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.

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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 Microalbuminuria: A Genoa Investigation on Complications (MAGIC) study have been described previously (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 (range 1.2–14.1 years).

Among the eligible patients, 266 were excluded for various reasons, including current allopurinol treatment and 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, blood pressure values, family history, and lifestyle habits were recorded. Creatinine clearance was estimated (estimated glomerular filtration rate [eGFR]) by means of the Cockcroft-Gault formula (5) using ideal body weight (6). Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (7). Because waist circumference measurements were only available for a subset of participants, we replaced abdominal obesity with overall adiposity, defined as BMI ≥30 kg/m^2.

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 (17 June 2006) for living individuals or the date of death was 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 ICD-9. The primary end point 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 , Cary, NC). Data are means ± SD or medians (interquartile range) as appropriate. Logarithmically transformed values of skewed variables were used for the statistical analysis. Comparisons between groups were made by ANOVA and χ^2 test. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% CI for the relationship between slightly elevated uric acid (SEUA) level

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Table 1—*Comparison of 14-year event rates and HRs on the basis of the presence or absence of metabolic syndrome and/or SEUA*

	Diabetes							
	All				Men		Women	
Variable	14-year rates per 100 ± SD	No. Events	HR (95%CI)*	*P* value	HR (95%CI)*	*P* value	HR (95%CI)*	*P* value
Unadjusted model								
Lower SUA quintiles without MS	2.7	14	—		—		—	—
SEUA without MS	6.4	6	2.32 (0.88–6.12)	0.0876	1.47 (0.41–5.37)	0.5,527	5.23 (1.05–26.04)	0.0430
Lower SUA quintiles with MS	8.8	8	3.45 (1.43–8.33)	0.0058	2.47 (0.85–7.24)	0.0982	6.81 (1.37–33.75)	0.0188
SEUA with MS	22.7	14	8.85 (3.88–20.20)	<0.0001	7.27 (2.65–20.08)	<0.0001	14.62 (3.27–65.35)	0.0004
Multivariate model								
SEUA with MS			9.31 (3.00–29)	<0.0001	11.63 (3.40–40)	<0.0001	10.85 (2.2–54)	0.0085
Lower SUA quintiles with MS			4.36 (1.80–10)	0.0016	2.47 (0.76–8.1)	0.1340	6.59 (1.3–33)	0.0210
SEUA without MS			2.75 (1.01–7.2)	0.0462	2.39 (0.62–9.2)	0.2064	5.22 (1.10–26)	0.0433
Age for each 1- year increment			1.05 (1.01–1.1)	0.0150	1.07 (1.01–1.1)	0.0162	—	—
Serum glucose ≥6.1 mmol/l			—	—	3.35 (1.10–9.8)	0.0269	—	—

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 sex, by backward elimination of insignificant baseline variables ($P \geq 0.05$, i.e., BMI ≥ 30 kg/m^2, systolic blood pressure, diastolic blood pressure, triglycerides ≥1.65 mmol/l, HDL cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women, and eGFR [milliliters per minute]). The presence of SEUA and/or metabolic syndrome showed a strong, independent relationship to the end-point for the whole cohort and for women. MS, metabolic syndrome. *Compared with the group with lower sex-specific quintiles of SUA and without metabolic syndrome.

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, included 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 ($P_{trend} < 0.0001$) (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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