Uric Acid and Insulin Sensitivity and Risk of Incident Hypertension

John P. Forman, MD, MSc; Hyon Choi, MD, DrPH; Gary C. Curhan, MD, ScD

Background: Uric acid, insulin sensitivity, and endothelial dysfunction may be important in the development of hypertension. Corresponding circulating biomarkers are associated with risk of hypertension, but because these factors may be interrelated, whether they independently affect risk is unknown.

Methods: In 1496 women aged 32 to 52 years without hypertension at baseline, we prospectively analyzed the associations between fasting plasma levels of uric acid, insulin, triglycerides, the insulin sensitivity index, and 2 biomarkers associated with endothelial dysfunction (homocysteine and soluble intercellular adhesion molecule-1) and the odds of incident hypertension. Odds ratios were adjusted for standard risk factors and then for all biomarkers plus estimated glomerular filtration rate and total cholesterol level. Population-attributable risk was estimated for biomarkers significantly associated with hypertension.

Results: All the biomarkers were associated with incident hypertension after adjustment for standard hypertension risk factors. However, after simultaneously controlling for all the biomarkers, estimated glomerular filtration rate, and total cholesterol level, only uric acid and insulin levels were independently associated with incident hypertension. Comparing the highest and lowest quartiles of uric acid levels, the odds ratio was 1.89 (95% confidence interval, 1.26-2.82). A similar comparison yielded an odds ratio of 2.03 (95% confidence interval, 1.35-3.05) for insulin levels. Using an estimated basal incidence rate of 14.6 per 1000 annually, 30.8% of all hypertension occurring in young women annually is associated with uric acid levels of 3.4 mg/dL or greater (to convert to micromoles per liter, multiply by 30.8). For insulin levels of 2.9 µU/mL or greater (to convert to picomoles per liter, multiply by 6.945), this proportion is 24.2%.

Conclusions: Differences in uric acid and insulin levels robustly and substantially affect the risk of hypertension in young women. Measuring these biomarkers in clinical practice may identify higher-risk individuals.

Hypertension is highly prevalent, affecting approximately one-third of Americans, and is a leading cause of morbidity and mortality. The etiology of hypertension is unclear in most patients. Proposed pathophysiologic mechanisms include (1) uric acid–induced activation of the renin-angiotensin system and injury to preglomerular renal vessels, (2) reduced insulin sensitivity and hyperinsulinemia with altered renal sodium handling and enhanced sympathetic tone, and (3) endothelial dysfunction with altered vascular tone and function. Measurement of these potential pathophysiologic factors may ultimately lead to identification of high-risk individuals and improved prevention.

Circulating biomarkers related to these pathophysiologic processes, specifically, uric acid, insulin, homocysteine, and endothelial dysfunction, have been associated with risk of hypertension in most studies. However, because these factors may be interrelated, it is unknown whether they are independently associated with risk of hypertension. Therefore, we measured uric acid, insulin, and triglyceride levels (to compute the insulin sensitivity index) and homocysteine and soluble intercellular adhesion molecule-1 (sICAM-1) levels (both associated with endothelial dysfunction) in a prospective nested case-control study of 1496 healthy women aged 32 to 52 years from the second Nurses’ Health Study to determine whether differences in these biomarkers precede and independently predict the onset of hypertension.

Methods

Study Population

The second Nurses’ Health Study is an ongoing prospective study of 116,671 female registered nurses that began in 1989. Participants are followed up via biennial questionnaires that gather information on health-related behaviors and medical events.
Follow-up of participants was greater than 90% through 2005. From 1997 to 1999, 29,616 participants contributed blood samples that were stored in liquid nitrogen (−130°C). We conducted a nested case-control study of incident hypertension in women who contributed blood samples and who did not have prevalent hypertension at the time of blood collection. The institutional review board at Brigham and Women’s Hospital approved this study.

We selected cases and controls from among those who met the following criteria at the time of blood collection: (1) blood sample collected after fasting for at least 8 hours, (2) no diagnosis of hypertension, (3) no use of antihypertensive medications, (4) no diagnosis of cancer (except nonmelanoma skin cancer), (5) no diagnosis of either coronary heart disease or diabetes mellitus, and (6) a body mass index (BMI) calculated as weight in kilograms divided by height in meters squared) less than 30. This last eligibility criterion was imposed because a high BMI is a powerful predictor of hypertension17,30 and the biomarkers under study.33,43

Using risk set sampling, we selected 750 cases who subsequently developed hypertension and 750 controls who did not. Controls were matched to cases on the following factors: age (within 1 year), race, date of blood sample collection (within 1 month), day of menstrual cycle if premenopausal (within 2 days), and time of day of the blood collection (within 2 hours). In addition, controls were required to have had at least 1 clinician examination during the 2 years before being selected as a control. After excluding 2 pairs with missing biomarker data, the final study population included 748 case-control pairs (N=1496).

BIOMARKER MEASUREMENT

Uric acid concentration was determined by oxidation with the specific enzyme uricase to form allantoin and hydrogen peroxide (Roche Diagnostics Corporation, Indianapolis, Indiana). The coefficient of variation (CV) using quality control samples was 3.4%. Insulin and triglyceride levels were used as biomarkers of insulin sensitivity and were measured using a radioimmunoassay and standard enzymatic methods, respectively (Roche Diagnostics Corporation); the CVs were 10.4% and 14.1%, respectively. The insulin sensitivity index (glucose disposal rate [M] corrected for fat-free mass, ie, MFFM) was calculated for participants using the following prediction equation, which includes fasting insulin and triglyceride levels (triglyceride levels converted to millimoles per liter):

\[
\text{MFFM} = e^{(2.63 - [0.20 \times \ln(\text{insulin}) - 0.31 \times \ln(\text{triglyceride})] / \ln(2)}
\]

This calculated MFFM value has been validated44 and has been accepted as an index of insulin sensitivity.44

Homocysteine concentration was measured using an enzymatic assay (Roche Diagnostics Corporation) (CV=7.4%), and the sICAM-1 level was measured using an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota) (CV=8.8%). Total cholesterol level was measured using a standard esterase-oxidase method (CV=3.3%), and creatinine was assayed using a modified version of the Jaffe method (CV=6.5%).

Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease Study formula48:

\[
186 \times \text{creatinine}^{-1.194} \times \text{age}^{-0.203} \times 1.212 \quad \text{(if black)}
\]

\[
\times 0.742 \quad \text{(if female)}
\]

ASCERTAINMENT OF OTHER COVARIATES

Age and BMI were obtained from the supplemental questionnaire that accompanied the submitted blood samples. Smoking status (never, past, or current), physical activity, and alcohol intake were ascertained from the biennial questionnaire that immediately followed submission of the blood sample (typically the 1999 biennial questionnaire). Family history of hypertension was obtained from the 1989 questionnaire; race was self-classified. Blood pressure (BP) was reported on the 1999 questionnaire in 9 systolic (SBP) categories (<105, 105-114, 115-124, 125-134, 135-144, 145-154, 155-164, 165-174, and \( \geq 175 \text{ mm Hg} \)) and 7 diastolic (DBP) categories (<65, 65-74, 75-84, 85-89, 90-94, 95-104, and \( \geq 105 \text{ mm Hg} \)). Based on these categories, we assigned participants a baseline BP using the middle value of each category; for example, if a participant reported her SBP and DBP as 125 to 134 mm Hg and 75 to 84 mm Hg, respectively, she was assigned a BP of 130/80 mm Hg. Self-reported BP in nurses has been previously validated as predictive of future cardiovascular events.40

ASCERTAINMENT OF HYPERTENSION

Clinician-diagnosed hypertension was self-reported by these health professionals on biennial questionnaires. Self-reported hypertension was highly reliable in participants in a similar cohort of nurses; specifically, the accuracy was 100% in a subsample of randomly selected participants who reported the diagnosis.47

Women were considered to have prevalent hypertension at the time of blood collection if they reported hypertension on the biennial questionnaire immediately after blood collection or on any previous questionnaire. For this study of incident hypertension, women with prevalent hypertension were excluded. In addition, women who reported taking antihypertensive medications on the questionnaire given immediately after blood collection were also excluded.

STATISTICAL ANALYSES

Because the continuous baseline variables, including the biomarker levels, were not normally distributed, differences in these variables between cases and controls were analyzed using the Wilcoxon rank sum test. Differences in categorical variables between cases and controls were compared using the \( \chi^2 \) test.

To examine the correlations among age, BMI, and the studied biomarkers, we used Spearman partial correlations, in which pairwise Spearman correlation coefficients were computed after adjusting for the other variables. For example, the Spearman correlation between BMI and uric acid level was adjusted for age, eGFR, and levels of insulin, triglycerides, homocysteine, and sICAM-1.

Associations between the biomarkers and incident hypertension were analyzed with the biomarkers as continuous variables and with the biomarkers divided into quartiles, with the lowest quartile defined as the reference group. We used conditional logistic regression conditioning on the matching factors to generate odds ratios (ORs) and 95% confidence intervals (CIs).

Two types of analyses were conducted. First, each biomarker was analyzed individually (ie, without other biomarkers in the model); the primary analyses adjusted for BMI (continuous), physical activity, alcohol intake, smoking status, and family history of hypertension. Further analyses were performed after adjusting for baseline SBP and DBP. Second, each biomarker was analyzed after also adjusting for eGFR, total cholesterol level, and all the other biomarkers.

Population-attributable risks were calculated for biomarkers using the adjusted quartile-specific OR from the final multivariable models and with the lowest quartile defined as the “unexposed” group. A baseline incidence rate of 14.6 cases per 1000 women annually (1.46% of the population per year) for the unexposed group was estimated using the incidence rate for the parent cohort (the second Nurses’ Health Study43). All
statistical analyses were conducted using a software program (SAS Institute Inc, version 9.1; Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics of the study population by case status are given in Table 1. The median age of the population was 43 years; because this was a matching factor, it did not differ in cases and controls. The median BMI was higher in cases (25.1) compared with controls (23.2). Cases were also less physically active, had higher baseline BP values, and were more likely to have a family history of hypertension. Except for eGFR, all the fasting biomarkers differed between cases and controls at baseline. Cases had higher levels of uric acid, insulin, triglycerides, total cholesterol, homocysteine, and sICAM-1; conversely, cases had lower MFFM scores.

Many of the biomarkers were correlated with each other and with age and BMI. The partial (ie, adjusted) Spearman correlation coefficients among these variables are given in Table 2. Besides the expected high correlation between MFFM and levels of insulin and triglycerides (which are used to compute MFFM), the strongest correlations were between BMI and uric acid.

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N=1496)</th>
<th>Cases (n=748)</th>
<th>Controls (n=748)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic/lifestyle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (5th-95th percentile), y</td>
<td>43 (36-49)</td>
<td>43 (36-49)</td>
<td>43 (36-49)</td>
<td></td>
</tr>
<tr>
<td>BMI, median (5th-95th percentile)</td>
<td>24.1 (19.6-29.2)</td>
<td>25.1 (20.1-29.3)</td>
<td>23.2 (19.1-28.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, median (5th-95th percentile), METS</td>
<td>12.4 (9.9-26.9)</td>
<td>11.2 (8.9-19.5)</td>
<td>13.4 (10.3-26.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>5.2</td>
<td>5.8</td>
<td>4.6</td>
<td>.29</td>
</tr>
<tr>
<td>Past smoker, %</td>
<td>22.7</td>
<td>23.5</td>
<td>21.9</td>
<td>.46</td>
</tr>
<tr>
<td>Alcohol intake, median (5th-95th percentile), g/d</td>
<td>1.6 (0.7-17.5)</td>
<td>1.5 (0.0-20.0)</td>
<td>1.0 (0.0-15.0)</td>
<td>.78</td>
</tr>
<tr>
<td>SBP, median (5th-95th percentile), mm Hg</td>
<td>120 (100-140)</td>
<td>130 (110-140)</td>
<td>110 (100-130)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP, median (5th-95th percentile), mm Hg</td>
<td>70 (60-87)</td>
<td>80 (70-90)</td>
<td>70 (60-80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Family history of hypertension, %</td>
<td>55.1</td>
<td>62.8</td>
<td>47.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fasting biomarkers, median (5th-95th percentile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>3.9 (2.7-5.6)</td>
<td>4.1 (2.8-5.8)</td>
<td>3.7 (2.5-5.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>85 (65-112)</td>
<td>86 (64-114)</td>
<td>84 (66-109)</td>
<td>.18</td>
</tr>
<tr>
<td>Insulin, µIU/mL</td>
<td>4.6 (2.1-13.2)</td>
<td>5.3 (1.4-15.6)</td>
<td>4.0 (1.1-10.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>78 (40-190)</td>
<td>88 (44-214)</td>
<td>70 (39-170)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MFFM</td>
<td>9.6 (6.0-15.0)</td>
<td>8.9 (5.4-14.0)</td>
<td>10.2 (6.5-15.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>186 (140-295)</td>
<td>191 (143-252)</td>
<td>181 (130-235)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Homocysteine, mg/L</td>
<td>1.57 (1.1-2.47)</td>
<td>1.61 (1.4-2.68)</td>
<td>1.53 (1.0-2.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>sICAM-1, ng/mL</td>
<td>241 (182-329)</td>
<td>245 (186-334)</td>
<td>238 (179-319)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; METS, metabolic equivalent task scores; MFFM, glucose disposal rate (M) corrected for fat-free mass; SBP, systolic blood pressure; sICAM-1, soluble intercellular adhesion molecule-1.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; homocysteine to micromoles per liter, multiply by 7.397; insulin to picomoles per liter, multiply by 0.0945; triglycerides to millimoles per liter, multiply by 0.0113; and uric acid to micromoles per liter, multiply by 59.485.

Both SBP and DBP were reported by participants in categories (see the “Ascertainment of Other Covariates” subsection of the “Methods” section).

Table 2. Partial Spearman Correlations Among Biomarkers, Age, and BMI

<table>
<thead>
<tr>
<th>UA</th>
<th>eGFR</th>
<th>Ins</th>
<th>Trig</th>
<th>MFFM</th>
<th>Hcy</th>
<th>sICAM-1</th>
<th>Age</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.17b</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ins</td>
<td>0.09c</td>
<td>0.10c</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trig</td>
<td>0.11b</td>
<td>0.001</td>
<td>0.19b</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFFM</td>
<td>-0.15b</td>
<td>-0.09b</td>
<td>-0.96b</td>
<td>-0.92b</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hcy</td>
<td>0.13b</td>
<td>-0.20b</td>
<td>-0.008</td>
<td>0.11b</td>
<td>-0.06d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.19d</td>
<td>-0.06d</td>
<td>0.06d</td>
<td>0.13b</td>
<td>-0.14b</td>
<td>0.06d</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.04</td>
<td>-0.12b</td>
<td>-0.01</td>
<td>0.11b</td>
<td>-0.07d</td>
<td>0.06d</td>
<td>-0.11b</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI</td>
<td>0.22b</td>
<td>0.03</td>
<td>0.27b</td>
<td>0.19b</td>
<td>-0.35b</td>
<td>0.01</td>
<td>0.08c</td>
<td>0.09b</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; Ins, fasting insulin; MFFM, glucose disposal rate (M) corrected for fat-free mass; sICAM-1, soluble intercellular adhesion molecule-1; Trig, fasting triglycerides; UA, uric acid.

*Each correlation coefficient is adjusted for the other biomarkers except for MFFM. Correlations between MFFM and other variables are not adjusted for Ins and Trig, except for the correlations between MFFM and Ins and Trig.  

*P < .001.  

c P < .01.  

d P < .05.
The median uric acid level was 3.9 mg/dL (to convert to micromoles per liter, multiply by 59.485), and less than 1% of the population had uric acid levels that would be considered abnormally elevated (≥7.0 mg/dL). When uric acid was examined in quartiles, the OR for the highest compared with the lowest quartile was 2.17 (95% CI, 1.51-3.11) (Table 3). When uric acid was examined in quartiles, the OR for the highest compared with the lowest quartile was 2.17 (95% CI, 1.51-3.11) (Table 3). After further adjusting for baseline SBP and DBP, the same comparison remained significant (OR, 1.79; 95% CI, 1.11-2.87).

Uric acid was also analyzed after further adjusting for eGFR and levels of total cholesterol, triglycerides, insulin, homocysteine, and sICAM-1 (Table 3); the results were attenuated but remained significant. Every 1-mg/dL increase in uric acid level was associated with a 1.25-fold higher odds of incident hypertension (95% CI, 1.89 (95% CI, 1.26-2.82).

INSULIN SENSITIVITY

The median values for insulin, triglycerides, and MFFM were 6.6 µIU/mL (to convert to picomoles per liter, multiply by 6.945), 78 mg/dL (to convert to millimoles per liter, multiply by 0.0113), and uric acid to micromoles per liter, multiply by 5.9485). Fewer than 10% of participants (r = 0.22), insulin (r = 0.27), triglycerides (r = 0.19), and MFFM (r = 0.35) and between eGFR and uric acid (r = -0.17) and homocysteine (r = -0.20) (P < .001 for all).

Table 3. Associations Between Multiple Biomarkers and Risk of Incident Hypertension

<table>
<thead>
<tr>
<th>Fasting Biomarker</th>
<th>Continuous</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>3.0 (1.5-3.3)</td>
<td>3.7 (3.4-3.9)</td>
<td>4.2 (4.0-4.5)</td>
<td>5.1 (4.6-8.8)</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>748</td>
<td>134</td>
<td>189</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Model 1 a</td>
<td>1.33 (1.15-1.53)</td>
<td>1.43 (1.02-2.00)</td>
<td>1.72 (1.21-2.46)</td>
<td>2.17 (1.51-3.11)</td>
<td></td>
</tr>
<tr>
<td>Model 2 b,c,d</td>
<td>1.25 (1.06-1.46)</td>
<td>1.27 (0.88-1.82)</td>
<td>1.62 (1.10-2.40)</td>
<td>1.89 (1.26-2.82)</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), µIU/mL</td>
<td>2.0 (0.2-2.8)</td>
<td>3.8 (2.9-4.6)</td>
<td>5.8 (4.7-7.0)</td>
<td>9.6 (7.1-128.8)</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>718</td>
<td>137</td>
<td>159</td>
<td>242</td>
<td></td>
</tr>
<tr>
<td>Model 1 a</td>
<td>1.14 (1.07-1.22)</td>
<td>1.08 (0.78-1.51)</td>
<td>1.37 (0.97-1.92)</td>
<td>2.41 (1.64-3.54)</td>
<td></td>
</tr>
<tr>
<td>Model 2 e</td>
<td>1.11 (1.03-1.18)</td>
<td>1.03 (0.73-1.45)</td>
<td>1.22 (0.85-1.74)</td>
<td>2.03 (1.35-3.05)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>48 (12-58)</td>
<td>68 (59-78)</td>
<td>92 (79-109)</td>
<td>143 (110-580)</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>748</td>
<td>147</td>
<td>162</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Model 1 a</td>
<td>1.07 (1.02-1.13)</td>
<td>1.13 (0.81-1.58)</td>
<td>1.67 (1.20-2.34)</td>
<td>1.75 (1.22-2.50)</td>
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<tr>
<td>Model 2 f,g</td>
<td>1.02 (0.96-1.08)</td>
<td>1.00 (0.70-1.44)</td>
<td>1.39 (0.95-2.03)</td>
<td>1.15 (0.75-1.76)</td>
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<tr>
<td>MFFM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.8 (2.6-7.8)</td>
<td>8.9 (7.9-9.5)</td>
<td>10.4 (9.6-11.5)</td>
<td>13.0 (11.6-24.3)</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>718</td>
<td>231</td>
<td>147</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Model 1 a</td>
<td>0.89 (0.84-0.93)</td>
<td>0.91 (0.63-1.30)</td>
<td>0.51 (0.35-0.74)</td>
<td>0.52 (0.35-0.76)</td>
<td></td>
</tr>
<tr>
<td>Model 2 e</td>
<td>0.92 (0.87-0.97)</td>
<td>1.00 (0.69-1.45)</td>
<td>0.62 (0.42-0.92)</td>
<td>0.69 (0.46-1.04)</td>
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<tr>
<td>Homocysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), mg/L</td>
<td>1.22 (0.68-1.35)</td>
<td>1.46 (1.35-1.57)</td>
<td>1.70 (1.58-1.87)</td>
<td>2.14 (1.88-6.63)</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>748</td>
<td>160</td>
<td>186</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Model 1 a</td>
<td>1.13 (1.05-1.22)</td>
<td>1.15 (0.84-1.57)</td>
<td>1.43 (1.03-1.99)</td>
<td>1.38 (0.99-1.93)</td>
<td></td>
</tr>
<tr>
<td>Model 2 g,h</td>
<td>1.08 (0.99-1.18)</td>
<td>1.19 (0.85-1.68)</td>
<td>1.40 (0.97-2.02)</td>
<td>1.27 (0.86-1.88)</td>
<td></td>
</tr>
<tr>
<td>sICAM-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), ng/mL</td>
<td>186 (93-217)</td>
<td>229 (218-241)</td>
<td>255 (242-269)</td>
<td>296 (270-697)</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>745</td>
<td>163</td>
<td>182</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>Model 1 a</td>
<td>1.08 (1.03-1.15)</td>
<td>1.30 (0.92-1.82)</td>
<td>1.29 (0.91-1.84)</td>
<td>1.58 (1.08-2.29)</td>
<td></td>
</tr>
<tr>
<td>Model 2 g,h</td>
<td>1.06 (0.99-1.12)</td>
<td>1.18 (0.82-1.71)</td>
<td>0.97 (0.74-1.61)</td>
<td>1.18 (0.78-1.79)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MFFM, glucose disposal rate (M) corrected for fat-free mass; sICAM-1, soluble intercellular adhesion molecule-1.

a Also adjusted for fasting insulin, triglyceride, homocysteine, and sICAM-1 levels as continuous variables.

b Also adjusted for uric acid, triglyceride, homocysteine, and sICAM-1 levels as continuous variables.

c Also adjusted for fasting insulin, triglyceride, homocysteine, and sICAM-1 levels as continuous variables.

d Also adjusted for uric acid, fasting insulin, homocysteine, and sICAM-1 levels as continuous variables.

e Also adjusted for uric acid, homocysteine, and sICAM-1 levels as continuous variables.

f Also adjusted for uric acid, fasting insulin, triglyceride, and sICAM-1 levels as continuous variables.

g Also adjusted for uric acid, fasting insulin, triglyceride, and homocysteine levels as continuous variables.

h Also adjusted for uric acid, fasting insulin, triglyceride, homocysteine, and sICAM-1 levels as continuous variables.

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The median homocysteine concentration in the study was 1.57 mg/L; 10% of participants had elevated homocysteine concentrations (>2.03 mg/L).31 The median sICAM-1 level was 241 ng/mL (similar to other populations).32-35

After multivariate adjustment, every 0.27 mg/L increase in homocysteine was associated with a 1.13-fold higher odds of incident hypertension (95% CI, 1.05-1.22) (Table 3). The attributable risk associated with hyperhomocysteinemia was 24.2% of hypertension occurring in young women is associated with an insulin level of 2.9 µIU/mL or greater.

### ESTIMATED POPULATION-ATTRIBUTABLE RISK

We estimated the percentage of incident hypertension potentially attributable to higher uric acid and insulin levels, which were the 2 biomarkers independently associated with hypertension (Table 4). The population-attributable risk associated with the top 3 quartiles of uric acid (ie, uric acid ≥3.4 mg/dL) was 6.51 cases of hypertension per 1000 women per year. Given an estimated baseline incidence rate of 14.6 cases per 1000 young women annually, 30.8% of hypertension occurring in young women is associated with an uric acid level of 3.4 mg/dL or greater. The attributable risk associated with insulin levels of 2.9 µIU/mL or greater was 4.65 cases per 1000 young women annually. Therefore, an estimated 24.2% of hypertension occurring in young women is associated with an insulin level of 2.9 µIU/mL or greater.
In 1496 nonobese young women without hypertension, diabetes mellitus, or coronary disease at baseline, small differences in uric acid and insulin levels independently predicted clinically important increases in the odds of the subsequent development of hypertension. A substantial magnitude of the population risk may be attributable to higher uric acid and insulin levels. Furthermore, these associations were observed within ranges of these biomarkers that would be considered “normal.”

Higher uric acid concentrations were independently associated with increased odds of developing hypertension. To date, 14 prospective studies12-23 have examined this association; of these, 12 studies12,15-25 have documented a direct association with either incident hypertension or increase in BP. Most of these studies were not fully adjusted for other physiologic variables, such as renal function, lipid levels, and measures of insulin resistance; controlling for these factors is important given that higher uric acid levels may be coincident with alterations in these other metabolic variables.52,56 Of the 3 studies13,21,23 that fully adjusted for these physiologic variables (eGFR, lipid levels, insulin levels, or insulin resistance), all involved considerably older populations and 2 consisted only of men. Thus, the present study represents the only fully adjusted study consisting of young women.

The proposed mechanism linking uric acid with the onset of hypertension stems from a rat model of moderate hyperuricemia.57-59 Mazzei et al58 showed that rats made hyperuricemic developed increases in BP that were reversible by lowering the uric acid concentration. Furthermore, hyperuricemia was associated with endothelial dysfunction, activation of the renin-angiotensin system, and preglomerular vascular disease.57-59

However, substantial quantities of circulating uric acid are only a feature of advanced primates in whom the uricase gene is deleted; rodents, in contrast, have very low uric acid levels due to functional uricase.60 Furthermore, uric acid is a powerful antioxidant,61,62 and intravenous infusion of uric acid into humans actually improves endothelial function.63 Thus, it is not clear that the association between uric acid and hypertension is causal. Even if a randomized trial showed that uric acid lowering by xanthine oxidase inhibition decreased BP, this would not establish causality because xanthine oxidase is an important enzyme in the generation of oxidative stress and endothelial dysfunction.64 Indeed, a recent study in patients with heart failure demonstrated that allopurinol use improved endothelial dysfunction, whereas uric acid level lowering to a similar degree using probenecid (a uricosuric) did not.65 Nevertheless, the present data demonstrate that in relatively healthy young women, small differences in plasma uric acid levels, even within the reference range, powerfully predict the development of hypertension.

We also observed direct associations between insulin and triglyceride levels and incident hypertension as well as an inverse association between a validated estimate of the insulin sensitivity index and incident hypertension. Triglyceride levels, however, were not independently associated in the final models. Several studies66-27 have examined the association between measures of insulin sensitivity (or resistance) and the risk of hypertension. In the present study, even after controlling for biomarkers from other proposed pathophysiologic pathways, we observed a strong association between insulin levels (and MFFM) and risk of incident hypertension.

Several theories exist to explain how insulin may promote hypertension. First, hyperinsulinemia may inhibit the sympathetic nervous system.6 Several placebo-controlled studies using euglycemic clamp techniques demonstrated that insulin infusion is associated with an increase in plasma norepinephrine concentrations and SBP.57 Second, insulin may stimulate the renin-angiotensin system and enhance renal sodium reabsorption. Euglycemic clamp studies66 have shown that insulin infusion increases plasma-renin activity and angiotensin II levels. Furthermore, insulin infusion into healthy individuals leads to a reduction in sodium excretion.67-69

Higher levels of homocysteine and sICAM-1 are associated with endothelial dysfunction,31-36 and, in turn, endothelial dysfunction has been proposed as a risk factor for hypertension.70 Only 2 prospective analyses69,20 have examined the association between homocysteine concentrations and the risk of incident hypertension; none have examined sICAM-1. Neither of the homocysteine studies observed an association with hypertension. Although we noted significant associations between homocysteine and sICAM-1 levels and incident hypertension after adjustment for standard risk factors and BP, these associations were no longer significant after the other biomarkers were considered.

The present study has limitations that deserve mention. First, we relied on self-reported hypertension and did not directly measure the BP of the participants; however, all the participants are registered nurses, and hypertension reporting by nurses is highly accurate.47 Second, controls may have been misclassified if they were unaware of existing hypertension, but because we required controls to have had a clinician examination during follow-up, this possibility is reduced. Furthermore, this sort of misclassification tends to produce less significant results; therefore, the present findings may represent an underestimate of true associations. Third, because the CVs for the insulin and triglyceride assays were greater than 10%, measurement error (and, as a result, misclassification of these biomarker levels) may have occurred. Because measurement error is typically random, this type of misclassification would also tend to produce less significant results; therefore, the observed associations between insulin levels, MFFM, and hypertension risk may indeed represent underestimations of the true relations. Fourth, we lacked information about the inflammatory biomarker C-reactive protein, which was observed in a previous study71 of women to be associated with hypertension; however, that study did not adjust for uric acid levels or markers of insulin sensitivity. Moreover, the present study included sICAM-1, which is also considered to be a prominent inflammatory biomarker.54,55 Fifth, we purposefully restricted the sample to women with BMI values less than 30. Although this
limits the generalizability of the findings to nonobese women, other studies have suggested that the associations between a variety of these biomarkers and hypertension are stronger in leaner individuals. Finally, the study population was almost entirely white. Therefore, the findings are not necessarily generalizable to other races.

In conclusion, small differences in uric acid levels and insulin sensitivity, even within ranges considered normal, are robustly and substantially associated with an increased risk of hypertension in young women. Measuring these biomarkers in clinical practice may identify higher-risk individuals. Future studies are required to determine whether strategies to lower the levels of these biomarkers translate into a lower risk of hypertension.

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Author Contributions: Dr Forman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Forman, Choi, and Curhan. Acquisition of data: Forman and Choi. Analysis and interpretation of data: Forman, Choi, and Curhan. Drafting of the manuscript: Forman. Critical revision of the manuscript for important intellectual content: Forman, Choi, and Curhan. Statistical analysis: Forman and Curhan. Obtained funding: Forman, Choi, and Curhan. Administrative, technical, and material support: Forman and Curhan. Study supervision: Curhan.

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