

High-Normal Serum Uric Acid Increases Risk of Early Progressive Renal Function Loss in Type 1 Diabetes

Results of a 6-year follow-up

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OBJECTIVE— We previously described a cross-sectional association between serum uric acid and reduced glomerular filtration rate (GFR) in nonproteinuric patients with type 1 diabetes. Here, we prospectively investigated whether baseline uric acid impacts the risk of early progressive renal function loss (early GFR loss) in these patients.

RESEARCH DESIGN AND METHODS— Patients with elevated urinary albumin excretion ($n = 355$) were followed for 4–6 years for changes in urinary albumin excretion and GFR. The changes were estimated by multiple determinations of albumin-to-creatinine ratios (ACRs) and serum cystatin C (GFRcystatin).

RESULTS— At baseline, the medians (25th–75th percentiles) for uric acid, ACR, and GFRcystatin values were 4.6 mg/dl (3.8–5.4), 26.2 mg/g (15.1–56.0), and 129 ml/min per 1.73 m² (111–145), respectively. During the 6-year follow-up, significant association ($P < 0.0002$) was observed between serum uric acid and development of early GFR loss, defined as GFRcystatin decline exceeding 3.3% per year. In baseline uric acid concentration categories (in mg/dl: <3.0 , 3.0–3.9, 4.0–4.9, 5.0–5.9, and ≥ 6), the risk of early GFR loss increased linearly (9, 13, 20, 29, and 36%, respectively). This linear increase corresponds to odds ratio 1.4 (95% CI 1.1–1.8) per 1 mg/dl increase of uric acid. The progression and regression of urinary albumin excretion were not associated with uric acid.

CONCLUSIONS— We found a clear dose-response relation between serum uric acid and risk of early GFR loss in patients with type 1 diabetes. Clinical trials are warranted to determine whether uric acid-lowering drugs can halt renal function decline before it becomes clinically significant.

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The paradigm of early diabetic nephropathy in type 1 diabetes has changed during the past few years. Previously, it focused on urinary leakage of small amounts of albumin, designated microalbuminuria, which was believed to predict progression to overt proteinuria

and ultimately end-stage renal disease (ESRD) (1). However, recent studies (2,3) documented that rather than progression, regression to normoalbuminuria is the fate of microalbuminuria in the majority of patients. Progression to proteinuria is the fate in a minority only. At the same

time, the onset of progressive renal function loss was observed in a subset of these patients well before the onset of proteinuria (4). Because this decline occurs while renal function is still normal, we label it “early” progressive renal function loss (early GFR loss). Whereas microalbuminuria may regress, remain stable, or progress during the course of diabetes, early GFR loss progresses to chronic kidney disease (CKD) and ESRD (4–6).

Because early GFR loss is detectable while renal function is normal or elevated, an opportunity may exist for effective intervention many years before the occurrence of meaningful loss of renal function. However, our knowledge of early GFR loss determinants is limited (4). Discovery of these determinants, especially modifiable ones, may enable the design of more effective programs for the prevention of CKD and ESRD.

A body of evidence suggests that elevated serum uric acid may cause kidney injury in animal models (7). Also, mounting evidence points to a role of elevated serum uric acid in the development of kidney disease in humans. In cohort studies of subjects without diabetes, hyperuricemia predicted the development of CKD stage 3 (8) and ESRD (9,10), and in community-based cohorts moderately elevated serum uric acid concentrations were associated with the development of CKD stage 3 (11,12). Recently, in a type 1 diabetic cohort in Denmark, moderately elevated uric acid concentrations were found to be associated with risk of proteinuria during an 18-year follow-up (13). However, changes in renal function were not examined.

The Second Joslin Study on the Natural History of Microalbuminuria in Type 1 Diabetes (Second Joslin Study) is a follow-up study designed to determine the natural history of early diabetic nephropathy in nonproteinuric patients with type 1 diabetes. In baseline data, high-normal serum uric acid concentration was strongly associated with reduced glomerular filtration rate (GFR), as estimated by

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serum cystatin C (GFR_{cystatin}) (14). Whether elevated serum uric acid preceded or followed reduced GFR could not be determined in that cross-sectional data. Therefore, we prospectively measured GFR_{cystatin} during 4–6 years of follow-up and investigated the association between baseline serum uric acid concentration and changes in renal function. A secondary aim was to explore the role of serum uric acid in the progression and regression of urinary albumin excretion.

RESEARCH DESIGN AND METHODS

The study protocol and informed consent procedures were approved by the Committee on Human Subjects of the Joslin Diabetes Center.

This study is a prospective follow-up study on the impact of baseline levels of serum uric acid on changes in renal function and urinary albumin excretion over the next 4–6 years of follow-up.

Participants included in this report are members of the Second Joslin Study, a prospective follow-up study described previously (14). Briefly, any patient aged 18–64 years with type 1 diabetes who attended the Joslin Clinic during 2003–2005 and had at least two albumin-to-creatinine ratios (ACRs) determined during the 2 preceding years was potentially eligible for enrollment with an entry examination. Eligibility was restricted further to New England residents with diabetes diagnosed before age 40 years and who were continuously treated with insulin. Exclusion criteria included presence of proteinuria, ESRD, kidney transplant, or comorbidity such as HIV, hepatitis C, or non-diabetes-related kidney disease. Ninety percent of patients identified themselves as white. A total of 667 patients were examined and enrolled in the Second Joslin Study.

Previously we found that risk of early GFR loss was very low in patients with type 1 diabetes and low normoalbuminuria (median ACR <10 mg/g in women and 8 mg/g in men) (4), we excluded such patients ($n = 183$) from the follow-up phase of the Second Joslin Study. The remaining 484 patients had baseline high normoalbuminuria (ACR median 8–24 mg/g in women and 10–16 mg/g in men, $n = 180$) or microalbuminuria (ACR median 25–354 mg/g in women and 17–249 mg/g in men, $n = 304$) and were followed until the end of 2009 with the aim of examining and obtaining serum and urine specimens annually.

For this study, we excluded 35 patients with CKD stage 3 or higher at baseline, two patients without baseline uric acid measurements, 35 patients treated with diuretics, and 1 treated with allopurinol. Of the remaining 411 patients eligible for follow-up, 355 (86%) had multiple measures (median = 5) of serum cystatin C to estimate GFR and multiple determinations of ACR (median = 5) during 4 years of follow-up.

Entry examination and measurements of exposures

At the entry examination, a trained study recruiter administered a questionnaire on medical and diabetes history, including medication usage; obtained blood and urine samples; and measured seated blood pressures twice, separated by a 5-min rest. Medical record review supplemented questionnaire information as needed.

Clinical characteristics (A1C, ACR, and serum cholesterol and HDL) measured at routine clinic visits during the preceding 2 years were retrieved from electronic laboratory records. The median of repeated determinations within the 2-year interval (including entry examination) was used as the baseline value. All other baseline characteristics were measured at entry examination.

Details of the assay for uric acid have been published previously (14). Uric acid was measured using a timed end point method on a Beckman Coulter Synchron CX9. Of the patients enrolled in this study, 262 had follow-up uric acid measurements within 2 years of baseline measurement. The correlation coefficient (Spearman) between first and second measurements was 0.78. In our lab, the interassay coefficient of variation for uric acid was <2%.

Follow-up examination

Participants were followed yearly to measure GFR_{cystatin} and level of microalbuminuria over the next 4–6 years. The examination and collection of specimens coincided with patients' routine clinic visits. Patients who stopped coming to the clinic were examined at their homes.

Measurement of GFR_{cystatin}

Serum cystatin C has been shown to estimate GFR and track GFR changes over time well in patients with diabetes and normal or elevated renal function (4,15,16). In 2009, serum cystatin C was measured in stored (–85 C) baseline and

follow-up samples in the collaborative studies clinical laboratory at the University of Minnesota using the Dade-Behring-Siemens BN ProSpec (Siemens Healthcare Diagnostics, Deerfield, IL). The method's interassay laboratory coefficient of variation is ~4.7%. GFR_{cystatin} was estimated from the serum concentration of cystatin C using a recently improved conversion formula (17) ($127.7 \times \text{CysC}^{-1.17} \times \text{age}^{-0.13} \times [0.91 \text{ if female, } 1.06 \text{ if black}]$) (13).

Measurement of urinary albumin excretion

The protocol for measuring urinary ACR in spot urines during prior clinic visits and during follow-up remained unchanged as described previously (14).

Definition of renal outcomes

While our primary outcome is early GFR loss, the study design allowed simultaneous assessment of changes in renal function and changes in urinary albumin excretion. The definition of these outcomes follows.

Early GFR loss

We calculated individual-specific slopes of GFR_{cystatin} during follow-up with linear mixed-effects regression (PROC MIXED, SAS version 9.1; SAS Institute, Cary, NC). From these slopes, we derived each individual's percent change per year in GFR_{cystatin}. Next, we grouped patients into 1) those with early GFR loss (if the loss of GFR_{cystatin} exceeded 3.3% per year) and 2) those with stable renal function (if the loss of GFR_{cystatin} was 3.3% or less per year). This criterion, a loss exceeding than 3.3% per year, was derived by us previously (4) and corresponds to the 2.5th percentile of the distribution of GFR slopes in an independent, similarly aged population without diabetes (18).

CKD stage 3 or greater

CKD stage 3 is defined as a GFR_{cystatin} value <60 ml/min per 1.73 m². Patients with CKD stage 3 or greater at baseline were excluded. If CKD stage 3 developed during the 4–6 years of follow-up, the outcome date was that of the first GFR_{cystatin} <60 ml/min per 1.73 m².

Change in ACR

To evaluate changes in urinary albumin excretion for each patient, we divided observation time into three 2-year intervals. The median ACR measurement in the

2-year interval preceding enrollment was the baseline value. Similarly, during the first two 2-year intervals after enrollment, the median ACR measurement in each was considered the first and second follow-up value, respectively. ACR progression was defined as a doubling of baseline ACR value during either of these intervals. ACR regression was defined as a halving of baseline ACR value during either interval.

Statistical methods

All statistical analyses were performed in SAS version 9.1 (SAS Institute). Comparisons between those with early GFR loss and those with stable renal function at the end of follow-up used medians and Wilcoxon rank sum tests for continuous variables and percentages and χ^2 tests for categorical variables. The odds of developing early GFR loss or ACR progression or regression were estimated with logistic regression. Characteristics associated with uric acid or early GFR loss were evaluated as potential confounders in multivariate models. Characteristics were retained if they changed the relation between uric acid and early GFR loss by $\geq 10\%$. Controlling for baseline values of an exposure of interest is controversial if the study outcome is change in that same characteristic over time (19). We provide results both ways: controlling and not controlling for baseline values of GFRcystatin for early GFR loss or ACR for change in ACR.

Longitudinal measures of log-transformed GFRcystatin levels were also analyzed using a linear mixed-effects model. This model takes into account irregular time measurements and correlation between longitudinal observations. In building the model, we applied a likelihood ratio test to fixed effects of uric acid and confounders. To account for correlation between longitudinal observations, two random effects, namely random intercept and random slope for time, were also included. In addition, the linear mixed-effects framework allowed deriving and making inference about the distribution of subject-specific slopes (and subsequently percent changes per year) for any subject after adjusting for potential confounders.

RESULTS— At the end of follow-up, study subjects were divided into two groups according to the primary outcome: the presence or absence of early GFR loss. A loss in GFRcystatin that ex-

ceeded 3.3% per year was classified as early GFR loss ($n = 79$), all others ($n = 276$) were considered to have stable renal function.

The two groups did not differ with regard to sex, but patients with early GFR loss were older at both diabetes diagnosis and study entry and had a longer duration of diabetes (Table 1). The two groups did not differ with regard to A1C or clinical characteristics associated with insulin resistance, such as insulin dose, BMI, and serum cholesterol (total or HDL). Patients with early GFR loss had significantly lower GFRcystatin, higher urinary ACR, and a higher prevalence of microalbuminuria at baseline. Early GFR loss patients were also more frequently treated with renoprotective drugs, although the two groups had similar systolic and diastolic blood pressures. Both groups had similar cigarette-smoking history. Most notably, those with early GFR loss had significantly higher serum uric acid levels than patients with stable renal function ($P < 0.0001$).

Table 1 also shows results of follow-up. The last GFRcystatin in patients with stable renal function was similar to that at baseline (124 vs. 131 ml/min per 1.73 m²), whereas it was significantly lower (86 vs. 115 ml/min per 1.73 m²) in those with early GFR loss. Median change per year in GFRcystatin was -1.8 and -4.4% , respectively. CKD stage 3 developed in 22 patients, among 19 patients with early GFR loss and among 3 those with stable renal function.

The two groups were also compared with regard to urinary albumin excretion during the 4-year follow-up. In the second follow-up interval, the median ACR value in the early GFR loss group was significantly higher than in the stable renal function group, as noted in the baseline interval, and in neither group did the median values increase by the end of follow-up. To take into account the baseline differences in ACR values, follow-up changes in ACR were expressed as fold changes from baseline in each interval. Progression was defined as a doubling of ACR in either interval, and regression was defined as a halving of ACR in either interval. ACR progressed in 34% of case subjects with early GFR loss compared with 17% of control subjects with stable renal function ($P = 0.001$). ACR regressed equally in the two groups (33% of case and in 37% of control subjects).

To further examine the relation between baseline uric acid and development

of renal outcomes, we analyzed the occurrence of these outcomes according to five categories of baseline serum uric acid (in mg/dl: <3.0 , 3–3.9, 4–4.9, 5–5.9, and ≥ 6). A clear dose-response relation is evident between increasing baseline serum uric acid levels and subsequent occurrence of early GFR loss (Fig. 1A). During the 4–6 years of follow-up, early GFR loss developed in 9, 13, 20, 29, and 36% of individuals in the five categories of increasing serum uric acid, respectively (P for trend = 0.0002).

Similarly, we explored a complementary outcome to early GFR loss (i.e., development of CKD stage 3 [or greater]). Although CKD stage 3 developed in only 22 patients during follow-up, a strong dose-response relation between baseline serum uric acid categories and development of CKD stage 3 is evident in Fig. 1B. In the five categories of increasing serum uric acid, 0, 4, 3, 6, and 19% of individuals developed CKD stage 3, respectively (P for trend = 0.0005). The association between baseline serum uric acid and progression of ACR (Fig. 1C) was not significant for trend ($P = 0.34$). Similarly, the association between baseline serum uric acid and regression of ACR (Fig. 1D) was not significant for trend ($P = 0.65$).

Estimates from multivariate logistic regression of the effect of a 1.0 mg/dl increase in serum uric acid on these renal outcomes are summarized in Table 2. The unadjusted odds ratio of developing early GFR loss with baseline serum uric acid change by 1 mg/dl was 1.5 (95% CI 1.3–1.9), and this estimate was little changed by adjustment for urinary ACR, sex, and A1C or even adjustment for baseline GFRcystatin. This association can be re-expressed as an individual with a serum uric acid of 6 mg/dl having twice the risk of developing early GFR loss as an individual with a serum uric acid of 4 mg/dl (odds ratio per 2 mg/dl change = 1.9). There was no effect measure modification (interaction) by sex, A1C, baseline GFRcystatin, or baseline ACR. Due to the small number of case subjects, we could not pursue a fully adjusted model for the time-to-event analysis of CKD stage 3. The lack of association between serum uric acid and progression or regression of ACR was confirmed by logistic regression in both the univariate and multivariate analyses (Table 2).

To further study the association between serum uric acid and early GFR loss, we analyzed continuous measures of changes in GFRcystatin using a linear

Table 1—Characteristics of nonproteinuric patients with type 1 diabetes according to whether renal function was stable during 4–6 years of follow-up or early GFR loss developed

Characteristic*	Stable renal function	Early GFR loss	P value
n	276	79	
Baseline characteristics			
% men	55	56	0.92
Age at diabetes diagnosis (years)	17 ± 10	20 ± 11	0.02
Duration of diabetes (years)	21 ± 9	24 ± 10	0.02
Age (years)	38 ± 12	44 ± 11	<0.0001
A1C (%)	8.2 (7.4–9.1)	8.3 (7.6–9.5)	0.17
Insulin dose (units/kg/day)	0.63 (0.53–0.83)	0.64 (0.48–0.86)	0.83
BMI (kg/m ²)	26 (23–29)	26 (24–32)	0.15
Serum cholesterol (mg/dl)	184 (166–204)	185 (167–204)	0.96
Serum HDL (mg/dl)	54 (46–65)	53 (46–64)	0.74
GFRcystatin (ml/min per 1.73 m ²)	131 (116–147)	115 (93–136)	<0.0001
ACR (mg/g)	34.6 (22.2–63.8)	51.6 (29.9–114.9)	<0.0001
% with microalbuminuria	56	75	0.003
% with renoprotective treatment	50	68	0.005
Systolic blood pressure (mmHg)	120 (111–128)	122 (114–129)	0.13
Diastolic blood pressure (mmHg)	70 (68–79)	72 (68–77)	0.60
Cigarette smoking			
% current	18	13	0.18
% past	24	34	
Serum uric acid (mg/dl)	4.5 (3.7–5.3)	5.10 (4.4–5.7)	<0.0001
Follow-up characteristics			
Duration of follow-up (years)	4.8 (4.1–5.5)	4.9 (3.9–5.7)	0.56
Number of cystatin determinations	5 (4–6)	5 (4–6)	0.33
Number of ACR determinations	5 (4–7)	6 (4–7)	0.58
Last GFRcystatin (ml/min per 1.73 m ²)	124 (109–139)	86 (65–99)	By design
Percent change per year in GFRcystatin	−1.8 (−2.4 to −1.2)	−4.4 (−5.0 to −3.8)	By design
Progressed to CKD stage 3 or greater [n (%)]	3 (1)	19 (24)	<0.0001
Last ACR (mg/g)†	17.1 (9.8, 42.1)	40.3 (13.8, 128.5)	<0.0001
Progression of ACR [n (%)]	48 (17)	27 (34)	0.001
Regression of ACR [n (%)]	103 (73)	26 (33)	0.47

Data are medians (25th–75th percentiles) and P values from Wilcoxon rank sum test for continuous variables (except for age at diabetes diagnosis, duration, and age, which are means ± SD and t tests) and percents with P values from χ^2 test for categorical data. *Values for A1C, serum cholesterol, serum HDL, and ACR were the medians of all determinations during the 2-year interval ending with the entry examination. †Median of all ACR measurements in the second 2-year follow-up interval.

mixed-effects model adjusting for all previous confounders. The interaction between changes in GFRcystatin over time and serum uric acid was statistically significant ($P = 0.01$). This interaction can be interpreted in terms of differing adjusted average percent change per year for each of the five categories of serum uric acid presented in Fig. 1. The average percent change for the five categories, from lowest to highest serum uric acid, was −0.6, −1.4, −1.8, −2.2, and −3.1% per year, respectively.

CONCLUSIONS— In this large, prospective cohort study of type 1 diabetic patients without proteinuria, we found that serum uric acid was a significant independent predictor of the development of early GFR loss after controlling for mul-

multiple confounders. For each 1 mg/dl increase in serum uric acid, there was a 40% increase in the odds of developing early GFR loss (odds ratio = 1.4 [95% CI 1.1, 1.8]). This increase in risk was linear across the entire normal range of serum uric acid levels. In contrast with these findings, we did not find any association between baseline serum uric acid and progression or regression of urinary albumin excretion. Our study is the first to provide prospective evidence of the “uncoupling” of determinants of early GFR loss from determinants of changes in urinary albumin excretion, the two cardinal manifestations of early diabetic nephropathy in type 1 diabetes.

Recently, in a type 1 diabetic cohort with long follow-up in Denmark, elevated baseline uric acid concentrations were asso-

ciated with the development of proteinuria but did not impact risk of microalbuminuria (13). Since that study did not report measures of change in renal function we cannot compare results for our main outcome. Our study aimed to study renal function changes during early diabetic nephropathy when patients had only minimally elevated ACR. With longer follow-up, we may have obtained similar results as the Danish cohort. However, as we showed in our recent study (5), declining renal function begins before proteinuria develops.

Although our findings are derived from an observational study, it is intriguing to consider that uric acid might play a pathogenic role in the development of early GFR loss in type 1 diabetes. This hypothesis can be tested further in ran-

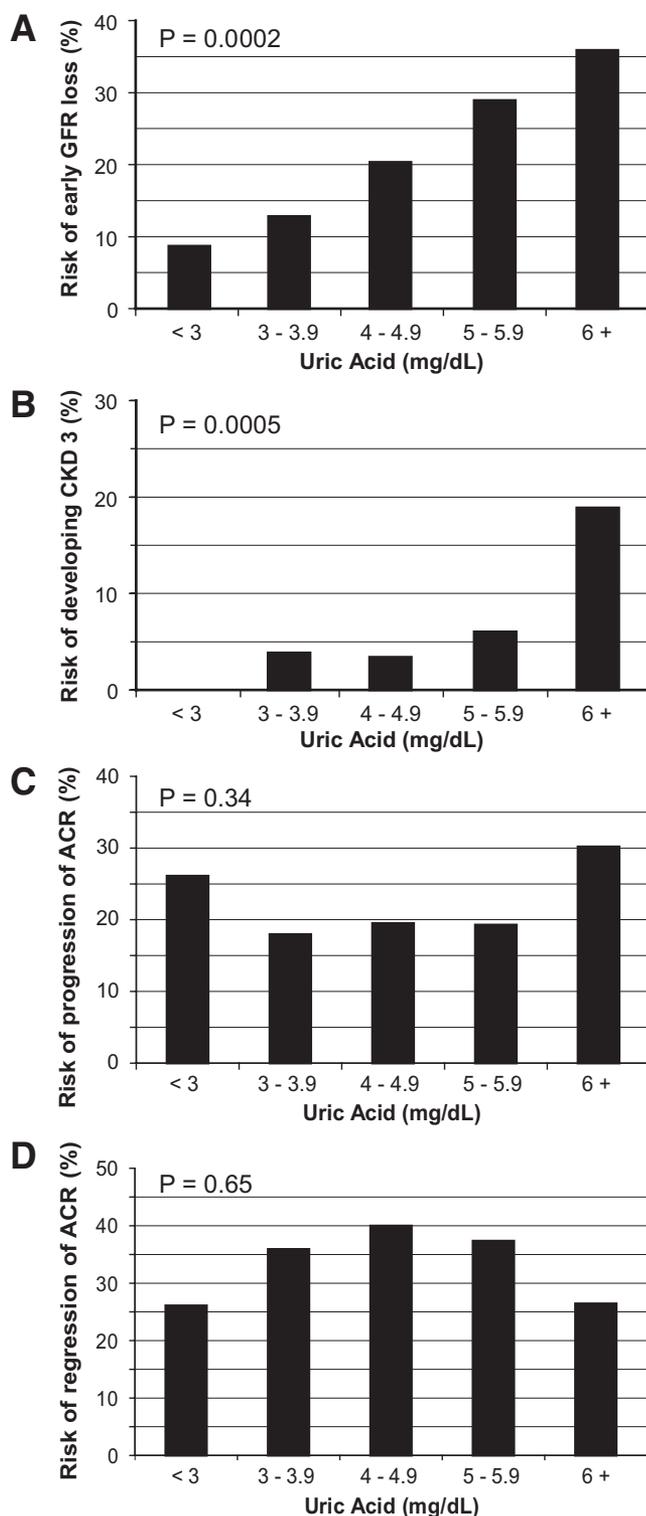


Figure 1—Risks during 4–6 years follow-up of early GFR loss (A), CKD stage 3 (B), progression of ACR (C), or regression of ACR according to baseline concentration of serum uric acid (D). Baseline serum uric acid values (mg/dl) were <3.0 for 23 patients, between 3.0 and 3.9 for 78 patients, between 4.0 and 4.9 for 118 patients, between 5.0 and 5.9 for 96 patients, and ≥ 6.0 for 53 patients. Median uric acid concentration in the cohort was 4.6 mg/dl. A: Test for trend in risk of early GFR loss with baseline serum uric acid category was significant, $P = 0.0002$. B: Test for trend in risk of CKD stage 3 with baseline serum uric acid category significant, $P = 0.0005$. C: Test for trend in risk of progression of ACR with baseline uric acid category was not statistically significant, $P = 0.34$. D: Test for trend in risk of regression of ACR with baseline uric acid category was not statistically significant, $P = 0.65$.

domized, controlled trials (RCTs) since drugs to reduce serum uric acid levels are available, being commonly used in gout therapy. These drugs reduce uric acid levels either by inhibiting its synthesis (allopurinol and febuxostat) or by increasing the urinary excretion of uric acid (probenecid, benzbromarone, and sulfapyrazone) (20,21). Several RCTs have shown that treatment with allopurinol improves brachial artery vasodilation in patients with chronic heart failure (22) and type 2 diabetes (23), but only a handful of studies, all in individuals without diabetes, have examined changes in renal function as the primary outcomes. One of these has shown that treatment with allopurinol can retard the renal function decline among patients with CKD and hyperuricemia (24). No RCT has been conducted to investigate the effect of uric acid-lowering drugs on the prevention of early renal function loss. However, in a prospective study of 48 hyperuricemic patients who were given allopurinol for 3 months, uric acid decreased from 8.0 to 5.5 mg/dl, while GFR increased from 79 to 93 ml/min per 1.73 m² (25). Importantly, such improvement in GFR occurred in the absence of a reduction of proteinuria.

The Second Joslin Study is a well-characterized, large prospective cohort study with excellent follow-up over 4–6 years, which allowed us to determine different phenotypes/outcomes of early diabetic nephropathy. However, some perceived and real limitations of this study should be considered. First, although we showed that repeated uric acid measurements taken up to 2 years apart were highly correlated ($r = 0.78$), some exposure misclassification may have occurred due to the reliance on a single baseline uric acid measurement. However, such nondifferential misclassification would bias the results toward the null hypothesis, making our findings of association even more notable. Second, we estimated renal function from serum cystatin C concentrations rather than measuring GFR directly. Although indirect, this method has been shown to estimate GFR well even in normal or elevated ranges, and multiple measurements of GFRcystatin over time have been demonstrated to be a reliable tool to assess changes of renal function in longitudinal studies (4,15,16). Importantly, to minimize spurious variation in the determination of GFRcystatin changes over time, all serum cystatin C measurements ($n =$

Table 2—Odds ratios for a 1.0 mg/dl increase in baseline serum uric acid concentration for the odds of developing selected renal outcomes during 4–6 years of follow-up

Renal outcome	Unadjusted measure of association (95% CI)	Adjusted measure of association (95% CI)*	Adjusted measure of association including adjustment for baseline level of outcome† (95% CI)
Early GFR loss	1.5 (1.3–1.9)	1.5 (1.2–1.9)	1.4 (1.1–1.8)
Progression of ACR	1.1 (0.9–1.4)	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Regression of ACR	1.0 (0.8–1.1)	1.1 (1.0–1.4)	1.1 (1.0–1.4)

*Adjusted for ACR, sex, and A1C in models with outcome early GFR loss; adjusted for baseline GFR, cystatin, sex, and A1C in models with outcomes progression or regression of ACR. †Adjusted for baseline GFR, cystatin, ACR, sex, and A1C in models with outcome early GFR loss; adjusted for baseline ACR, GFR, cystatin, sex, and A1C in models with outcomes progression or regression of ACR.

1,871) were carried out in 2009, in the same laboratory and using the same reagents. Furthermore, to calculate individual GFR, cystatin slopes, we utilized appropriate methods of longitudinal analysis (i.e., linear mixed-effects model), taking into account irregular time measurements and correlation between longitudinal observations. Finally, since our study is an observational one, any conclusion about a causal relationship between serum uric acid and the development of early GFR loss in type 1 diabetes should be considered as tentative. This hypothesis will have to be tested by adequately powered RCTs evaluating the effect of uric acid-lowering drugs on the decline of renal function specifically among individuals with diabetes.

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