Serum uric acid levels predict new onset type 2 diabetes in hospitalized patients with primary hypertension: the MAGIC study

Running title: SUA predicts new onset diabetes in hypertension

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**Objectives.** Recent studies suggest that uric acid may predict the development of diabetes in the general population. Whether this association holds true in primary hypertension, and is independent of renal function and metabolic syndrome (MS) is unclear at present.

**Research, Design, and Methods.** In a prospective, observational study, 758 untreated hypertensive patients were evaluated at baseline and followed-up for 11 years.

**Results.** A total of 8,332 person-years of follow-up revealed that slightly elevated uric acid levels (i.e., ≥318 micromol/L for females and ≥420 micromol/L for males) at baseline were associated with a significantly higher risk of developing diabetes (HR 3.65, 95% CI 1.99 to 6.69, P <0.0001), even after adjustment for several confounding factors such as MS (HR of 2.78, 95% CI 1.35 to 5.70, P=0.0054).

**Conclusions.** Uric acid is an independent predictor of diabetes in primary hypertension.

The coexistence of diabetes and hypertension acts as a multiplier of cardiovascular risk (1). Therefore, identifying early predictors for the development of diabetes in hypertensive patients could be useful for devising more effective strategies to reduce cardiovascular risk.

Recent studies provide both a pathogenetic and epidemiological rationale for a role of serum uric acid (SUA) in the development of diabetes (2,3).

However, prospective studies investigating the impact of SUA in the development of carbohydrate disorders in primary hypertension are still lacking.

**RESEARCH DESIGN AND METHODS**
Details of the MAGIC study (Microalbuminuria: A Genoa Investigation on Complications) have previously been described (4). In brief, a total of 1,024 untreated patients with primary hypertension and without diabetes were recruited between 1993 and 1997 from among those attending several outpatient hypertension clinics in the Genoa area and were followed-up for a median of 11.0 years (1.2-14.1 years).

Among the eligible patients, 266 were excluded for various reasons, including current allopurinol treatment, history of gout or kidney stones. Attendance was voluntary, and each participant provided written informed consent. All surveys were approved by the Ethics Committee of our Institution.

During the baseline visit, at the end of the washout period, if any, height, weight, BP values, family history, and lifestyle habits were recorded. Creatinine clearance was estimated (eGFR) by means of the Cockcroft–Gault formula (5) using ideal body weight (6). Metabolic syndrome (MS) was defined according to the National Cholesterol Education Program Adult treatment Panel III (7). Since waist circumference measurements were only available for a subset of participants, we replaced abdominal obesity with overall adiposity, defined as a BMI ≥30 Kg/m².

After baseline evaluation, patients were treated on the basis of current guidelines by the referring general practitioner or specialist until censoring. The number of
events that occurred between baseline examination and the censoring date (June 17, 2006) for living persons, or the date of death were collected by examining the records of the Nominative Cause of Death Registry, the Hospitalization Discharge Records, and the Ligurian Resident Population Registry. The completeness of case findings from the sample was >98%. When an event was reported, original source documents were retrieved and reviewed independently by two members of the End-Point Committee. Events were coded according to the World Health Organization’s International Classification of Diseases, Ninth Revision (ICD-9). The primary endpoint was the development of diabetes defined as hospitalization with a diagnosis of type 2 diabetes.

Analyses were performed using Statview for Windows (version 5.0.1; SAS Institute Inc., Cary, USA). Data are expressed as mean ±SD, or median and interquartile range as appropriate. Logarithmically transformed values of skewed variables were used for the statistical analysis. Comparisons between groups were made by ANOVA and χ² test. Cox proportional hazard regression was used to estimate the hazard ratio (HR) and 95% CI for the relationship between slightly elevated uric acid level (SEUA) and/or MS and diabetes. Values of P<0.05 were considered statistically significant.

RESULTS

The study cohort was composed of 758 Caucasian hypertensive patients (56% men) aged 49±10 years with neither diabetes, prior cardiovascular events or overt nephropathy. During 8,332 person-years of follow-up, 42 patients developed diabetes; the incidence rate was 5.0/1,000 person-years. The mean SUA level was 312±90 micromol/L (348±84 micromol/L in men and 258±72 micromol/L in women). As expected, patients who developed diabetes were more likely to fulfill criteria for diagnosis of MS at baseline (49 vs 17 %, P<0.0001), and showed higher SUA and ACR baseline levels.

Patients included in the highest gender specific quintile (i.e., ≥318 micromol/L if female and ≥420 micromol/L if male) constituted the SEUA group and showed a higher incidence of diabetes (13% vs 4% P<0.001), as compared to the reference group. The unadjusted HR for the development of diabetes was 3.65 (95% CI 1.99 to 6.69, ) for SEUA and remained significant both in males (HR 2.86, 95% CI 1.33 to 6.17) and in females (HR 5.85, 95% CI 2.08 to 16.47). Univariate Cox analysis showed that each variation in BMI (HR 1.21, 95% CI 1.11 to 1.31), serum fasting glucose (HR 1.05, 95% CI 1.02 to 1.08), triglycerides (HR 1.012, 95% CI 1.009 to 1.014), HDL-cholesterol (HR 0.97, 95% CI 0.95 to 0.99), SUA (HR 1.34, 95% CI 1.11 to 1.62), ACR (HR 1.85, 95% CI 1.04 to 3.33) and the presence of MS (HR 4.28, 95% CI 2.25 to 8.16), were all significantly predictors of diabetes. The relationship between SUA and the development of the endpoint persisted even after adjustment for several variables, included age, gender, eGFR, components of MS and MS as a whole (HR 2.78, 95% CI 1.35-5.70, P=0.0054). The presence of SEUA and/or MS increased the event rates of diabetes over the 14 years of follow-up (P for trend <0.0001, Table 1). The independent contribution of SEUA was stronger in females, with a five-fold greater risk of developing diabetes in women with SEUA and without MS as compared to women with neither of these risk factors (Table 1). While the presence of both conditions
entails an almost ten-fold higher risk of developing diabetes regardless of gender, the presence of only one of the two abnormalities is significantly related to diabetes in females but not in males (Table 1).

DISCUSSION
The present study shows that over long term follow-up, SUA is a powerful predictor of incident type 2 diabetes in primary hypertension, especially in females. The excess of risk associated with SEUA was similar to that observed in the presence of obesity (3.59, P<0.0001), comparable to that in the presence of MS (4.28, P<0.0001), and was independent of the presence of MS and other potential confounders. Interestingly, SEUA proved to be the only risk factor independently related to the development of diabetes in females.

Although our study cannot address pathophysiological mechanisms, the independent contribution of SUA to the risk of incident diabetes that we report integrate and support previous findings both in animal models and in clinical studies (8-10).

The strengths of the present study include the prospective design and the fact that it relates to patients not on medication at baseline and at relatively low risk of developing diabetes. Our data do not prove a cause-effect relationship, however, showing that hypertensive men with uric acid ≥420 micromol/L and women with uric acid ≥318 micromol/L have an increased risk of developing diabetes, confirm (11-12) and emphasize the usefulness of a more widespread, systematic evaluation of uric acid in an effort to guide the management of hypertension, especially in females.

Author Contributions. F.V. conceived and designed the research, acquired, analyzed and interpreted the data, performed statistical analysis, and wrote the manuscript, G.L. analyzed and interpreted the data, contributed to discussion and reviewed/edited manuscript, M.V. researched data, G.D. contributed to discussion, R.P. contributed to discussion and reviewed/edited manuscript.

ACKNOWLEDGMENTS
There are no conflicts of interest.

REFERENCES
Table. Comparison of fourteen year event rates and hazard ratios on the basis of presence/absence of metabolic syndrome and/or SEUA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabtases</th>
<th>All</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower SUA quintiles without MS</td>
<td>14-year rates per 100±SD</td>
<td>2.7</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>SEUA without MS</td>
<td>6.4</td>
<td>6</td>
<td>2.32 (0.88-6.12)</td>
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<tr>
<td>Lower SUA quintiles with MS</td>
<td>8.8</td>
<td>8</td>
<td>3.45 (1.43-8.33)</td>
<td>0.0058</td>
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<tr>
<td>SEUA with MS</td>
<td>22.7</td>
<td>14</td>
<td>8.85 (3.88-20.20) &lt;0.0001</td>
<td>7.27 (2.65-20.08) &lt;0.0001</td>
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<tr>
<td>Multivariate model</td>
<td></td>
<td></td>
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<tr>
<td>SEUA with MS</td>
<td>9.31 (3.00-29) &lt;0.0001</td>
<td>11.63 (3.40-40) &lt;0.0001</td>
<td>10.85 (2.2-54) 0.0085</td>
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</tr>
<tr>
<td>Lower SUA quintiles with MS</td>
<td>4.36 (1.80-10) 0.0016</td>
<td>2.47 (0.76-8.1) 0.1340</td>
<td>6.59 (1.3-33) 0.0210</td>
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<tr>
<td>SEUA without MS</td>
<td>2.75 (1.01-7.2) 0.0462</td>
<td>2.39 (0.62-9.2) 0.2064</td>
<td>5.22 (1.10-26) 0.0433</td>
<td></td>
</tr>
<tr>
<td>Age for each 1 year increment</td>
<td>1.05 (1.01-1.1) 0.0150</td>
<td>1.07 (1.01-1.1) 0.0162</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum glucose ≥ 6.1 mmol/L</td>
<td>-</td>
<td>-</td>
<td>3.35 (1.10-9.8) 0.0269</td>
<td>-</td>
</tr>
</tbody>
</table>

Covariates that were considered potential confounders of the relationship between SEUA and development of diabetes were included in the multivariate models. The final models for the optimal prediction of diabetes were fitted, in each gender, by backward elimination of insignificant baseline variables (P ≥ 0.05, i.e., BMI ≥ 30 Kg/m², Systolic BP, diastolic BP, Triglycerides ≥ 1.65 mmol/L, HDL cholesterol < 1.04 mmol/L in males ad < 1.29 mmol/L in females, eGFR ml/min). The presence of SEUA and/or MS showed a strong, independent relationship to the end-point for the whole cohort and for the females.

* Compared to the group with lower gender specific quintiles of serum uric acid and without Metabolic Syndrome. HR, hazard ratio; SUA, serum uric acid; MS, metabolic syndrome, eGFR, estimated glomerular filtration rate