



Uric Acid Is an Independent Risk Factor for Decline in Kidney Function, Cardiovascular Events, and Mortality in Patients With Type 1 Diabetes

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OBJECTIVE

Previous studies have provided inconclusive results on the role of uric acid (UA) in risk prediction. Here we aimed to improve the power and precision of the predictive value of UA for the risk of decline in kidney function, cardiovascular events (CVEs), and mortality in patients with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

Plasma UA was measured in 670 patients with T1D and various degrees of albuminuria, ranging from normoalbuminuria to macroalbuminuria. Associations of UA with an estimated glomerular filtration rate (eGFR) decline of $\geq 30\%$, CVEs, and mortality were analyzed. The median follow-up time was 5.3 years [interquartile range (IQR) 2.7–6.2 years] for a decline in eGFR of $\geq 30\%$, 5.8 years (2.5–6.4 years) for progression in albuminuria status, 5.1 years (4.7–5.6 years) for CVE, and 6.2 years (5.8–6.7 years) for mortality. Both univariable and multivariable associations of UA with relevant outcomes and variables were reported. Hazard ratios (HRs) were calculated per doubling of the UA level.

RESULTS

A doubling in UA level was associated with a higher risk of decline in eGFR of $\geq 30\%$ ($n = 89$) (HR 3.18 [IQR 1.71–5.93]; $P < 0.001$), CVE ($n = 94$) (HR 2.25 [IQR 1.20–4.21]; $P = 0.011$), and mortality ($n = 58$) (HR 2.58 [IQR 1.12–5.90]; $P = 0.025$) in adjusted analyses. Adding UA to the adjusted model including conventional risk factors improved the relative integrated discrimination index by 12.6% for a decline in eGFR of $\geq 30\%$ ($P < 0.001$), 6.5% for CVE ($P = 0.010$), and 11.8% ($P = 0.003$) for mortality. A doubling in UA level was also associated with a steeper decline in eGFR ($P < 0.0026$) and a steeper increase in urine albumin-to-creatinine ratio ($P < 0.0027$) in adjusted analysis.

CONCLUSIONS

In individuals with T1D, a higher UA level is associated with a higher risk of decline in kidney function, CVE, and mortality, independently of other risk factors. Our results suggest that UA has a promising role in risk stratification among individuals with T1D.

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In humans, uric acid is the end product of the purine nucleotide metabolism (1). Previous studies have provided inconclusive results to the role of uric acid for risk prediction. Studies have shown that elevated uric acid levels independently predict the incidence and development of chronic kidney disease both in patients without diabetes and in patients with diabetes (2–4). However, other studies have not been able to confirm these findings (5–7).

In a large Chinese population of patients with hypertension with and without diabetes, high levels of uric acid were a risk factor for all-cause and cardiovascular mortality (8). Higher uric acid level was also a significant risk factor for mortality in patients with congestive heart failure. Wheeler et al. (9) performed a case-control comparison in the general population using 2,456 patients with coronary heart disease and comparing them with 3,962 matched control subjects. They found that the association between high levels of uric acid and the risk of coronary heart disease attenuated after adjustment for traditional risk factors (9).

A cross-sectional study (10), including data from 10,956 persons from the general population with a maximum of 10 years of follow-up, found that persons with high uric acid levels had a higher risk of cardiovascular and all-cause mortality, although this relationship was not significant after adjusting for kidney function and traditional risk factors. It should, however, be considered that many of the traditional risk factors used in the model were self-reported. They also found that the association between uric acid levels and cardiovascular mortality was U-shaped, suggesting that both low and high levels of uric acid were associated with risk of cardiovascular mortality. In contrast to these findings, Liu et al. (7) demonstrated, in a population of patients with chronic stage 3–5 kidney disease with and without diabetes, that higher uric acid level was a risk factor for cardiovascular events and all-cause mortality after adjustment for traditional risk factors.

To the best of our knowledge, there are no published studies that have investigated the association between high levels of uric acid and the risk of cardiovascular and all-cause mortality in patients with type 1 diabetes.

We have previously investigated, in a cross-sectional analysis (5), the association of high levels of uric acid and diabetic complications in patients with type 1 diabetes. Here we found that high levels of uric acid were significantly associated with lower estimated glomerular filtration rate (eGFR), but not with the annual decline in eGFR after adjustment for traditional risk factors. A higher uric acid level was associated with a risk of complications, but the association attenuated after adjustment. In the present article, we are now able to add follow-up data on the hard end points of end-stage renal disease (ESRD), cardiovascular disease, and all-cause mortality to the investigation, and to collect an additional mean 1.2 years of extra follow-up data and sufficient data for assessing the annual decline in eGFR (eGFR slope) during follow-up for more patients. Here we aim to improve the power and precision of the value of uric acid for predicting the risk of decline in kidney function (including slopes for eGFR and urine albumin-to-creatinine ratio [UACR]), ESRD, progression in albuminuria status, cardiovascular events, and mortality in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Participants

Between 2009 and 2011, Caucasian patients with type 1 diabetes were recruited to enter a cross-sectional study at Steno Diabetes Center Copenhagen. The details of the study have been previously described (5,11,12). The cohort was stratified by levels of albuminuria (normoalbuminuria, microalbuminuria, and macroalbuminuria) regardless of the presence of retinopathy. Patients with ESRD, defined as receiving dialysis or renal transplantation, or GFR/eGFR of <15 mL/min/1.73 m², were not included in the study. All participants gave written informed consent, and the study was approved by the regional ethics committee.

Procedures

Uric acid was measured in plasma by a dry chemistry (MicroSlide) colorimetric slide test (VITROS 5600). The plasma samples were stored immediately after collection in freezers at -80°C and were stored for up to 8 years prior to analysis.

The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation using isotope dilution mass spectrometry–traceable serum creatinine measured using an enzyme method (Hitachi 912 Chemistry Analyzer; Roche Diagnostics GmbH, Mannheim, Germany) (13).

Three 24-h urine collections were performed to measure the urine albumin excretion rate (UAER) using an enzyme immunoassay (Vitros, Raritan, NJ). Participants were categorized as normoalbuminuric if the UAER was <30 mg/day, as microalbuminuric if UAER was or previously had been recorded between 30 and 299 mg/day, and as macroalbuminuric if the UAER was or previously had been recorded at >300 mg/day, in two of three consecutive measurements. All patients classified as normoalbuminuric did not have any history of microalbuminuria or macroalbuminuria prior to enrollment in the study.

HbA_{1c} was measured by high-performance liquid chromatography (Bio-Rad Laboratories, Munich, Germany).

Brachial blood pressure was measured after at least 10 min of rest in the sitting position with an automatic device and appropriately sized cuff. Mean arterial pressure was calculated as the diastolic blood pressure plus one-third of pulse pressure.

Participants were classified as current smokers if they smoked one or more cigarettes, cigars, or pipes per day, and all others were classified as nonsmokers.

Follow-up

In 2016, patients were traced through the Danish National Death Register and the Danish National Health Register (14,15), from which data for mortality, including date and cause of death, hospital admission, and ICD-10 diagnoses, were obtained. Deaths were classified as cardiovascular unless any other cause was determined. The cardiovascular event end point was defined as cardiovascular death, nonfatal acute myocardial infarction (ICD-10 codes I21–I24), nonfatal stroke (ICD-10 codes I61–I66), coronary interventions (procedural codes KFNA-D), and peripheral arterial interventions, including amputations. ESRD was defined as stage 5 chronic kidney disease (ICD-10 code N18.5), chronic dialysis (procedural code BJFD2), kidney transplantation (procedural codes

KKAS 00, 10, and 20), or sustained eGFR <15 mL/min/1.73 m².

Information on eGFR and UACR during follow-up was obtained at outpatient visits and was traced through electronic laboratory records. The renal end points were defined as 1) a decline in eGFR of $\geq 30\%$, as proposed by Coresh et al. (16) and as eGFR slopes, and 2) progression in albuminuria status defined as progression from normoalbuminuria (<30 mg/g) to microalbuminuria (30–299 mg/g), from normoalbuminuria to macroalbuminuria (>300 mg/g), or microalbuminuria to macroalbuminuria in two of three consecutive measurements.

The yearly change in albuminuria was calculated based on all of the available measurements from outpatient visits during follow-up in participants with at least two measurements and a minimum follow-up time duration of 3 years. Decline in eGFR was assessed as the time to the first occurrence of a $\geq 30\%$ decrease from baseline (16) and as the yearly change in eGFR. In total, sufficient information to calculate the early change in eGFR was available in 510 persons, and for UACR in 511 persons. Supplementary Fig. 1 shows a flowchart of the available data for the individual analysis.

Of the 670 patients, 94 had more than one event registered. Of these patients, 64 had two events registered, 27 had three events registered, and 3 patients had four events registered. At the event of multiple end points being registered, only the first was included for analysis. The median (interquartile range [IQR]) follow-up time was 5.3 years (2.7–6.2 years) for a decline in eGFR $\geq 30\%$, 5.3 years (4.8–5.7 years) for ESRD, 5.8 years (2.5–6.4 years) for progression in albuminuria status, 5.1 years (4.7–5.6 years) for cardiovascular events, and 6.2 years (5.8–6.7 years) for mortality.

Statistical Analysis

The distribution of uric acid and UAER was skewed, and therefore these variables were log₂ transformed in all the linear analyses and given as medians with IQRs. Normally distributed variables are given as the mean \pm SD, and categorical variables as total numbers with corresponding percentages. Baseline clinical characteristics were compared in participants with and without a cardiovascular event using unpaired *t* test and χ^2 test for continuous and categorical variables, respectively.

Hazard ratios (HRs) and 95% CIs were calculated using the Cox proportional hazard model for all end points and presented per doubling of uric acid. Adjustment included traditional risk factors and the following confounders: sex; age; BMI; HDL cholesterol; smoking; HbA_{1c}; mean arterial pressure; UAER; treatment with renin-angiotensin-aldosterone system (RAAS) blockers, statins, or antiplatelet agents; and eGFR.

We tested the linearity of the log of uric acid for the outcomes by plotting the parameter estimates of quintiles versus the means of each quintile and by demonstrating that parameter estimates of quintiles did not differ significantly from zero in a model containing the continuous variable. For all outcomes, except ESRD, the assumption was fulfilled. Therefore, we calculated the risk for participants in the highest sex-specific quartile (Q4) compared with participants in the three lowest sex-specific quartiles (Q1–Q3) in the analyses of ESRD. For the analyses of changes in eGFR and UACR, we applied linear regressions model and calculated the β -estimates per doubling of uric acid. The adjusted models included baseline sex; age; BMI; HDL cholesterol; smoking; HbA_{1c}; mean arterial pressure; UAER; treatment with RAAS blockers, statins, or antiplatelet agents; and eGFR. A general linear model was applied for calculating the albuminuria and eGFR slopes (yearly changes) for each individual using multiple follow-up measures in the R statistical platform (<https://www.r-project.org/>).

Next, the relative integrated discrimination index (rIDI), which has been suggested to be a strong method for assessing new biomarkers in supplement to traditional risk factors (17), was calculated. Finally, Kaplan-Meier functions and the log-rank test were applied to compare risks across sex-specific quartiles of uric acid.

We tested for heterogeneity in the HRs for the influence of sex and for the influence of levels of albuminuria (normoalbuminuria, microalbuminuria, and macroalbuminuria) by introducing the appropriate interaction terms in the Cox model. We have also tested for interaction between age or diabetes duration with uric acid and found no indication of interaction.

A two-tailed α -level of ≤ 0.05 was considered to be significant. Statistical

analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

Of the 670 patients, 372 (55%) were male, the mean \pm SD age was 55 ± 13 years, and the eGFR was 82 ± 26 mL/min/1.73 m². The median (IQR) uric acid concentration was 0.30 mmol/L (0.23–0.37 mmol/L), equivalent to 5.04 mg/dL (3.87–6.22 mg/dL). Participants who had experienced a cardiovascular event (Table 1) were predominantly male and older; had a longer duration of diabetes; had a lower eGFR; and had higher UAER, HbA_{1c}, blood pressure, and uric acid.

The uric acid concentration in the sex-specific quartiles were as follows: Q1: women <0.21 mmol/L; men <0.27 mmol/L; Q2: women ≥ 0.21 to <0.25 mmol/L; men ≥ 0.27 to <0.32 mmol/L; Q3: women ≥ 0.25 to ≤ 0.33 mmol/L; men ≥ 0.32 to ≤ 0.37 mmol/L; and Q4: women >0.33 mmol/L; men >0.37 mmol/L.

Uric Acid Association With Renal End Points, Cardiovascular Events, and Mortality

During follow-up, 13% of patients ($n = 89$) had a decline in eGFR of $\geq 30\%$, 3% ($n = 21$) had received a diagnosis of ESRD, 5.4% ($n = 36$) had albumin progression, 14% ($n = 94$) experienced a cardiovascular event, and 9% ($n = 58$) died. Cause of death was registered in 19% of patients ($n = 11$) to cardiovascular disease, in 12% ($n = 7$) to cancer, in 26% ($n = 15$) to diabetes-related diseases (i.e., not cardiovascular disease), and in 19% ($n = 11$) to other cases.

Comparison of the proportion of end points across sex-specific quartiles of uric acid showed that uric acid in the upper quartile consistently encompassed the highest number of events for all end points compared with the three lower quartiles. The event rates across the quartiles of decline in eGFR of $\geq 30\%$ (8, 9, 25, 50; $P < 0.001$), albuminuria progression (6, 8, 9, 12; $P = 0.65$), ESRD (0, 0, 3, 18; $P < 0.001$), cardiovascular events (9, 13, 21, 50; $P < 0.001$), and mortality (5, 6, 19, 27; $P < 0.001$). Kaplan-Meier plots (Fig. 1) illustrates the risk of decline in eGFR of $\geq 30\%$, cardiovascular events, and mortality across the sex-specific quartiles demonstrating highly

Table 1—Clinical characteristics in 667 participants with type 1 diabetes with or without a cardiovascular event stratified by the occurrence of a CVE during a median of 5.1 years of follow-up

| | Without a CVE | With a CVE | <i>P</i> |
|------------------------------------|------------------|-------------------|----------|
| Number of participants | 573 | 94 | |
| Female (%) | 47 | 34 | 0.033 |
| Age (years) | 54 ± 13 | 61 ± 9 | <0.001 |
| Diabetes duration (years) | 31 ± 16 | 41 ± 13 | <0.001 |
| eGFR (mL/min/1.73 m ²) | 84 ± 25 | 67 ± 26 | <0.001 |
| UAER (mg/24 h) | 14.5 (7.6–52.5) | 47.9 (20.0–218.8) | <0.001 |
| HbA _{1c} (mmol/mol) | 64 ± 13 | 68 ± 12 | 0.005 |
| HbA _{1c} (%) | 8 ± 1.2 | 11 ± 1.1 | 0.005 |
| HDL cholesterol (mmol/L) | 1.7 ± 0.5 | 1.6 ± 0.6 | 0.08 |
| LDL cholesterol (mmol/L) | 2.4 ± 0.7 | 2.6 ± 0.9 | 0.07 |
| BMI (kg/m ²) | 25.4 ± 6.0 | 25.7 ± 4.1 | 0.65 |
| Treatment with | | | |
| Antihypertensive drugs (%) | 67 | 99 | <0.001 |
| Diuretics (%) | 46 | 79 | <0.001 |
| RAAS blockers (%) | 63 | 93 | <0.001 |
| Antiplatelet agent* (%) | 48 | 81 | <0.001 |
| Statins (%) | 57 | 81 | <0.001 |
| Smokers (%) | 20 | 22 | 0.68 |
| Systolic blood pressure (mmHg) | 131 ± 17 | 137 ± 19 | 0.001 |
| Diastolic blood pressure (mmHg) | 74 ± 9 | 73 ± 10 | 0.007 |
| Plasma uric acid (mmol/L) | 0.29 (0.23–0.35) | 0.37 (0.29–0.47) | <0.001 |

Data represent percentage (%), mean ± SD, or median (IQR). *P* values represent differences between participants with or without a CVE. CVE, cardiovascular event. *Antiplatelets are acetylsalicylic acid and clopidogrel.

significant trends ($P < 0.001$ for all; log-rank test).

The increase in uric acid level, expressed as the HR per doubling of uric acid, at baseline was associated with a higher risk of decline in eGFR of $\geq 30\%$ in both the unadjusted and adjusted analyses ($P < 0.001$) (Table 2). Moreover, the addition of uric acid to the adjusted model containing conventional risk factors including eGFR improved the rIDI by 12.6% ($P < 0.001$). Uric acid level in the highest quartile was associated with a higher risk of ESRD in the unadjusted analysis ($P < 0.001$), but the association was attenuated after adjustment ($P = 0.35$) when compared with the three lower quartiles. Uric acid was not associated with progression of albuminuria.

An increase of uric acid, expressed as HR per doubling of uric acid, was associated with a higher risk of cardiovascular events in both the unadjusted and adjusted analysis ($P < 0.011$), and the addition of uric acid to the adjusted model improved rIDI by 8.7% ($P = 0.010$).

An increase of uric acid, expressed as HR per doubling of uric acid, was a significant predictor of mortality in both the unadjusted and adjusted analysis

($P = 0.025$). Adding uric acid to the adjusted model improved the rIDI by 11.8% ($P = 0.003$).

None of the tests for heterogeneity in relation to the influence of sex or levels of albuminuria reached significance in either the unadjusted or adjusted analyses ($0.09 < P < 0.87$).

In the regression model of changes in eGFR and UACR during follow-up, the increase of uric acid, expressed as HR per doubling of uric acid, was associated with a steeper yearly decline in eGFR ($P = 0.0026$) (Table 3) in the adjusted analysis and in a steeper yearly increase in UACR in both the unadjusted and adjusted analysis ($P < 0.0027$).

Sensitivity Analysis

The results were similar overall when diabetes duration was included in the adjusted analysis.

CONCLUSIONS

We investigated the value of uric acid for predicting the risk of the development of complications in patients with type 1 diabetes. The key findings can be summarized as follows: 1) an increase of uric acid, expressed as HR per doubling of

uric acid, is a significant and independent risk factor for loss of renal function, both when assessed as the development of a decline in eGFR of $\geq 30\%$ or as a yearly decline in eGFR, and cardiovascular events and mortality; 2) uric acid is a contributing factor in risk stratification models on top of established risk factors for the same end points evaluated with the rIDI statistics; and 3) an increase of uric acid, expressed as HR per doubling of uric acid, is an independent risk factor for an increase in UACR.

To the best of our knowledge, the predictive value of uric acid has never been evaluated in relation to the prospective development of cardiovascular events and mortality in patients with type 1 diabetes. Previous studies have provided inconclusive results as to the role of uric acid in the risk of the development of diabetic kidney disease. Here we demonstrated that an increase of uric acid, expressed as HR per doubling of uric acid, was independently associated with a higher risk of decline in eGFR of $\geq 30\%$, whereas we had no power to assess the association with the risk of ESRD. This is in contrast to the study by Hsu et al. (18), who found that uric acid in the lowest and the highest quartile was a significant predictor of ESRD in the general population along with traditional risk factors. Liu et al. (7) demonstrated no independent association between uric acid in the upper quartiles and rapid renal progression (eGFR slope below -6 mL/min/1.73 m²/year) or increased risk for commencing renal replacement therapy in patients with stage 3–5 chronic kidney disease with and without diabetes. We have previously demonstrated that uric acid in the highest quartile was associated with a GFR decline of below -5 mL/min/1.73 m²/year in the adjusted model in patients with type 1 diabetes (6). We also found that uric acid interacted with both albuminuria and GFR, so that uric acid, albuminuria, and eGFR were no longer predictors on their own (6). In the current study, we also demonstrated that an increase of uric acid, expressed as HR per doubling of uric acid, was significantly associated with a steeper yearly decline in eGFR after adjustment for traditional risk factors. This is interesting because this contrasts with the cross-sectional data previously reported in this cohort (5). Here we found no association between

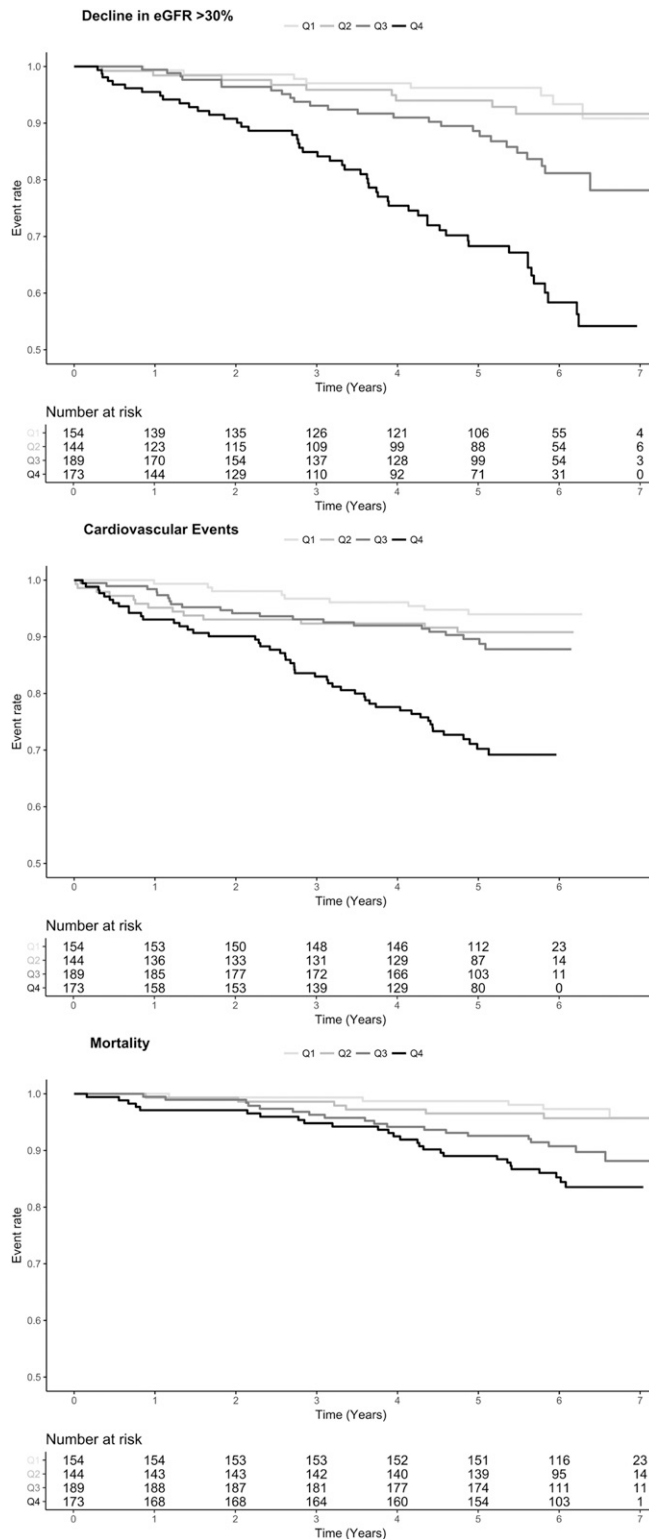


Figure 1—Kaplan-Meier failure function estimates for quartiles of uric acid for a risk of decline in eGFR of $\geq 30\%$ (top), cardiovascular events (middle), and mortality (bottom; $P < 0.001$ for all, log-rank test).

uric acid in the highest sex-specific quartile and annual decline in eGFR compared with the three lower quartiles. We consider that the differences in these results may be explained by the fact that we

were able to include more patients in the analyses; the first analysis had 476 patients with eGFR follow-up data whereas the new analysis included 510 patients with eGFR follow-up data. We were also able

to increase the period of follow-up from 4.1 to 5.3 years in the current study. Thus, the current study has significantly improved the precision of the slope estimates as well as the power to evaluate the association between decline in GFR and uric acid.

In our study, we found that an increase of uric acid, expressed as HR per doubling of uric acid, was not associated with the progression of albuminuria categories, but an increase of uric acid was significantly associated with a steeper yearly increase in UACR. This may be explained by the relatively few patients progressing from normoalbuminuria, to microalbuminuria, to macroalbuminuria. At Steno Diabetes Center Copenhagen, we have previously reported an association between uric acid in the highest quartile at baseline and an increased risk for the development of persistent macroalbuminuria in patients with type 1 diabetes followed from the onset of diabetes with 18 years of follow-up (19). Jalal et al. (20) demonstrated that uric acid levels at baseline predict the transition from normoalbuminuria to microalbuminuria or macroalbuminuria as well as the progression of subclinical atherosclerosis in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study, including patients with type 1 diabetes.

In our study, the increase of uric acid, expressed as HR per doubling of uric acid, was significantly associated with higher risk of cardiovascular events. This is interesting because we did not find any association between uric acid in the upper sex-specific quartile and the presence of cardiovascular disease in the cross-sectional analysis previously reported in this cohort (5). Liu et al. (7) demonstrated that high levels of uric acid were a predictor of cardiovascular events in subjects with stage 3–4 chronic kidney disease. Zoppini et al. (21) conducted a study in patients with type 2 diabetes and found that higher uric acid level was associated with increased risk of cardiovascular mortality, with a 20% increase in the cardiovascular risk for each 0.95 mmol/L increment of uric acid independently of conventional risk factors. The study by Madero et al. (22) included young patients who predominantly did not have diabetes but had stage 3–4 chronic kidney disease and found that hyperuricemia was an independent risk factor for cardiovascular mortality. Other

Table 2—Risk of mortality, cardiovascular events, decline in eGFR \geq 30%, albumin progression, and ESRD in relation to an increase of uric acid in patients with type 1 diabetes expressed as HR per doubling of uric acid

| | Total mortality | | CVE | | Decline in eGFR \geq 30% | | Albumin progression | | ESRD | |
|---------------------------------|---------------------|--------|---------------------|--------|----------------------------|--------|---------------------|------|---------------------|--------|
| | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Number of participants included | 667 | | 667 | | 669 | | 667 | | 665 | |
| Events, n (%) | 58 (8.7) | | 94 (14.0) | | 89 (13.3) | | 36 (5.4) | | 21 (3.2) | |
| Unadjusted | 3.74 (2.23–6.28) | <0.001 | 4.16 (2.76–6.28) | <0.001 | 5.25 (3.47–7.95) | <0.001 | 1.28 (0.66–2.51) | 0.47 | 18.2 (5.36–61.8) | <0.001 |
| Adjusted* | 2.58 (1.12–5.90) | 0.025 | 2.25 (1.20–4.21) | 0.011 | 3.18 (1.71–5.93) | <0.001 | 0.95 (0.37–2.46) | 0.91 | 2.23 (0.41–12.1) | 0.35 |
| rDI (%) | 11.8 | 0.003 | 6.5 | 0.010 | 12.6 | <0.001 | 1.4 | 0.93 | — | — |

Values are HR (95% CI), which express the risk per doubling of uric acid and for ESRD express the risk for participants in Q4 vs. Q1–3. Adjustment included sex; age; BMI; HDL cholesterol; smoking; HbA_{1c}; mean arterial pressure; UAER; treatment with RAAS blockers, statins, or antiplatelet agents; and eGFR. CVE, cardiovascular event. *The adjusted analyses included 628 participants because of missing variables.

studies, however, have not been able to confirm these findings (23–25).

We demonstrated that an increase of uric acid, expressed as HR per doubling of uric acid, was independently and significantly associated with a higher risk of all-cause mortality. This contrasts with the study performed by Zoppini et al. (21), who found a significant association with cardiovascular mortality, but no association between uric acid and all-cause mortality, but this study was conducted in patients with type 2 diabetes. Kuo et al. (26) showed a U-shaped association among uric acid, all-cause mortality, and cardiovascular mortality, as the risk of mortality was higher in patients with high or very low uric acid levels independent of traditional risk factors, in a cohort study of patients with and without diabetes. In the present study, we found no U-shaped association between uric acid levels and all-cause mortality, cardiovascular disease, and decline in kidney function.

Preclinical studies have identified mechanisms that are thought to be the way uric acid induces cardiovascular

and renal disease. In animal models, uric acid is causally linked with hypertension mediated by renal vasoconstriction due to activation of the renin-angiotensin system and reduction in endothelial levels of nitric oxide (27–29). It has also been demonstrated that high levels of uric acid per se induced and accelerated kidney disease without depositing uric acid crystals. Introducing xanthine oxidase inhibitor or a uricosuric agent to reduce uric acid levels in rats has been shown to reduce and prevent hypertension, renal hypertrophy, and proteinuria (28,29).

Several studies have investigated the effect of uric acid lowering by allopurinol in the clinical setting, but these studies have been small in sample size and open labeled, and generalization of the results is limited because of the selected study populations, and the results have been inconclusive. Thus, in a short-term study we found no effect of allopurinol on UAER/UAER, which may be explained the short duration of the study as longer studies did show a benefit (30). We are currently investigating the long-term

(3 years) effect of lowering uric acid levels in persons with type 1 diabetes as part of a multicenter trial, using a randomized, placebo-controlled study design in the Preventing Early Renal Function Loss (PERL) study (31).

The strengths of this study include that the cohort is large and well defined, and represents 20% of the type 1 diabetes population in the region. Moreover, the cohort contains all stages of albuminuria, and no persons were lost to follow-up. Limitations include the lack of generalizability because of patient recruitment from a single center, potentially limiting its application, as well as uric acid concentrations being measured in stored plasma samples. There is no consensus in the literature as to whether uric acid is stable when stored at -80°C (32,33). Information on the prescription of uric acid-lowering therapy, including specific information on treatment with losartan, was not available. Moreover, information on the diagnosis of gout was lacking. Patients who declined to participate were younger than those who participated, and thus we cannot exclude that the results are less representative for a younger cohort. Finally, we have previously published different associations between uric acid and a decline in renal function in the same cohort; thus, this could be a chance finding, but we believe that the increased precision from the longer duration of follow-up, the inclusion of additional follow-up data, and the consistency in the findings across renal end points support the current results.

In conclusion, the increase of uric acid, expressed as HR per doubling of uric acid,

Table 3—Associations between uric acid and yearly change in eGFR and UACR in patients with type 1 diabetes followed for 5.3 years

| | Yearly change in eGFR (n = 510) | | Yearly change in UACR (n = 511) | |
|------------|---------------------------------|--------|---------------------------------|--------|
| | β (SE) | P | β (SE) | P |
| Unadjusted | -0.37 (0.22) | 0.09 | 0.0035 (0.001) | <0.001 |
| Adjusted* | -0.90 (0.30) | 0.0026 | 0.035 (0.011) | 0.0027 |

Uric acid is log₂ transformed, thus 1 unit corresponds to a doubling of uric acid. The β -estimates represent the effect per doubling of uric acid. Adjustment included sex; age; BMI; HDL cholesterol; smoking; HbA_{1c}; mean arterial pressure; UAER; treatment with RAAS blockers, statins, or antiplatelet agents; and eGFR. *The adjusted analyses, for both eGFR and UACR, included 481 participants because of missing variables.

is associated with a higher risk of decline in kidney function, cardiovascular events, and mortality, independent of other risk factors in patients with type 1 diabetes. Our results suggest that uric acid has a promising role in risk stratification among patients with type 1 diabetes, including improved rIDI, and as a target for the prevention of renal function loss.

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Duality of Interest. Outside of this study, P.R. has given lectures for Astra Zeneca, Novo Nordisk, Eli Lilly, Bayer, and Boehringer Ingelheim; has served as a consultant for AbbVie, Astra Zeneca, BMS, Eli Lilly, Boehringer Ingelheim, Astellas, Janssen, and Novo Nordisk, with all fees given to Steno Diabetes Center Copenhagen; and has an equity interest in Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.P.-L. interpreted the data and wrote the manuscript. T.W.H. performed the statistical analysis and reviewed/edited the manuscript. N.T. and S.A.W. collected all data regarding the follow-up. S.T. performed the original study, including data collection, and reviewed/edited the manuscript. T.S.A. calculated the follow-up data on eGFR decline and review/edited the manuscript. P.R. reviewed/edited the manuscript. P.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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