

# Elevated Serum Uric Acid Concentrations Independently Predict Cardiovascular Mortality in Type 2 Diabetic Patients

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**OBJECTIVE** — There is limited information on whether increased serum uric acid levels are independently associated with cardiovascular mortality in type 2 diabetes. We assessed the predictive role of serum uric acid levels on all-cause and cardiovascular mortality in a large cohort of type 2 diabetic individuals.

**RESEARCH DESIGN AND METHODS** — The cohort included 2,726 type 2 diabetic outpatients, who were followed for a mean period of 4.7 years. The independent association of serum uric acid levels with all-cause and cardiovascular mortality was assessed by Cox proportional hazards models and adjusted for conventional risk factors and several potential confounders.

**RESULTS** — During follow-up, 329 (12.1%) patients died, 44.1% ( $n = 145$ ) of whom from cardiovascular causes. In univariate analysis, higher serum uric acid levels were significantly associated with increased risk of all-cause (hazard ratio 1.19 [95% CI 1.12–1.27],  $P < 0.001$ ) and cardiovascular (1.25 [1.16–1.34],  $P < 0.001$ ) mortality. After adjustment for age, sex, BMI, smoking, hypertension, dyslipidemia, diabetes duration, A1C, medication use (allopurinol or hypoglycemic, antihypertensive, lipid-lowering, and antiplatelet drugs), estimated glomerular filtration rate, and albuminuria, the association of serum uric acid with cardiovascular mortality remained statistically significant (1.27 [1.01–1.61],  $P = 0.046$ ), whereas the association of serum uric acid with all-cause mortality did not.

**CONCLUSIONS** — Higher serum uric acid levels are associated with increased risk of cardiovascular mortality in type 2 diabetic patients, independent of several potential confounders, including renal function measures.

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Cardiovascular disease (CVD) represents the most common cause of morbidity and mortality in the type 2 diabetic population (1,2). Several biochemical parameters have been associated with increased risk for CVD in type 2 diabetes (3–5). Increased levels of serum uric acid are quite common in type 2 diabetic patients (6), and they might represent an additional CVD risk factor in these patients (7,8).

Whereas several prospective studies have consistently demonstrated that ele-

vated serum uric acid levels are an independent risk factor for CVD mortality in the general population (9–13), there is currently a paucity of available data on the association between serum uric acid levels and CVD mortality in the type 2 diabetic population. In a small retrospective study of 535 type 2 diabetic patients, it was found that higher serum uric acid levels were significantly associated with an increased risk of all-cause mortality (14). However, no information was available on specific causes of mortality in such

studies, and no adjustment was made for important risk factors, such as diabetes duration and albuminuria. In another small study of 581 elderly type 2 diabetic patients, it was found that higher serum uric acid levels independently predicted cardiovascular mortality, but the authors did not adjust for glycemic control, use of medications, and albuminuria (15). In this respect, it is important to emphasize that the progressive decline in kidney function, which frequently occurs with aging and the course of type 2 diabetes, is also generally paralleled by progressive increases in serum uric acid levels (16). Thus, the presence of renal dysfunction, as assessed by glomerular filtration rate and albuminuria, should be always taken into account when the association of serum uric acid levels with mortality is explored, especially in the type 2 diabetic population.

The aim of this prospective study was to investigate whether an association does exist between serum uric acid concentrations and all-cause and cardiovascular mortality in a large cohort of type 2 diabetic individuals, independent of several baseline confounding factors, including markers of kidney function.

## RESEARCH DESIGN AND METHODS

The study was performed within the framework of the Verona Diabetes Study, an observational longitudinal study on chronic complications in type 2 diabetic outpatients attending the Diabetes Clinic at the University Hospital of Verona (2,17,18). For this study, we initially considered all type 2 diabetic outpatients, who regularly attended our clinic during years 2000–2002 ( $n = 3,924$ ). Type 2 diabetes was established when diagnosis was made at age  $>35$  years, irrespective of treatment, or when the disease was treated with diet or oral hypoglycemic agents, irrespective of age at diagnosis. After excluding 1) patients ( $n = 881$ , 22.5% of total), who had a history of malignancy, severe chronic obstructive pulmonary disease, end-stage renal disease, or CVD (defined as angina, myocardial infarction, coronary or peripheral revascularization procedures,

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and stroke), and 2) those ( $n = 198$ ; 5% of total), who had missing data for albuminuria, serum uric acid, and creatinine concentrations, 2,845 type 2 diabetic patients (72.5% of total) were included in the study. The local ethics committee approved the study protocol. All participants gave their informed consent.

BMI was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure was measured with a standard mercury manometer. Information on diabetes duration, previous diseases, current use of medications, and smoking status was obtained for all patients by interviews during medical visits.

In all patients, venous blood was withdrawn in the morning after an overnight fast for a standard biochemical workup. Serum uric acid, lipids, creatinine, and other biochemical blood measurements were determined by automatic colorimetric methods (DAX 96; Bayer Diagnostics, Milan, Italy). LDL cholesterol was calculated by the Friedewald formula. A1C was measured by a high-performance liquid chromatography analyzer (Diamat; Bio-Rad, Milan, Italy), and the upper limit of normality was 5.8%. Glomerular filtration rate (GFR) was estimated from the abbreviated Modification of Diet in Renal Disease (MDRD) formula (19) as follows: estimated GFR (eGFR) =  $186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$  (if black) or  $\times 0.742$  (if female). Urinary albumin was measured by an immunonephelometric method on an early morning spot sample, collected three times, and was expressed as the albumin-to-creatinine ratio. Microalbuminuria and macroalbuminuria were defined as an albumin-to-creatinine ratio  $>2.5$  and  $>30$  mg/mmol for men and  $>3.5$  and  $>30$  mg/mmol for women, respectively (20).

Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg or current use of any treatment with antihypertensive medications. Detailed information regarding specific classes of antihypertensive drugs was not currently available in our informatic database. Atherogenic dyslipidemia was diagnosed when plasma triglycerides were  $\geq 1.7$  mmol/l and/or HDL cholesterol was  $<1.04$  mmol/l or when patients were taking lipid-lowering agents. Hyperuricemia was diagnosed when the serum uric acid concentration was  $\geq 416$   $\mu\text{mol/l}$  in men

and  $\geq 386$   $\mu\text{mol/l}$  in women, respectively, or when patients were taking allopurinol.

Vital status was ascertained by examining the electronic databases of the Social Health Unit of the Veneto Region, which include all records of mortality occurring within the Veneto Region as well as individual causes of death. The ascertainment at the end of follow-up (mean  $\pm$  SD duration  $4.7 \pm 0.8$  years, range 1–5 years) was 96% complete. Subjects ( $n = 119$ ) who moved and could not be traced were classified as being lost during the follow-up and then were excluded from analysis.

Participants who attended the follow-up examinations ( $n = 2,726$ ) were essentially similar to those of the initial cohort ( $n = 3,924$ ), to those who had missing data for albuminuria, serum uric acid, and creatinine concentrations ( $n = 198$ ), and to those who did not attend the follow-up examinations ( $n = 119$ ) in terms of demographic variables, glycemic control, and diabetes duration.

The causes of death were identified by reviewing death certificates, which were available in 100% of cases. Death certificates were coded by trained nosologists using the ICD-9. The death was attributed to cardiovascular causes when ICD-9 codes were 390–459.

### Statistical analysis

Subjects were stratified into tertiles of serum uric acid, which were calculated separately in men (i.e., lower tertile  $<270$ , middle tertile 270–330, and upper tertile  $>330$   $\mu\text{mol/l}$ ) and women ( $<230$ , 230–300, and  $>300$   $\mu\text{mol/l}$ , respectively). Skewed variables were logarithmically transformed to improve normality before analyses. ANOVA and the  $\chi^2$  test with Yates's correction for continuity (for categorical variables) were used to compare clinical and biochemical features across tertiles of serum uric acid. Kaplan-Meier analysis was used to determine univariate survival according to sex-specific serum uric acid tertiles, and the significance was calculated by the log-rank test. The Cox proportional hazards model was used to assess the independent association of serum uric acid levels (included as a continuous variable) with all-cause and cardiovascular mortality. Three multivariate regression models were performed. The first one included serum uric acid (micromoles per liter), age (years), sex (male vs. female), BMI (kilograms per square meter), A1C (percentage), diabe-

tes duration (years), smoking status (current vs. former/never), hypertension (yes/no; see definition above), atherogenic dyslipidemia (yes/no; see definition above), LDL cholesterol (millimoles per liter), and current use of medications (allopurinol, antiplatelet, and hypoglycemic drugs) (yes/no). A second multivariate regression model also included eGFR (milliliters per minute per  $1.73$   $\text{m}^2$ ), and a third model also included albuminuria (categorized as normal, microalbuminuria, and macroalbuminuria). In supplementary multivariate regression analyses, serum uric acid levels were replaced by hyperuricemia included as a categorical measure. The covariates included in the three multivariate regression models were chosen as potential confounders based on their biological plausibility or statistical association with mortality in univariate analysis. Forced entry models were used, i.e., all covariates were simultaneously included in the regression models. Results are presented as hazard ratios (HRs) with 95% CIs, and statistical significance was evaluated by the likelihood ratio test. HRs for continuous variables were computed for 1-SD change. Statistical analyses were performed with SPSS (version 14.0).  $P < 0.05$  was considered statistically significant.

**RESULTS** — Hyperuricemia was present in 16.1% ( $n = 438$ ) of the whole cohort of participants. Among them, 225 type 2 diabetic patients were taking allopurinol. The baseline clinical and biochemical characteristics of participants grouped by sex-specific serum uric acid tertiles are shown in Table 1. Compared with those in the lower tertile, patients in the upper tertile of serum uric acid levels were more likely to be male, older, overweight/obese, and hypertensive and to be taking oral hypoglycemic, antihypertensive, and antiplatelet agents. They also had a shorter duration of diabetes and were less likely to be smokers and treated with insulin. Patients in the upper tertile of serum uric acid levels also had higher values of LDL cholesterol, triglycerides, and albuminuria and lower values of A1C, HDL cholesterol, and eGFR.

During the follow-up period, 329 (12.1%) participants died, 145 (44.1%) of whom from cardiovascular causes. Numbers of deaths and cumulative incidence rates of all-cause mortality were 81 (9.8%), 103 (10.7%), and 145 (15.4%) across tertiles of serum uric acid levels, respectively ( $P < 0.001$  for trend). Ac-

**Table 1—Baseline clinical and biochemical characteristics of type 2 diabetic patients stratified into sex-specific tertiles of serum uric acid levels**

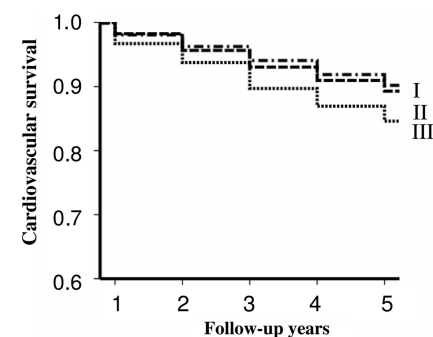
	Tertile I	Tertile II	Tertile III	P
Sex (male/female)	475/349	482/479	550/391	<0.001
Age (years)	67 ± 10	67 ± 10	68 ± 9	0.006
Current smokers	26.1	20.7	23.2	0.009
Diabetes duration (years)	16 ± 9	15 ± 9	15 ± 9	0.004
BMI (kg/m <sup>2</sup> )	27.1 ± 4.4	28.3 ± 4.5	29.4 ± 4.8	<0.001
Hypertension	80	85.6	90.8	<0.001
A1C (%)	7.7 ± 1.5	7.5 ± 1.5	7.4 ± 1.4	<0.001
LDL cholesterol (mmol/l)	3.3 ± 0.9	3.4 ± 0.9	3.4 ± 0.9	0.016
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<0.001
Triglycerides (mmol/l)	1.4 ± 1.0	1.6 ± 1.0	1.8 ± 1.0	<0.001
eGFR (ml/min per 1.73 m <sup>2</sup> )	80.5 ± 18.7	74.7 ± 17.7	66.8 ± 18.7	<0.001
Microalbuminuria	18.3	20.0	23.3	0.025
Macroalbuminuria	4.3	5.1	6.9	0.025
Serum uric acid (μmol/l)	207 ± 36	280 ± 26	388 ± 91	ND
Oral hypoglycemic drugs	54.2	60.6	57.2	0.004
Insulin therapy	37.0	30.0	31.0	0.004
Antihypertensive drugs	64.9	73.7	82.0	<0.001
Lipid-lowering drugs	44.8	46.1	47.7	0.464
Antiplatelet drugs	39.1	41.3	46.7	0.004
Allopurinol therapy	4.4	7.8	12.1	<0.001

Data are expressed as means ± SD, percent, or proportions. Cohort size, *n* = 2,726. *P* values refer to one-way ANOVA or the  $\chi^2$  test (for categorical variables). ND, not determined.

cordingly, the number of deaths and cumulative incidence rates of CVD mortality were 28 (3.4%), 43 (4.5%), and 74 (7.9%), respectively (*P* < 0.001 for trend).

Figure 1 shows the results of the Kaplan-Meier survival analysis for CVD mortality. Patients in the third tertile of serum uric acid levels had a remarkably lower survival probability than those in the first and second tertiles (*P* < 0.001 by the log-rank test).

In univariate Cox regression analysis, higher serum uric acid levels were significantly associated with an increased risk



**Figure 1—Kaplan-Meier curves of cardiovascular mortality in 2,726 type 2 diabetic patients stratified by sex-specific tertiles of serum uric acid levels. Statistical significance was estimated by the log-rank test (*P* < 0.001 for the third tertile vs. the other two tertiles).**

of all-cause (HR 1.19 [95% CI 1.12–1.27], *P* < 0.001) and CVD mortality (1.25 [1.16–1.34], *P* < 0.001). The independent association of serum uric acid levels with mortality was tested by several multivariate regression models. Higher serum uric acid levels were associated with increased risk of CVD mortality, with a ~20% increase in the CVD risk for each SD (95 μmol/l) increment, independent of age, sex, conventional risk factors, current use of medications, and other potential confounders (Table 2, model 1). When this association was also adjusted for eGFR (model 2) or for both eGFR and albuminuria (model 3), higher serum uric acid levels remained a significant positive predictor of CVD mortality. Almost identical results were found when allopurinol users (*n* = 225) were excluded from statistical analysis (data not shown). The possible presence of a statistical interaction between serum uric acid levels and eGFR was tested by introducing the product term of these two variables in Cox regression models. In the fully adjusted regression model, this interaction term was not significantly associated with CVD mortality (adjusted HR 0.88 [0.71–1.05], *P* = 0.15).

Higher serum uric acid levels were also associated with increased risk of all-cause mortality independent of age, sex,

conventional risk factors, glycemic control, medications, and eGFR (model 1: adjusted HR 1.14 [95% CI 1.06–1.23], *P* < 0.001; model 2: 1.12 [1.01–1.25], *P* = 0.043). However, the significant association between serum uric acid and all-cause mortality disappeared after further adjustment for albuminuria (model 3: 1.08 [0.96–1.27], *P* = 0.374). Interestingly, the lack of an independent association between serum uric acid levels and all-cause mortality was also confirmed by a Cox multivariate regression model in which only age, sex, eGFR, and albuminuria were included as covariates (1.06 [0.91–1.24], *P* = 0.42). Almost identical results were also found after patients who died of cardiovascular diseases were excluded. Also in this case, the significant association between serum uric acid levels and non-CVD mortality disappeared after adjustment for age, sex, eGFR, and albuminuria (0.93 [0.74–1.16], *P* = 0.51).

**CONCLUSIONS**— To our knowledge, this is the largest prospective study with the specific aim of assessing the association of serum uric acid levels with all-cause and CVD mortality in a type 2 diabetic population. Notably, in the present study the association between serum uric acid levels and mortality was adjusted for several baseline confounding factors, such as age, sex, adiposity, smoking, hypertension, dyslipidemia, diabetes duration, glycemic control, medication use, and kidney function measures.

The major finding of this study is that higher levels of serum uric acid are independently associated with increased CVD mortality but not all-cause mortality. The failure to find an independent association between serum uric acid levels and all-cause mortality after additional adjustment for albuminuria is not readily explainable, but it is unlikely that this is due to a reduced statistical power to detect an association. Indeed, the lack of an independent association between serum uric acid levels and all-cause mortality was also confirmed by a Cox regression model in which fewer covariates (i.e., age, sex, eGFR, and albuminuria) were included. Another interesting finding of our study is that higher serum uric acid levels are also independently associated with increased CVD mortality in patients with kidney dysfunction.

Whether increased serum uric acid concentrations are just a risk indicator or a causative risk factor of CVD (21,22)

Table 2—Predictors of cardiovascular mortality as assessed by multivariate Cox proportional hazards models

	Multivariate model 1	P	Multivariate model 2	P	Multivariate model 3	P
Serum uric acid ( $\mu\text{mol/l}$ )	1.21 (1.10–1.33)	<0.001	1.19 (1.02–1.38)	0.024	1.27 (1.01–1.61)	0.046
Age (years)	3.34 (2.54–4.38)	<0.001	2.76 (2.03–3.74)	<0.001	3.12 (2.11–4.62)	<0.001
Sex (male vs. female)	1.30 (0.91–1.87)	NS	1.38 (0.93–2.05)	NS	0.95 (0.57–1.58)	NS
Current smoking	1.30 (0.76–2.27)	NS	1.25 (0.69–2.23)	NS	1.18 (0.56–2.53)	NS
Diabetes duration	1.20 (1.01–1.44)	0.050	1.17 (0.97–1.42)	NS	1.26 (0.98–1.61)	NS
BMI ( $\text{kg/m}^2$ )	0.96 (0.77–1.20)	NS	0.96 (0.76–1.20)	NS	0.87 (0.65–1.15)	NS
A1C (%)	1.10 (0.90–1.35)	NS	1.01 (0.82–1.25)	NS	1.02 (0.78–1.35)	NS
Hypertension (mmHg)	0.91 (0.49–1.70)	NS	0.83 (0.41–1.69)	NS	0.64 (0.24–1.65)	NS
Atherogenic dyslipidemia	0.77 (0.53–1.16)	NS	0.69 (0.51–1.12)	NS	0.73 (0.45–1.19)	NS
LDL cholesterol (mmol/l)	1.17 (0.99–1.39)	NS	1.12 (0.94–1.34)	NS	1.16 (0.93–1.46)	NS
Oral hypoglycemic drugs	0.69 (0.36–1.35)	NS	0.93 (0.43–1.99)	NS	0.69 (0.26–1.81)	NS
Insulin therapy	1.28 (0.63–2.60)	NS	1.39 (0.62–3.15)	NS	1.00 (0.39–2.63)	NS
Antiplatelet agents	1.07 (0.74–1.55)	NS	1.11 (0.76–1.65)	NS	1.46 (0.89–2.39)	NS
Allopurinol therapy	1.24 (0.71–2.16)	NS	1.10 (0.62–1.95)	NS	1.12 (0.57–2.22)	NS
eGFR			0.56 (0.44–0.72)	<0.001	0.72 (0.53–0.96)	0.040
Microalbuminuria					1.55 (0.89–2.72)	NS
Macroalbuminuria					3.01 (1.55–5.81)	0.001

Data are HRs (95% CI). Cohort size,  $n = 2,726$ . The HRs for continuous variables were computed for 1-SD change. Atherogenic dyslipidemia was defined as triglycerides  $\geq 1.7$  mmol/l and/or low HDL cholesterol  $< 1.04$  mmol/l or on treatment. Hypertension was defined as blood pressure  $\geq 140/90$  mmHg or receiving treatment.

cannot be determined from epidemiological studies such as ours. Higher serum uric acid levels may indirectly contribute to the increased CVD risk through a close association with established risk factors, such as older age, hypertension, dyslipidemia, poor glycemic control, and chronic kidney disease. However, because in our study higher serum uric acid levels were associated with increased risk of CVD mortality independent of a broad spectrum of known risk factors, it is conceivable that serum uric acid might confer an excess risk over and above the risk expected as a result of the underlying established risk factors.

Recognition of the underlying biological mechanism(s) linking serum uric acid levels with CVD mortality is beyond the specific scope of this study. However, some putative biological mechanisms may be mentioned. Experimental studies in animals have suggested that elevated serum uric acid levels may increase the expression of chemokines and cytokines in the vasculature, activate the renin-angiotensin system, and increase systemic C-reactive protein expression (23). Accordingly, treatment with allopurinol may improve endothelial function in subjects with hyperuricemia (24) and in hypertensive type 2 diabetic patients with normal serum uric acid levels (25). However, additional studies are needed to elucidate the underlying molecular mech-

anisms before causality can be firmly established.

Overall, these findings might have potential clinical implications. Our results support the implication that the measurement of serum uric acid concentrations in individuals with type 2 diabetes may be helpful in CVD risk prediction. If results of future studies support the conclusion that increased levels of serum uric acid may play a direct role in the pathophysiology of CVD, hyperuricemia will be another target for the treatment of type 2 diabetes.

The present study has several important limitations that merit comment. These include a single baseline measurement of the variables of interest, a possible selection bias of excluding nearly 5% of the patients who had incomplete biochemical data for analysis, a possible impact of losses to follow-up, an inability to adjust for certain specific antihypertensive agents (e.g., ACE inhibitors, angiotensin receptor blockers, or loop diuretics), and an issue of multiple testing with a propensity for false-positive associations. In addition, we used eGFR instead of a directly measured GFR to define chronic kidney disease. Nonetheless, current GFR estimates facilitate the detection, evaluation, and management of chronic kidney disease, and many organizations recommend the use of prediction equations for the evaluation of kidney

function in large epidemiological studies and in clinical practice (19,20). Finally, whether these observations can also be extended to non-Caucasian ethnic groups remains to be determined.

Notwithstanding these limitations, our study has several important strengths, including its prospective design, the large number of participants, and the ability to adjust for a wide range of known risk factors and potential confounders. In addition, our patients were free of diagnosed CVD, malignancy, and kidney failure; the evaluation of patients with such complications would almost certainly have confounded interpretation of the data.

In summary, our findings suggest that higher serum uric acid levels are associated with increased risk of CVD mortality in type 2 diabetic individuals, independent of conventional risk factors, diabetes-related variables, medication use, and renal function measures.

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