Serum Uric Acid Levels and Incident Chronic Kidney Disease in Patients With Type 2 Diabetes and Preserved Kidney Function

Giacomo Zoppini, md[1]
Giovanni Targher, md[1]
Michel Chonchol, md[2]
Vittorio Ortalda, md[3]

Cataldo Abaterusso, md[3]
Isabella Pichiri, md[1]
Carlo Negri, md[1]
Enzo Bonora, md[1]

OBJECTIVE—Recent studies have suggested an association between hyperuricemia and adverse renal outcomes in nondiabetic populations. Data on the relationship between hyperuricemia and the risk of incident chronic kidney disease (CKD) in type 2 diabetic patients with normal or near-normal kidney function are lacking. We determined whether baseline serum uric acid levels predict the subsequent development of CKD in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—We followed 1,449 type 2 diabetic patients with normal kidney function and without overt proteinuria for 5 years for the occurrence of incident CKD (defined as overt proteinuria or estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2).

RESULTS—During a 5-year follow-up period, 194 (13.4%) patients developed incident CKD. The cumulative incidence of CKD was significantly greater in patients with hyperuricemia than in those without hyperuricemia (29.5 vs. 11.4%, $P < 0.001$). In univariate logistic regression analysis, the presence of hyperuricemia roughly doubled the risk of developing CKD (odds ratio [OR] 2.55 [95% CI 1.71–3.85], $P < 0.001$). After adjusting for age, sex, BMI, smoking status, diabetes duration, systolic blood pressure, antihypertensive treatment, insulin therapy, HbA$_{1c}$, eGFR, and albuminuria, hyperuricemia was associated with an increased risk of incident CKD (adjusted OR 2.10 [1.16–3.76], $P < 0.01$). In continuous analyses, a 1-SD increment in the serum uric acid level was significantly associated with a 21% increased risk of CKD.

CONCLUSIONS—In type 2 diabetic individuals with preserved kidney function, hyperuricemia seems to be an independent risk factor for the development of incident CKD.

Diabetes Care 35:99–104, 2012

The tide of type 2 diabetes is rising in the U.S. and all over the world, thereby becoming an increasingly powerful threat to global health (1). Type 2 diabetes also has become the leading cause of end-stage renal disease in the world, and the number of patients diagnosed each year with end-stage renal disease attributed to type 2 diabetes is rising (2).

The pathophysiology of diabetic nephropathy is complex and still not fully elucidated (3). Several prospective studies have suggested that hyperuricemia is associated with an increased risk of incident cardiovascular events and death in both nondiabetic and type 2 diabetic individuals (4–9). Hyperuricemia also is largely prevalent in patients with chronic kidney disease (CKD) (10,11). However,

hyperuricemia might have a pathogenic role in the development and progression of CKD, rather than solely reflecting decreased renal uric acid excretion. Indeed, several (12–17), but not all (18–20), prospective studies recently have shown a significant association between hyperuricemia and adverse renal outcomes in both the general population and other nondiabetic high-risk patient populations. However, epidemiologic data are limited about the relationship between hyperuricemia and adverse renal outcomes in patients with type 1 (21,22) or type 2 (23) diabetes.

In a post hoc analysis of 1,342 patients with type 2 diabetes and nephropathy participating in the Reduction of End Points in Non–Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) Trial, the investigators reported that the risk of adverse renal outcomes was decreased by 6% per 0.5 mg/dL decrement in serum uric acid levels during the first 6 months of treatment with losartan (23). These findings support the view that serum uric acid may be a modifiable risk factor for renal disease in type 2 diabetic patients (23).

To our knowledge, however, no large prospective studies are available on the relationship between hyperuricemia and incident CKD in patients with type 2 diabetes and normal or near-normal kidney function. Thus, the purpose of this prospective, observational study was to determine whether baseline serum uric acid levels are associated with an increased incidence of CKD in a large cohort of type 2 diabetic patients with preserved kidney function at baseline and without a previous history of cardiovascular disease.

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 (24). Data included in this analysis are based on a cohort of

1,449 white type 2 diabetic outpatients, who were recruited over the period of January 2000 to January 2002 and then followed up until December 2007. These participants represent ~40% of the whole cohort of type 2 diabetic individuals (n = 3,924) who regularly attended our diabetes clinic during the years 2000–2002, after excluding *1*) patients with overt proteinuria or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (n = 701); *2*) those who had a previous history of cardiovascular disease (defined as angina, myocardial infarction, ischemic stroke, and coronary revascularization), severe chronic obstructive pulmonary disease, and malignancies (n = 727); and *3*) those who had incomplete baseline laboratory data for analysis (n = 1,047).

Baseline demographics, blood pressure, plasma lipids, and HbA$_{1c}$ were not significantly different between the 1,449 participants of the study and those (n = 1,047) who had incomplete laboratory data (data not shown). All participants were periodically seen (every 6–9 months) for routine medical examinations of glycemic control and chronic complications of diabetes. More details about the study design and recruitment methods have been reported elsewhere (9). The local ethics committee approved the study protocol. All participants gave their informed consent.

Clinical and laboratory data
BMI was calculated by dividing weight in kilograms by the square of height in meters. A physician measured blood pressure in duplicate with a mercury sphygmomanometer (at the right upper arm using an appropriate cuff size) after the patient had been seated quietly for at least 5 min. Subjects were considered to have arterial hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any antihypertensive medications. Detailed information in our informatic database regarding specific classes of antihypertensive medications (e.g., ACE inhibitors, angiotensin receptor blockers, or diuretics) currently is available in a subset of 632 participants. Information on comorbid conditions and smoking history was obtained from all patients by interviews during medical examinations.

Venous blood was drawn in the morning after an overnight fast. Serum uric acid (uricase/peroxidase enzymatic method), creatinine (measured using a Jaffé rate-blanked and compensated assay), and other biochemical blood measurements were determined by standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy). Both intra- and interassay coefficients of variation for serum uric acid were within 2.5%. LDL was calculated by the Friedewald equation. HbA$_{1c}$ was measured by an automated high-performance liquid chromatography analyzer (Bio-Rad Diamat, Milan, Italy); the upper limit of normal for our laboratory was 5.8%.

Subjects were considered to have hyperuricemia if their serum uric acid level was ≥416 μmol/L (≥7.0 mg/dL) in men and ≥386 μmol/L (≥6.5 mg/dL) in women or if they were on allopurinol therapy. These cutoff values of the serum uric acid level are those commonly used to define hyperuricemia in our clinical laboratory.

eGFR was estimated from the four-variable Modification of Diet in Renal Disease (MDRD) study equation, as follows: eGFR = 175.0 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × 1.212 (if black) × 0.742 (if female) (25). eGFR also was estimated from the CKD–Epidemiology Collaboration (CKD-EPI) creatinine equation (26). Urinary albumin excretion was measured from an early-morning urine sample on at least two consecutive occasions as the albumin-to-creatinine ratio (ACR) by an immunonephelometric method. Micro-albuminuria was defined as an ACR >2.5 and <30 mg/mmol for men and >3.5 and <30 mg/mmol for women (1,25). For this study, incident CKD was defined as the occurrence of an eGFR <60 mL/min/1.73 m^2 or persistent macro-albuminuria (i.e., ACR ≥30 mg/mmol for both sexes in at least two of three consecutive samples) in participants with normal or near-normal kidney function at baseline.

Statistical analysis
Data are presented as means ± SD or proportions. Skewed variables were logarithmically transformed to improve normality prior to analysis. The unpaired *t* test and the χ^2 test with Yates correction for continuity (for categorical variables) were used to compare the baseline characteristics of participants stratified by the presence or absence of sex-specific hyperuricemia (Table 1). A multivariable logistic regression analysis also was used to identify the factors independently associated with the development of incident CKD. Three forced-entry multivariable logistic regression models were performed. In all

Table 1—*Baseline clinical and biochemical characteristics of patients with type 2 diabetes and normal kidney function stratified by sex-specific hyperuricemia*

	Without hyperuricemia	With hyperuricemia*	P
n	1,290	159	
Sex (men/women)	783/507	105/54	0.223
Age (years)	66 ± 10	67 ± 9	0.449
Diabetes duration (years)	16 ± 9	14 ± 8	0.024
BMI (kg/m^2)	27.8 ± 4	30.3 ± 5	<0.001
Current smokers (%)	24.5	19.0	0.048
Hypertension (%)	83.7	95.0	<0.001
Systolic blood pressure (mmHg)	136 ± 18	139 ± 16	<0.001
Diastolic blood pressure (mmHg)	80 ± 8	81 ± 9	0.109
HbA$_{1c}$ (%)	7.41 ± 1.3	7.12 ± 1.2	0.001
LDL cholesterol (mmol/L)	3.37 ± 0.8	3.41 ± 0.8	0.749
Triglycerides (mmol/L)	1.52 ± 0.8	1.84 ± 1.2	<0.001
HDL cholesterol (mmol/L)	1.45 ± 0.4	1.31 ± 0.3	<0.001
eGFR (mL/min/1.73 m^2)	82.1 ± 14	76.6 ± 13	<0.001
Microalbuminuria (%)	19.0	23.9	0.172
Insulin therapy users (%)	29.7	29.6	0.973
Antihypertensive drug users (%)	71.4	89.9	<0.001
Allopurinol users (%)	0	60.4	ND
Uric acid (μmol/L)	271.9 ± 66	380.5 ± 122	ND
Incident CKD (%)†	11.4	29.5	<0.001

Data are means ± SD or proportions. Cohort size, n = 1,449. P values refer to the *t* test or the χ^2 test (for categorical variables). ND, not determined. *Hyperuricemia was defined as allopurinol use or uric acid level ≥416 μmol/L in men and ≥386 μmol/L in women. Hypertension was defined as blood pressure ≥140/90 mmHg and/or drug treatment. †Incident CKD was defined as the occurrence of an eGFR <60 mL/min/1.73 m^2 or persistent macroalbuminuria.

these models, serum uric acid was included as either a dichotomous or a continuous variable. The first model was adjusted for age (years) and sex (male versus female); the second model was further adjusted for BMI (kg/m^2), HbA$_{1c}$ (%), diabetes duration (years), smoking history (yes or no), systolic blood pressure (yes; mmHg), antihypertensive treatment (yes or no), insulin therapy (yes or no), eGFR (mL/min/1.73 m^2), and albuminuria (mg/mmol). In the third model, we additionally adjusted for the changes of systolic blood pressure and HbA$_{1c}$ at the end of follow-up plus the same set of covariates that were included in the second model. These covariates were chosen as potential confounding factors on the basis of their significance in univariate analyses or on the basis of their biological plausibility. Results are presented as odds ratios (ORs) with 95% CIs. ORs for all continuous variables were computed for each SD change. Statistical analysis was performed using the statistical package SPSS version 14.0. P values <0.05 were considered statistically significant.

RESULTS—The 1,449 patients (888 men, mean age 66 years) with type 2 diabetes included in the study had a mean baseline serum uric acid level of 284 ± 81 μmol/L with a significant difference between sexes (298 ± 80 vs. 261 ± 77 μmol/L in men and women, respectively, P < 0.001). They also had a mean baseline eGFR of 82 ± 14 mL/min/1.73 m^2, and 80.5% (n = 1,166) of patients had normal albuminuria and 19.5% (n = 283) had microalbuminuria; by study design, no participants had macroalbuminuria. Approximately 85% of participants had hypertension at baseline (defined as blood pressure ≥140/90 mmHg or drug treatment). The glycemic control of participants was fairly good (mean HbA$_{1c}$ 7.4%).

Clinical and biochemical characteristics of participants grouped according to the presence or absence of hyperuricemia are summarized in Table 1. Patients with hyperuricemia (n = 159 [11%]) had a shorter duration of diabetes, higher BMI, higher systolic blood pressure, higher triglycerides, and lower values of HbA$_{1c}$, HDL cholesterol, and baseline eGFR than their counterparts without hyperuricemia. In addition, they were less likely to be smokers and were more likely to have hypertension and to be treated with antihypertensive agents. Detailed information regarding specific classes of antihypertensive drugs currently was available only

in a subset of 632 subjects. No significant differences were found in the use of ACE inhibitors, angiotensin receptor blockers, or diuretics in the hyperuricemic versus normouricemic group (data not shown). Frequency of microalbuminuria also tended to be greater in those with hyperuricemia, but the difference did not achieve statistical significance. Sex distribution, age, LDL cholesterol, and the proportion of patients using insulin did not differ between the groups.

During a mean follow-up of 5 years, 194 (13.4%) patients developed incident CKD (148 developed an eGFR <60 mL/min/1.73 m^2, 29 developed persistent macroalbuminuria, and 17 developed both conditions). During the follow-up, 36 subjects died of any cause, of whom 5 had developed incident CKD; they were considered alive for statistical analyses. Of note, a significantly greater proportion (P < 0.001) of patients with hyperuricemia developed incident CKD (29.5%) during the follow-up in comparison with those without hyperuricemia (11.4%) (Table 1).

At the end of the follow-up period, the rates of hypertension were 93.7% (127 new patients developed incident hypertension) in the normouricemic group and 98.1% (5 patients developed incident hypertension) in the hyperuricemic group, respectively. At the end of follow-up, mean HbA$_{1c}$ was 7.51 ± 1.2% and 7.27 ± 1.2% in the normouricemic and the hyperuricemic groups, respectively. Conversely, mean values of plasma lipids slightly decreased in both groups at the end of follow-up (LDL cholesterol 2.88 ± 0.7 and 2.62 ± 0.6 mmol/L, triglycerides 1.36 ± 0.7 and 1.59 ± 0.9 mmol/L, and HDL cholesterol 1.32 ± 0.3 and 1.21 ± 0.3 mmol/L, respectively).

As shown in Table 2, in univariate logistic regression analysis, the presence of hyperuricemia (included as a categorical variable) roughly doubled the risk of developing CKD (OR 2.55 [95% CI 1.71–3.85], P < 0.001). The significant association between hyperuricemia and the risk of incident CKD was consistent in all subgroups evaluated (Fig. 1).

Also shown in Table 2, after adjusting for age and sex (model 1), hyperuricemia was associated with subsequent development of CKD. Results remained essentially unchanged after additionally adjusting for BMI, diabetes duration, smoking status, systolic blood pressure, HbA$_{1c}$, eGFR, albuminuria, and use of insulin or antihypertensive agents (model 2). The association between hyperuricemia and incident CKD remained statistically significant even when we additionally adjusted for changes of HbA$_{1c}$ and systolic blood pressure at the end of follow-up (model 3).

Almost identical results also were observed when analyses were repeated with serum uric acid as a continuous variable (Table 3). In such cases, a 1-SD increment (i.e., 81 μmol/L) in the serum uric acid level was associated with a 21% increased risk of incident CKD after adjusting for potential confounders (model 2). Similar results were found after additional adjustment for changes of HbA$_{1c}$ and systolic blood pressure at the end of follow-up (model 3).

Results remained essentially unchanged when we used the newer CKD-EPI equation (instead of the MDRD study equation) to estimate GFR in our patient cohort. Also, in this case, elevated levels of serum uric acid, either as a dichotomous variable (adjusted OR 2.74 [95% CI 1.73–4.33], P < 0.001) or as a continuous

Table 2—Association between hyperuricemia (included as a categorical variable) and incident CKD in patients with type 2 diabetes

	OR (95% CI)	P
Unadjusted association	2.55 (1.71–3.85)	<0.001
Multiple adjusted association		
Model 1	2.68 (1.76–4.09)	<0.001
Model 2	2.10 (1.16–3.76)	<0.01
Model 3	2.01 (1.10–3.74)	0.01

Cohort size, n = 1,449. In these univariable and multivariable logistic regression models, hyperuricemia was included as a categorical variable (defined as allopurinol use or uric acid level ≥416 μmol/L in men and ≥386 μmol/L in women). Multivariable logistic regression models were adjusted as follows: model 1: age and sex; model 2: model 1 plus BMI, smoking status, duration of diabetes, insulin therapy, HbA$_{1c}$, eGFR, albuminuria, systolic blood pressure, and use of antihypertensive drugs; and model 3: model 1 plus BMI, smoking status, duration of diabetes, insulin therapy, eGFR, albuminuria, use of antihypertensive drugs, and changes of both HbA$_{1c}$ and systolic blood pressure at the end of follow-up.
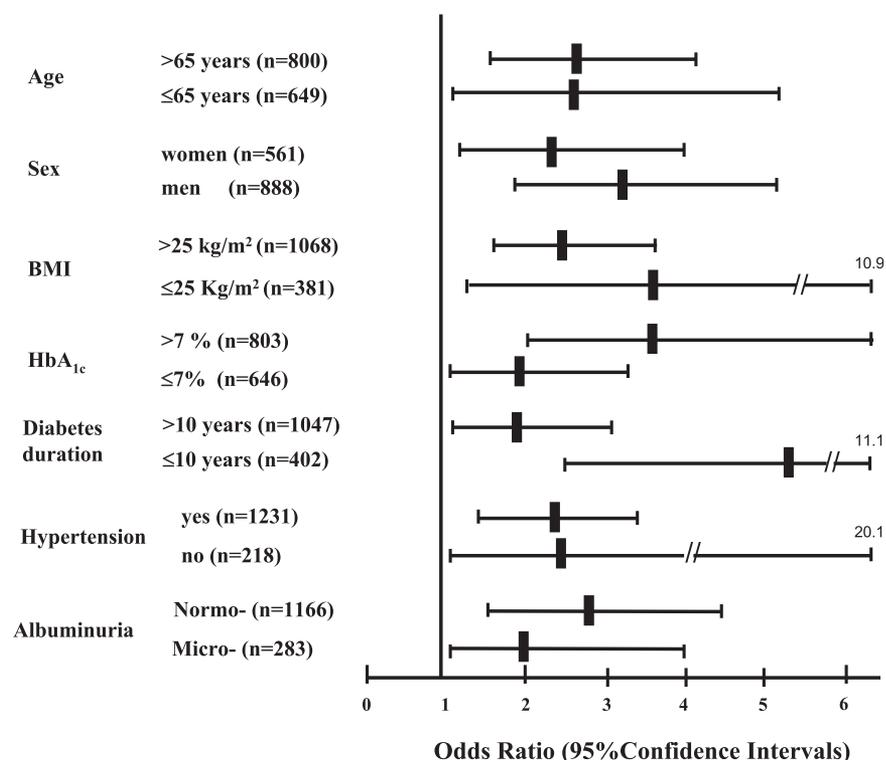
Figure 1—*Association of sex-specific hyperuricemia with the development of incident CKD within subgroups. Data are expressed as ORs and 95% CIs.*

variable (1.25 [1.05–1.49], *P* = 0.01), were closely associated with an increased risk of incident CKD, independently of age, sex, BMI, diabetes duration, smoking status, systolic blood pressure, HbA$_{1c}$, eGFR, albuminuria, and use of insulin or antihypertensive agents.

In all multivariable regression models, together with elevated uric acid levels, other independent predictors of incident CKD were older age, use of antihypertensive drugs (or hypertension when it was included as a categorical variable in the regression models), lower eGFR, and higher

albuminuria at baseline (see Supplementary Tables 1–3).

CONCLUSIONS—Several (12–17), but not all (18–20), prospective studies have suggested a significant association of hyperuricemia with the development and progression of kidney disease in mainly nondiabetic populations. However, prospective data on the relationship between hyperuricemia and adverse renal outcomes in patients with type 2 diabetes are scarce (23). In a post hoc analysis of 1,342 patients with type 2 diabetes and

CKD participating in the RENAAL trial, Miao et al. (23) reported that losartan lowered serum uric acid by 0.16 mg/dL (*P* = 0.031) compared with placebo during the first 6 months and that the risk of renal events, defined as a doubling of serum creatinine or end-stage renal disease, was significantly decreased by 6% per 0.5 mg/dL decrement in uric acid. This effect was independent of other risk markers, including eGFR and albuminuria. The authors concluded that a part of the losartan's renoprotective effect could be attributed to its effect on serum uric acid (23).

To our knowledge, this is the first large prospective study specifically aimed at examining the association of serum uric acid levels with the risk of incident CKD in patients with type 2 diabetes and normal or near-normal kidney function. In this 5-year observational study, we found that hyperuricemia is strongly associated with an increased incidence of CKD (i.e., defined as eGFR <60 mL/min/1.73 m^2 or overt proteinuria) in a cohort of 1,449 white type 2 diabetic individuals with a baseline eGFR >60 mL/min/1.73 m^2 (~80% normoalbuminuric). Of note, this association seems to be independent of a broad number of risk factors and confounders, including HbA$_{1c}$, hypertension, eGFR, and albuminuria. In continuous analyses, a 1-SD increment (i.e., 81 μmol/L) in the serum uric acid level was associated with a 21% increased risk of incident CKD.

Overall, our findings are corroborated by previous observations of two small prospective studies showing a strong, graded relationship between elevated uric acid levels and the risk of early decline in renal function in nonproteinuric patients with type 1 diabetes (21,22).

It still is unclear whether hyperuricemia is a risk factor for, or simply a marker of, kidney disease, because of its complex interrelationships with other established risk factors, especially hypertension, or important comorbidities. Of note, in this study we excluded patients who had a previous history of malignancy, severe chronic obstructive pulmonary disease, and cardiovascular disease. Moreover, we found that elevated uric acid levels were associated with an increased risk of incident CKD, independently of a broad spectrum of established risk factors, including hypertension, diabetes-related variables, and renal function measures. Thus, it is conceivable that hyperuricemia might confer an excess risk over and above

Table 3—*Association between serum uric acid levels (included as a continuous variable) and incident CKD in patients with type 2 diabetes*

	OR (95% CI)	*P*
Unadjusted association	1.23 (1.07–1.43)	<0.005
Multiple adjusted association		
Model 1	1.23 (1.08–1.46)	<0.005
Model 2	1.21 (1.02–1.45)	<0.05
Model 3	1.20 (1.03–1.57)	<0.05

Cohort size, *n* = 1,449. In these univariable and multivariable logistic regression models, hyperuricemia was included as a continuous variable (for a 1-SD change in serum uric acid level). Multivariable logistic regression models were adjusted as follows: model 1: age and sex; model 2: model 1 plus BMI, smoking status, duration of diabetes, insulin therapy, HbA$_{1c}$, eGFR, albuminuria, systolic blood pressure, and use of antihypertensive drugs; and model 3: model 1 plus BMI, smoking status, duration of diabetes, insulin therapy, eGFR, albuminuria, use of antihypertensive drugs, and changes of both HbA$_{1c}$ and systolic blood pressure at the end of follow-up.

the risk attributable to underlying established risk factors.

The recognition of the biological mechanism(s) linking hyperuricemia to the development and progression of kidney disease is beyond the scope of this study. However, putative underlying mechanisms may include chronic inflammation, endothelial dysfunction, vascular smooth muscle proliferation, and impaired nitric oxide generation (27–29). Furthermore, experimental evidence suggests that hyperuricemia may exert adverse effects on oxidative metabolism, platelet adhesiveness, and aggregation (27–29). In animal models, elevated uric acid levels can lead to arteriolopathy of preglomerular vessels, impaired autoregulation, glomerular hypertension, as well as endothelial dysfunction (30). Kidney damage in hyperuricemic rats is not dependent on blood pressure and instead involves the renin-angiotensin and cyclooxygenase-2 systems (29,30).

Overall, our findings may have important clinical implications. Our data indicate that serum uric acid is an independent risk factor for the development of CKD, thus supporting the view that the measurement of serum uric acid levels in patients with type 2 diabetes might be helpful in the risk prediction of CKD. This makes hyperuricemia another potential target for the treatment of type 2 diabetes. Two small prospective, randomized, controlled trials involving nondiabetic and diabetic patients with hyperuricemia and CKD, who were randomly assigned to treatment with allopurinol or to continue with the usual therapy for 12–24 months, demonstrated that the allopurinol group showed less kidney dysfunction compared with patients in the control group (31,32). Future larger, randomized controlled trials on drugs that lower serum uric acid need to be conducted to evaluate the causal relationship between serum uric acid and the development and progression of diabetic kidney disease.

Some limitations of our study merit comment. First, because our cohort comprises white, type 2 diabetic individuals who were followed at an outpatient diabetes clinic, our results may not necessarily be generalizable to other diabetic populations. Other potential limitations of our study include a possible selection bias of excluding the patients who had missing laboratory data at baseline and an inability to adjust for certain specific antihypertensive agents. However, in the subset of 632 participants in which such information currently was available in our informatic database, we did not find any significant difference in the use of ACE inhibitors, angiotensin receptor blockers, or thiazide diuretics between those with and those without hyperuricemia. In addition, we used an eGFR (i.e., the four-variable MDRD study equation and the CKD-EPI creatinine equation) instead of a directly measured GFR to define kidney function. It is known that current GFR estimates have greater inaccuracy in populations without known CKD than in those with kidney disease. Nonetheless, current GFR estimates facilitate the detection, evaluation, and management of CKD, and many organizations recommend the use of prediction equations for the evaluation of kidney function in large epidemiologic studies and in clinical practice (1,10,25,26). Finally, whether these observations also can be extended to nonwhite ethnic groups remains to be determined.

Strengths of our study include its prospective design, the large number of participants from both sexes, the long duration of follow-up, the complete nature of the dataset, and the ability to adjust for a wide range of known risk factors and potential confounders. In addition, our patients were free of diagnosed cardiovascular disease, severe chronic obstructive pulmonary disease, and malignancies; the evaluation of patients with such complications would almost certainly have confounded interpretation of the data.

In summary, this study demonstrated an association between hyperuricemia and the risk of incident CKD, independent of several potential confounders, including hypertension, eGFR, and albuminuria, in a large cohort of type 2 diabetic patients with a baseline eGFR >60 mL/min/1.73 m^2 and without a previous history of cardiovascular disease. Additional studies are needed to examine the reproducibility of our results and to further elucidate the biological mechanisms underlying the relationship between hyperuricemia and incident CKD in type 2 diabetes. The advantage(s) of treating hyperuricemia in type 2 diabetes in order to reduce the risk of adverse renal outcomes remains to be demonstrated.

References

1. American Diabetes Association. Standards of medical care in diabetes: 2011. Diabetes Care 2011;34(Suppl. 1):S11–S61
2. Eggers PW. Has the incidence of end-stage renal disease in the USA and other countries stabilized? Curr Opin Nephrol Hypertens 2011;20:241–245
3. Brenner BM, Parving H-H, Mauer M, Ritz E. Diabetic nephropathy. In *The Kidney*. Brenner BM, Ed. Philadelphia, WB Saunders, 2004, p. 1777–1818
4. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131: 7–13
5. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992: National Health and Nutrition Examination Survey. JAMA 2000;283:2404–2410
6. Niskanen LK, Laaksonen DE, Nyyssönen K, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 2004;164:1546–1551
7. Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. Arthritis Rheum 2009;61:225–232
8. Ioachimescu AG, Brennan DM, Hoar BM, Kashyap SR, Hoogwerf BJ. Serum uric acid, mortality and glucose control in patients with type 2 diabetes mellitus: a PreCIS database study. Diabet Med 2007;24:1369–1374
9. Zoppini G, Targher G, Negri C, et al. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care 2009;32:1716–1720
10. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(Suppl. 1):S1–S266
11. Tangri N, Weiner DE. Uric acid, CKD, and cardiovascular disease: confounders, culprits, and circles. Am J Kidney Dis 2010; 56:247–250
12. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 2001;24:691–697

13. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis 2004;44:642–650

14. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. J Am Soc Nephrol 2008;19:1204–1211

15. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19:2407–2413

16. Bellomo G, Venanzi S, Verdura C, Saronio P, Esposito A, Timio M. Association of uric acid with change in kidney function in healthy normotensive individuals. Am J Kidney Dis 2010;56:264–272

17. Sonoda H, Takase H, Dohi Y, Kimura G. Uric acid levels predict future development of chronic kidney disease. Am J Nephrol 2011;33:352–357

18. Chonchol M, Shlipak MG, Katz R, et al. Relationship of uric acid with progression of kidney disease. Am J Kidney Dis 2007;50:239–247

19. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F; MMKD Study Group. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. Exp Gerontol 2008;43:347–352

20. Madero M, Sarnak MJ, Wang X, et al. Uric acid and long-term outcomes in CKD. Am J Kidney Dis 2009;53:796–803

21. Ficociello LH, Rosolowsky ET, Niewczas MA, et al. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. Diabetes Care 2010;33:1337–1343

22. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. Diabetes 2009;58:1668–1671

23. Miao Y, Ottenbros SA, Laverman GD, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. Hypertension 2011;58:2–7

24. Muggeo M, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: the Verona Diabetes Study. Diabetes Care 2000;23:45–50

25. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function: measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473–2483

26. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612

27. Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002;13:2888–2897

28. Lippi G, Montagnana M, Franchini M, Favaloro EJ, Targher G. The paradoxical relationship between serum uric acid and cardiovascular disease. Clin Chim Acta 2008;392:1–7

29. Hovind P, Rossing P, Johnson RJ, Parving HH. Serum uric acid as a new player in the development of diabetic nephropathy. J Ren Nutr 2011;21:124–127

30. Mazzali M, Kanellis J, Han L, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991–F997

31. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51–59

32. Goicoechea M, de Vinuesa SG, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010;5:1388–1393