Serum Uric Acid Levels Predict New-Onset Type 2 Diabetes in Hospitalized Patients With Primary Hypertension: The MAGIC Study

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OBJECTIVE — 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 is not clear 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 µmol/l for women and ≥420 µmol/l for men) at baseline were associated with a significantly higher risk of developing diabetes (hazard ratio 3.65 [95% CI 1.99–6.69], P < 0.0001), even after adjustment for several confounding factors such as metabolic syndrome (2.78 [1.35–5.70], P = 0.0054).

CONCLUSIONS — Uric acid is an independent predictor of diabetes in primary hypertension.
and/or metabolic syndrome and diabetes. $P < 0.05$ was 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, nor 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 ± SD SUA level was 312 ± 90 μmol/l (348 ± 84 μmol/l in men and 258 ± 72 μmol/l in women). As expected, patients who developed diabetes were more likely to fulfill the criteria for diagnosis of metabolic syndrome at baseline (49 vs. 17%; $P < 0.0001$) and showed higher SUA and albumin-to-creatinine ratio baseline levels.

Patients included in the highest sex-specific quintile (i.e., ≥318 μmol/l if female and ≥420 μmol/l if male) constituted the SEUA group and showed a higher incidence of diabetes (13 vs. 4%; $P < 0.001$) than the reference group. The unadjusted HR for the development of diabetes was 3.65 (95% CI 1.99–6.69) for SEUA and remained significant in both men (HR 2.86 [95% CI 1.33–6.17]) and women (5.85 [2.08–16.47]). Univariate Cox analysis showed that variations in BMI (1.21 [1.11–1.31]), serum fasting glucose (1.05 [1.02–1.08]), triglycerides (1.012 [1.009–1.014]), HDL cholesterol (0.97 [0.95–0.99]), SUA (1.34 [1.11–1.62]), and albumin-to-creatinine ratio (1.85 [1.04–3.33]) and the presence of the metabolic syndrome (4.28 [2.25–8.16]) were all significant predictors of diabetes. The relationship between SUA and the development of the end point persisted even after adjustment for several variables, including age, sex, eGFR, components of metabolic syndrome and metabolic syndrome as a whole (2.78 [1.35–5.70]; $P = 0.0054$).

The presence of SEUA and/or metabolic syndrome increased the event rates of diabetes over the 14 years of follow-up ($P_{\text{trend}} < 0.0001$) (Table 1). The independent contribution of SEUA was stronger in women, with a 5-fold greater risk of developing diabetes in women with SEUA and without metabolic syndrome compared with that of women with neither of these risk factors (Table 1). Whereas the presence of both conditions entails an almost 10-fold higher risk of developing diabetes regardless of sex, the presence of only one of the two abnormalities is significantly related to diabetes in women but not in men (Table 1).

**CONCLUSIONS**— 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 women. The excess of risk associated with SEUA was similar to that observed in the presence of obesity (3.59; $P < 0.0001$) and comparable to that in the presence of metabolic syndrome (4.28; $P < 0.0001$) and was independent of the presence of metabolic syndrome and other potential confounders. Of interest, SEUA proved to be the only risk factor independently related to the development of diabetes in women.

Although our study cannot address pathophysiological mechanisms, the independent contribution of SUA to the risk of incident diabetes that we report integrates and supports 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 receiving medication at baseline and at a relatively low risk of developing diabetes. Our data do not prove a cause-effect relationship; however, showing that hypertensive men with uric acid ≥420 μmol/l and women with uric acid ≥318 μmol/l have an increased risk of developing diabetes confirms (11,12) and emphasizes the usefulness of a more widespread, systematic evaluation of uric acid in an effort to guide the management of hypertension, especially in women.
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F.V. conceived and designed the research, acquired the data, 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 the manuscript. M.V. researched data. G.D. contributed to discussion. R.P. contributed to discussion and reviewed/edited the manuscript.

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