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The association between serum uric acid to creatinine ratio and renal disease progression in type 2 diabetic patients in Chinese communities

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ABSTRACT

Aims: Serum uric acid (UA) increases in patients with kidney disease due to the impaired UA clearance. The present study sought to evaluate the association between UA/creatinine ratio (UA/Cr) and renal disease progression in patients with type 2 diabetes mellitus (T2DM) in Chinese communities.
Methods: In the present retrospective longitudinal study, 3432 Chinese T2DM patients recruited from 11 community healthcare centers in Nanjing, China were included. Renal disease progression was defined as the occurrence of estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 or doubling of baseline serum creatinine level. Cox regression analysis was used to estimate the association between UA/Cr and renal disease progression.
Results: During a median follow-up of 30 months, 58 (1.70%) patients experienced progression of renal disease, which was more common among those with older ages, longer diabetes duration, and higher baseline eGFR. Multivariate analysis revealed that UA/Cr was an independent risk factor for renal disease progress (hazard ratio 1.364 [95% CI 1.131–1.646], $P = 0.001$) independently of age, sex, and other potential confounders.
Conclusions: UA/Cr might be a novel predictor of chronic kidney disease progression in T2DM patients.

1. Introduction

The number of patients with chronic kidney disease (CKD) has increased dramatically in the past decades, whereas diabetes is the leading cause of CKD and end-stage renal disease (ESRD) worldwide.[1–4] Uric acid (UA) was thought as an indicator of renal function initially. However, in recent years, UA was demonstrated as a contributor of chronic renal insufficiency both in patients with or without diabetes.[5–7] The risk of renal function decline indicated by estimated glomerular filtration rate (eGFR) is correlated with UA levels in Type 1 diabetes mellitus (T1DM),[8,9] and both hyperuricemia and high-normal serum UA are independent risk factors of renal disease progression in type 2 diabetes mellitus (T2DM).[10,11]

Serum UA has a close relationship with metabolic disorders including diabetes. Elevated serum UA predicts the onset of T2DM and has been linked to both micro- and macro-vascular complications of diabetes.[12–14] Therefore, serum UA was even suggested to be a biomarker of renal and cardiovascular risk in diabetes and a potential additional therapeutic target.[15] However, it is well known that UA, which is the final product of purine metabolism, is mainly eliminated by kidney, which is responsible for the elimination of >70% of UA production daily.[16] Thus, the serum level of UA will be affected by renal function and increase in patients with kidney disease due to the impaired UA clearance.[17] Indeed, question still waits for a definitive answer whether UA is a cause of CKD or an association to it.[18]

Given that the incidence of diabetic kidney disease (DKD) or CKD was high, occurring in 20–40% of patients with diabetes,[19] it is reasonable to consider the impact of kidney functions on UA level in UA-related researches, especially in diabetes population. A previous report demonstrated that a renal function-normalized UA, UA to creatinine ratio (UA/Cr), was a better predictor of incident CKD than UA alone in patients with T2DM.[20] However, despite the possible superiority of UA/Cr which can potentially provide new information for the understanding of the association between UA and renal disease progression, clinical data of this index are limited. Thus, the present study sought to evaluate the association between UA/Cr and renal disease progression in patients with T2DM in Chinese communities.

2. Material and methods

2.1. Patients

For this observational longitudinal study, data from a Diabetes Community Management Program ("5 + 1" Program) with 5 diabetes

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management targets (HbA1c <7%; blood pressure < 140/80 mm Hg; low density lipoprotein <2.6 mmol/L; stop tobacco, and use of aspirin) and 1 annual screening of diabetes and its complications,[21] were analyzed. A database was established using a Web site-based registry system (www.chinasdtm.com).[22] All patients received instructions of lifestyle modification including diet and exercise, oral antidiabetics, and/or insulin. The program was approved by the Institutional Review Board of Jiangsu Province Institute of Geriatrics. Informed consent was obtained from each patient.

5256 outpatients diagnosed with diabetes according to the 1999 WHO criteria[23] were recruited and followed up from 11 community healthcare centers in Nanjing, China from May 2011 to March 2017. We excluded those patients who had T1DM, proteinuria, myocardial infarction, paralysis, Coronary Artery Bypass Grafting (CABG), severe chronic obstructive pulmonary disease (COPD), cancer, and eGFR <60 mL/min/1.73 m^2 at baseline, and patients receiving uric-acid lowering drugs or missing key data during the follow up. Finally, 3432 patients were included for the analysis.

2.2. Clinical and laboratory data

Clinical data of all samples including personal information, the history of disease, medications, and physical examinations such as body weight, height, and blood pressure (BP) were collected by community physicians. BP was measured with a standard mercury manometer after at least 5 min of rest. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m). All of the laboratory data were also collected by the community physicians including fasting lipid profiles, UA, serum creatinine, glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

eGFR was calculated using the CKD-Epidemiology Collaboration (CKD-EPI) creatinine equation.[24] Renal function-normalized UA was calculated as serum UA/serum creatinine. Renal disease progression was defined as the occurrence of eGFR <15 mL/min/1.73 m^2 or doubling of baseline serum creatinine level.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS software (20.0; SPSS, Chicago, IL, USA). All data are expressed as mean ± standard deviation (SD), median (interquartile range) or percentage, where appropriate. Comparisons between two groups were made using Student's *t*-tests or Chi-square tests. For data not normally distributed, non-parametric Mann–Whitney *U* test was adopted for the analysis. Kolmogorov-Smirnov test was used to evaluate the normality of variables. Cox hazards regression analysis was performed to test the association of UA/Cr and renal disease progression. All the variables included in the multivariate Cox regression models were described in the section of Results. All statistical tests were two-sided and a *P* value of <0.05 was considered statistically significant.

3. Results

A total of 3432 patients [1760 (51.3%) males] were included in the analysis. Their average age was 66.70 ± 9.40 years. During a median follow-up of 30 months, 58 (1.70%) patients experienced progression of renal disease. During the follow-up, 32 patients died. We used the last available data in the clinic visits for their renal function assessment.

Table 1 summarizes the baseline characteristics of patients grouped by whether they met the definition of renal disease progression described above. Compared with those patients without renal disease progression, patients with renal disease progression had an older age, a longer diabetes duration, lower LDL-C cholesterol, and, unexpectedly, lower serum creatinine ($P < 0.001$). The renal function-normalized uric acid (UA/Cr) was significant higher in patients with renal disease progression than those without this situation ($P < 0.001$).

Consistently, when the patients were divided into four groups according to the UA/Cr quartile, 2.7% of the patients in the group of the highest Q4 (UA/Cr > 4.90) presented renal disease progression, higher than that of the lowest Q1 group (UA/Cr < 3.12, 1.5%, $P = 0.064$). The association between UA/Cr with renal disease progression was further tested by multivariate Cox regression analysis. As shown in Table 2, UA/Cr, but not UA, was a predictor of renal disease progression (HR 1.294 [95% CI 1.102–1.519], $P = 0.002$). In the multiple adjusted model, UA/Cr was still an independent predictor of renal disease progression after adjusted for age, gender, BMI, systolic blood pressure (SBP), FBG, TC, TG, HDL-C, and LDL-C (Table 3).

4. Discussion

The present longitudinal study found that renal function-normalized UA, i.e. UA to serum creatinine ratio, was associated with renal disease progression in a cohort of T2DM patients in Chinese communities.

UA is demonstrated as an indicator for kidney disease progression, but not in all studies.[25,26] UA is the end product of purine nucleotide metabolism, and 2/3 of serum UA is excreted through kidney, which is

Table 1
Baseline characteristics of patients with diabetes according to renal disease progression.

	Without renal disease progression	With renal disease progression	*P*-value
n	3374	58	
Gender (male, %)	1731 (51.3)	29 (50.0)	0.844
Age (years)	66.6 ± 9.4	70.9 ± 9.3	0.001
Diabetes duration (years)	10.0 ± 6.6	12.1 ± 6.6	0.017
BMI (kg/m^2)	25.3 ± 3.1	25.5 ± 3.4	0.726
SBP (mm Hg)	129.1 ± 14.4	131.3 ± 13.9	0.229
HB (g/L)	139.0 ± 15.0	132.7 ± 22.0	0.116
FBG (mmol/L)	7.08 ± 2.24	7.04 ± 2.59	0.891
HbA1c (%)	6.87 ± 1.71	7.23 ± 1.72	0.187
Total cholesterol (mmol/L)	4.35 ± 1.09	4.07 ± 0.96	0.057
Triglyceride (mmol/L)	1.24 ± 1.45	1.07 ± 0.88	0.378
HDL cholesterol (mmol/L)	0.87 ± 0.52	0.82 ± 0.43	0.448
LDL cholesterol (mmol/L)	2.24 ± 0.94	1.80 ± 0.77	0.001
UA (mmol/L)	285.8 ± 85.5	263.5 ± 82.3	0.048
Serum creatinine (μmol/L)	71.99 ± 14.65	59.21 ± 15.55	<0.001
eGFR (mL/min/1.73 m^2)	84.87 ± 12.91	91.87 ± 12.86	<0.001
SUA/Scr	4.09 ± 1.35	4.76 ± 1.98	<0.001

BMI: body mass index; SBP: systolic blood pressure; FBG: fasting blood glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid; eGFR: estimated glomerular filtration rate; SD: standard deviation.
Data are expressed as mean ± SD.

Table 2
Multivariate Cox regression for renal disease progression by baseline characteristics.

	Wald	SEM	HR (95% CI)	*P*-value
Age (years)	5.279	0.015	1.035 (1.005–1.066)	0.022
Total cholesterol (mmol/L)	4.826	0.132	0.749 (0.578–0.969)	0.028
LDL cholesterol (mmol/L)	16.192	0.163	0.519 (0.377–0.714)	<0.001
Serum creatinine (Scr, μmol/L)	35.579	0.012	0.933 (0.912–0.955)	<0.001
UA (μmol/L)	4.737	0.002	0.996 (0.993–1.000)	0.030
UA/Cr	9.885	0.082	1.294 (1.102–1.519)	0.002
eGFR (mL/min/1.73 m^2)	17.843	0.045	1.046 (1.024–1.068)	<0.001

UA: serum uric acid; HR: hazard ratio; CI: confidence interval; Cr: serum creatinine; eGFR: estimated glomerular filtration rate.

a complex process involving kidney glomerular filtration, proximal renal tubules absorption, proximal renal tubules (distal part) secretion and absorption.[27] Decreased GFR and enhanced absorption function will lead to varying degrees of UA up-regulation. In addition, since baseline kidney function itself is a known risk factor of renal disease progression,[28] it is obvious that the association between UA and renal disease progression will be influenced by renal function. If UA is a real risk factor for renal disease progression, the renal-function normalized UA, which might represent the net production of UA, may be better than UA alone as an indicator. Actually, in the present study we revealed that UA/Cr was positively associated with CKD progression defined as an eGFR <15 mL/min/1.73 m^2 or doubling of baseline serum Cr level. In another study, UA/Cr was also proved to be better than UA as a predictor of incident CKD, which was defined as the occurrence of an eGFR <60 mL/min/1.73m^2 in patients with T2DM.[20]

Recently, increasing evidence demonstrated the utilities of UA/Cr in diabetic populations. Al-Daghri NM et al.[29] showed that UA/Cr has strongly associated with the metabolic syndrome and its components in T2DM patients, supporting our hypothesis that UA/Cr may reflect the endogenic UA levels more precisely and have a closer relationship with metabolic disorders. In addition, UA/Cr was recently shown to significantly correlate with β-cell function in T2DM patients independently of potential confounders including sex, BMI and renal function.[30] Our data provided new evidence regarding the clinical utility of the renal-function normalized UA. Many studies suggested the association between elevated serum UA level and cardiovascular disease (CVD) risk,[31–33] and elevated UA levels are strongly and independently associated with cardiovascular and all-cause mortality in people with suspected or definite CVD.[18,34] It will be interesting to evaluate the clinical utility of UA/Cr in CVD populations in the future.

It was found that patients with renal disease progression had higher eGFRs at baseline in the present study. When these patients were further divided into two groups based on the occurrence of eGFR <15 mL/min/1.73 m^2 or doubling of baseline serum creatinine level, patients with the occurrence of eGFR <15 mL/min/1.73 m^2 had higher, but patients with doubled serum creatinine had much lower creatinines than those without renal disease progression (data not shown), indicating it might be explained by that doubling of baseline creatinine is more likely to occur with lower creatinine.

Table 3
Hazard ratio of baseline UA/Cr for renal disease progression.

	Wald	SEM	HR (95% CI)	*P*-value
Crude	9.885	0.082	1.294 (1.102–1.519)	0.002
Multiple adjusted[a]	8.913	0.085	1.288 (1.091–1.521)	0.003
Multiple adjusted[b]	8.214	0.090	1.293 (1.085–1.541)	0.004
Multiple adjusted[c]	10.509	0.096	1.364 (1.131–1.646)	0.001

UA: serum uric acid; HR: hazard ratio; CI: confidence interval; Cr: serum creatinine; eGFR: estimated glomerular filtration rate; BMI: body mass index; SBP: systolic blood pressure; LDL-C: low-density lipoprotein cholesterol.

[a] Adjusted for age and gender.

[b] Adjusted for age, gender and BMI.

[c] Adjusted for age, gender, BMI, SBP, FBG, TC, TG, HDL-C and LDL-C.

It should be mentioned that there were some limitations in the present study. First of all, we have >5000 patients in the database, but only 3432 patients are included in the analysis. In China, due to the limitation of health care resources, the management of patients with chronic diseases is relatively inadequate, especially in community health services, resulting in poor disease control and follow-up. Secondly, because of lack of the medication information in the database, we could not exclude the influence of medications on the progress of renal function, especially the usage of angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) in the present study. Third, as the patients were recruited from 11 different community healthcare centers in Nanjing, the data came from different laboratories, which may induce some biases. At last, our research only represents the management of diabetes mellitus in Nanjing communities. We plan to cooperate with other medical centers and communities to further validate our findings.

In conclusion, in the present study we found that the kidney function normalization of uric acid, such as UA/Cr is associated with progression of chronic renal disease in diabetic patients. Further studies are needed to clarify this issue.

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References

1. Iseki K. Chronic kidney disease in Japan. Intern Med 2008;47:681-9.
2. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. J Am Soc Nephrol 2007;18:2644-8.
3. Lou QL, Ouyang XJ, Gu LB, et al. Chronic kidney disease and associated cardiovascular risk factors in Chinese with type 2 diabetes. Diabetes Metab J 2012;36:433-42.
4. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225-32.
5. De Cosmo S, Viazzi F, Pacilli A, et al. Serum uric acid and risk of CKD in type 2 diabetes. Clin J Am Soc Nephrol 2015;10:1921-9.
6. Obermayr RP, Temml C, Gutjahr G, et al. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19:2407-13.
7. Barkas F, Elisaf M, Liberopoulos E, et al. Uric acid and incident chronic kidney disease in dyslipidemic individuals. Curr Med Res Opin 2017:1-17.
8. 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;33:1337-43.
9. Rosolowsky ET, Ficociello LH, Maselli NJ, et al. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol 2008;3:706-13.
10. Zoppini G, Targher G, Chonchol M, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. Diabetes Care 2012;35:99-104.
11. Bartakova V, Kuricova K, Pacal L, et al. Hyperuricemia contributes to the faster progression of diabetic kidney disease in type 2 diabetes mellitus. J Diabetes Complications 2016;30:1300-7.
12. Katsiki N, Papanas N, Fonseca VA, et al. Uric acid and diabetes: is there a link? Curr Pharm Des 2013;19:4930-7.
13. Kushiyama A, Tanaka K, Hara S, et al. Linking uric acid metabolism to diabetic complications. World J Diabetes 2014;5:787-95.
14. Yu S, Chen Y, Hou X, et al. Serum uric acid levels and diabetic peripheral neuropathy in type 2 diabetes: a systematic review and meta-analysis. Mol Neurobiol 2016;53:1045-51.
15. Lytvyn Y, Perkins BA, Cherney DZ. Uric acid as a biomarker and a therapeutic target in diabetes. Can J Diabetes 2015;39:239-46.
16. Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. Am J Kidney Dis 1998;32:917-33.
17. Jalal DI, Maahs DM, Hovind P, et al. Uric acid as a mediator of diabetic nephropathy. Semin Nephrol 2011;31:459-65.
18. Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: a review. J Adv Res 2017;8:537-48.
19. Microvascular complications and foot careDiabetes Care 2017;40:S88-98.
20. Gu L, Huang L, Wu H, et al. Serum uric acid to creatinine ratio: a predictor of incident chronic kidney disease in type 2 diabetes mellitus patients with preserved kidney function. Diab Vasc Dis Res 2017;14:221-5.
21. Shan S, Gu L, Lou Q, et al. Evaluation of glycemic control in patients with type 2 diabetes mellitus in Chinese communities: a cross-sectional study. Clin Exp Med 2017;17:79-84.

22. Gu L, Lou Q, Wu H, et al. Lack of association between anemia and renal disease progression in Chinese patients with type 2 diabetes. J Diabetes Investig 2016;7:42-7.
23. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
24. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
25. Miao Y, Ottenbros Sa Fau - Laverman GD, Laverman Gd Fau - Brenner BM, 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.
26. Madero M, Sarnak MJ, Wang X, et al. Uric acid and long-term outcomes in CKD. Am J Kidney Dis 2009;53:796-803.
27. Edwards NL. The role of hyperuricemia and gout in kidney and cardiovascular disease. Cleve Clin J Med 2008;75:S13-6.
28. Yang XL, So WY, Kong AP, et al. End-stage renal disease risk equations for Hong Kong Chinese patients with type 2 diabetes: Hong Kong Diabetes Registry. Diabetologia 2006;49:2299-308.
29. Al-Daghri NM, Al-Attas OS, Wani K, et al. Serum uric acid to creatinine ratio and risk of metabolic syndrome in Saudi type 2 diabetic patients. Sci Rep 2017;7, 12104.
30. Minchao LI, Liubao GU, Jun Y, et al. Serum uric acid to creatinine ratio correlates with beta-cell function in type 2 diabetes mellitus patients. Diabetes Metab Res Rev 2018;34, e3001.
31. Ndrepepa G. Uric acid and cardiovascular disease. Clin Chim Acta 2018;484:150-63.
32. Katsiki N, Karagiannis A, Athyros VG, et al. Hyperuricaemia: more than just a cause of gout? J Cardiovasc Med 2013;14:397-402.
33. Mortada I. Hyperuricemia, type 2 diabetes mellitus, and hypertension: an emerging association. Curr Hypertens Rep 2017;19:69.
34. Wang R, Song Y, Yan Y, et al. Elevated serum uric acid and risk of cardiovascular or all-cause mortality in people with suspected or definite coronary artery disease: a meta-analysis. Atherosclerosis 2016;254:193-9.