quartile of plasma UA\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Per 1-SD Increase in Plasma UA (1.25 mg/dl)</th>
<th>Quartile of Plasma UA (mg/dl; Median [Range])</th>
<th>P (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted RR</td>
<td>1.02 (0.92 to 1.13)</td>
<td>4.6 (2.4 to 5.1)</td>
<td>5.5 (5.2 to 5.9)</td>
</tr>
<tr>
<td>Multivariable\textsuperscript{b} RR</td>
<td>1.02 (0.87 to 1.18)</td>
<td>174</td>
<td>188</td>
</tr>
<tr>
<td>No. of cases</td>
<td>1.00 (reference)</td>
<td>0.96 (0.72 to 1.28)</td>
<td>1.12 (0.84 to 1.49)</td>
</tr>
<tr>
<td>Multivariable\textsuperscript{b} RR</td>
<td>1.00 (reference)</td>
<td>0.88 (0.60 to 1.30)</td>
<td>1.05 (0.71 to 1.57)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditional logistic regression, case-control pairs matched on age. RR, relative risk.

\textsuperscript{b}Adjusted for BMI, eGFR, alcohol intake, smoking status, interval change in weight, physical activity, race, family history of hypertension, and baseline systolic and diastolic BP (BP ascertained 1 yr before blood collection).
Table 3. Risk for incident hypertension per 1-SD increase in plasma UA, stratified by age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Per 1-SD Increase in Plasma UA (1.25 mg/dl)</th>
<th>Quartile of Plasma UA (mg/dl; Median [range])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;60 yr</td>
<td>Age ≥60 yr</td>
</tr>
<tr>
<td>No. of cases</td>
<td>325</td>
<td>420</td>
</tr>
<tr>
<td>Multivariableb RR</td>
<td>1.38 (1.05 to 1.81)</td>
<td>0.90 (0.74 to 1.10)</td>
</tr>
<tr>
<td>Multivariablec RR</td>
<td>1.24 (0.93 to 1.66)</td>
<td>0.94 (0.77 to 1.16)</td>
</tr>
<tr>
<td>Age ≥60 yr no. of cases</td>
<td>71</td>
<td>89</td>
</tr>
<tr>
<td>multivariableb RR</td>
<td>1.00 (reference)</td>
<td>1.48 (0.78 to 2.80)</td>
</tr>
<tr>
<td>multivariablec RR</td>
<td>1.00 (reference)</td>
<td>1.30 (0.66 to 2.36)</td>
</tr>
<tr>
<td>Age ≥60 yr no. of cases</td>
<td>103</td>
<td>99</td>
</tr>
<tr>
<td>multivariableb RR</td>
<td>1.00 (reference)</td>
<td>0.68 (0.41 to 1.15)</td>
</tr>
<tr>
<td>multivariablec RR</td>
<td>1.00 (reference)</td>
<td>0.72 (0.42 to 1.23)</td>
</tr>
</tbody>
</table>

bAdjusted for BMI, eGFR, alcohol intake, smoking status, interval change in weight, physical activity, race, family history of hypertension, and baseline systolic and diastolic BP (BP ascertained 1 yr before blood collection). P = 0.04 for interaction.
cAdjusted for everything in model b and also for fasting insulin, triglycerides, and total cholesterol levels.

decreasing UA levels (2–4,34). A recent report demonstrated that UA level was associated with lower basal renal plasma flow and blunted renal vasconstriction that typically is seen with angiotensin II infusion during high-salt balance, lending support to the hypothesis that UA may activate the renal RAS directly (35). Second, vascular smooth muscle cell proliferation and inflammation as a result of UA may lead to irreversible damage to small renal vessels, leading to persistence of hypertension and salt sensitivity (36).

This mechanism may be less important when hypertension develops at an older age, when stiffening of the aorta may be a principal mechanism (37). Furthermore, because increasing age is associated with activation of the renal RAS and with renal vasconstriction (38,39), it is not surprising that the association between UA and hypertension may be blunted in older individuals.

Finally, we adjusted simultaneously for both renal function and other metabolic derangements, including fasting insulin, triglyceride, and cholesterol levels. We adjusted for these factors to assess whether elevated UA might be simply a feature of a broader metabolic syndrome and not an independent risk factor for incident hypertension (16,17,26–33). Further adjustment for these laboratory values substantially attenuated the positive association that we observed among younger men, and the association became NS. Conversely, if UA is causal in the development of the metabolic syndrome, as was suggested in rat experiments by Nakagawa et al. (40), then adjustment for these other metabolic derangements may be inappropriate.

Our study has potential limitations that deserve mention. First, we relied on self-reported hypertension and did not measure directly the BP of our participants; however, all participants are health professionals, and hypertension reporting was shown previously to be highly accurate in this cohort (19). Second, controls may have been misclassified if they were unaware of existing hypertension and thus did not report it, but because we required control subjects to have had a clinician examination during the study period, this possibility is reduced. Third, we purposefully restricted our sample to men with BMI values <30 kg/m². Although this limits the generalizability of our findings to nonobese men, Nakanishi et al. (11) found that the association between UA and hypertension was stronger among leaner men. Finally, we may have had insufficient power to detect an association in the age-stratified analyses; therefore, a true association among younger but not older men remains possible.

Conclusion

Plasma UA level was not associated with incident hypertension in older men; the association that was observed among men who were younger than 60 yr was confounded in fully adjusted models. We believe that these findings are important for several reasons. Our study is the first to examine this association in older men, who shoulder the larger share of the hypertension disease burden. This study also is the first to control simultaneously for renal function and metabolic factors, including insulin resistance and dyslipidemia, in addition to other confounders. Our findings should be confirmed by subsequent studies in older individuals; moreover, future investigations of the UA–hypertension relation should control for metabolic factors that may confound this association.

Acknowledgments

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Disclosures

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