

Changes in serum uric acid levels as a predictor of future decline in renal function in older adults with type 2 diabetes

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Abstract

Given that factors affecting renal function remain unknown, this study aimed to identify key predictors of estimated glomerular filtration rate (eGFR) deterioration, which is a representative of renal function decline in older adults with type 2 diabetes (T2DM). In an exploratory prospective observational study, we enrolled 268 Japanese people with T2DM aged ≥ 20 years who were followed up at Shinshu University Hospital. Among those, 112 eligible individuals aged ≥ 65 years were included in the present study. Factors associated with 3-year changes in eGFR (Δ eGFR) and eGFR deterioration (Δ eGFR < 0) were identified using bivariate and multivariable analyses. Regarding baseline values of the subjects, the mean age was 73.5 years, mean blood pressure was 131/74 mmHg, mean hemoglobin A1c was 7.1%, mean eGFR was 62.0 mL/min/1.73 m², mean urinary albumin excretion was 222.6 mg/gCre, and mean serum uric acid (UA) was 5.5 mg/mL. In bivariate analysis, the 3-year change in UA (Δ UA) levels was significantly correlated with Δ eGFR ($r = -0.491$, $P < .001$), but the baseline UA was not ($r = 0.073$, $P = .444$). Multiple linear regression analysis revealed that Δ UA was a significant negative predictor of Δ eGFR in the model that included sex, age, body mass index, serum albumin, and Δ UA as explanatory variables. Moreover, multiple logistic regression analysis demonstrated that Δ UA had a positive association with Δ eGFR < 0 (odds ratio 2.374; 95% confidence interval 1.294–4.357). Thus, future renal function decline can be predicted by Δ UA but not by baseline UA in older adults with T2DM. Further research is needed to determine whether lowering the serum UA level can prevent eGFR decline.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ACR = urinary albumin-to-creatinine ratio, Alb = albumin, ARB = angiotensin-II receptor blocker, BMI = body mass index, CKD = chronic kidney disease, Cre = creatinine, DKD = diabetic kidney disease, DN = diabetic nephropathy, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, FTG = fasting triglyceride, HbA1c = hemoglobin A1c, IFCC = International Federation of Clinical Chemistry, LDL-C = low-density lipoprotein cholesterol, NGSP = National Glycohemoglobin Standardization Program, SGLT2 = sodium-glucose cotransporter 2, T2DM = type 2 diabetes, UA = uric acid.

Keywords: older adult, prediction, renal function, type 2 diabetes, uric acid

1. Introduction

Diabetic nephropathy (DN) is a type of diabetic microangiopathy classically defined as progressive deterioration of renal function, followed by the onset of microalbuminuria or proteinuria caused by diabetes. Recently, diabetic kidney disease (DKD), which

includes DN, regardless of the presence of microalbuminuria or proteinuria, has been proposed as a wide-ranging concept related to renal impairment.^[1] DKD is the leading cause of chronic kidney disease (CKD) and subsequent end-stage kidney disease. In addition, DKD is associated with an increased risk of

Editor: Fabio Comim.

This study was approved by the Institutional Review Board of Shinshu University School of Medicine (approval number: 3592). All procedures were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

All study participants provided informed consent prior to study enrollment.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Shibata Y, Yamazaki M, Kitahara J, Okubo Y, Oiwa A, Sato A, Komatsu M. Changes in serum uric acid levels as a predictor of future decline in renal function in older adults with type 2 diabetes. *Medicine* 2021;100:40(e27420).

Received: 3 April 2021 / Received in final form: 2 August 2021 / Accepted: 13 September 2021

<http://dx.doi.org/10.1097/MD.00000000000027420>

cardiovascular diseases including myocardial infarction, stroke, and heart failure.^[2,3] Therefore, the prevention of DKD development and progression has been a critical issue in diabetic individuals. Potential risk factors for DKD progression include increased hemoglobin A1c (HbA1c), systolic blood pressure, albuminemia grade, early decline in the glomerular filtration rate, duration of diabetes, age, serum uric acid (UA) level, presence of concomitant microvascular complications, and a positive family history.^[4] In the previous large prospective studies, the occurrence of DN in individuals with type 2 diabetes (T2DM) was suppressed especially by the appropriate control of blood glucose, blood pressure, and blood lipid, in addition to the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs).^[5-7]

The exacerbation of DKD is one of the most serious problems in older adults with T2DM. With regard to geriatric conditions, a lower level of the estimated glomerular filtration rate (eGFR) was associated with a higher risk of frailty in community-dwelling Japanese older people with a history of T2DM and/or hypertension.^[8] Older adults with T2DM, low eGFR (<60 mL/min/1.73 m²), and proteinuria also frequently experience diabetic micro- and/or macroangiopathies.^[9] The prediction of a decline in renal function based on risk factors associated with DKD progression can aid in better prognosis and improvement in the quality of life of the older adults with diabetes. However, the factors affecting renal function remain controversial. In the Japanese Elderly Diabetes Intervention Trial, a nationwide randomized, controlled, prospective, interventional study of elderly Japanese subjects with T2DM, hyperuricemia was a significant factor involved in the doubling time of serum creatinine (Cre), in addition to a positive history of cardiovascular disease and non-intensive (conventional) therapy.^[10] Meanwhile, in the Italian Association of Clinical Diabetologist-Annals Study, which had a large cohort of older people with T2DM, variables such as age, body mass index (BMI), albuminemia, elevated serum triglyceride levels, and reduced high-density lipoprotein levels increased the odds ratios for eGFR <60 mL/min/1.73 m² in the older adults with diabetes.^[11] Therefore, using serial data from our prospective observational study, we aimed to examine key factors for predicting the decline in renal function and refine strategies for DKD prevention in older adults with T2DM.

2. Material and methods

2.1. Subjects

This study was performed using initial 3-year data from an ongoing 5-year observational study of diabetes-related outcomes in adults with T2DM, an exploratory study launched in 2012. For the observational study, from August 2012 to June 2016, we consecutively enrolled individuals with T2DM aged 20 years and over who had been followed up at Shinshu University Hospital for a minimum of 1 year. People with cancer or a history of cancer within 5 years before registration were excluded. A clinical database was created to accumulate participants' information, including laboratory data, obtained annually. For the present study, among the 268 individuals enrolled in the observational study, 63 participants were excluded due to lack of the third-year data sets, loss to follow-up, or death. Then, 93 participants aged <65 years were further excluded. Finally, 112 older adults aged ≥65 years at the time of enrollment were eligible for the present analysis (Supplementary Figure, Supplemental Digital Content,

<http://links.lww.com/MD2/A528>). Treatment was provided with an effort to achieve the goals of HbA1c <6.9% (<7.4% in patients aged ≥75 years), blood pressure <130/80 mm Hg (<140/85 mmHg in patients aged 65–74 years, and <150/90 mmHg in patients aged ≥75 years, or with a history of cerebral infarction), low-density lipoprotein cholesterol (LDL-C) ≤120 mg/dL (≤100 mg/dL in patients with a history of coronary vascular disease), and the intensification of early cancer detection. The blood pressure target was uniquely determined by reference to the target values in a prospective observational study of older Japanese adults with T2DM (Nagano Study) and the Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). Specifically, the Nagano Study set <140/70 mmHg as a target for subjects aged <69 years and <145/80 mmHg for those aged 70 years.^[12] Meanwhile, the JSH 2009 guidelines recommended that treatment should be performed with a target of <140/90 mmHg in older people with hypertension and <130/80 mmHg in older diabetic individuals with hypertension.^[13] The guideline also noted that <150/90 mmHg would be acceptable as an intermediate target in terms of careful reduction in blood pressure. Informed consent was obtained from all participants.

2.2. Study design

Participants' information on the following variables was obtained annually: age, sex, smoking habits, drinking habits, diabetic complications, comorbidities, and medications. BMI was calculated using the height and weight measured at the time of enrollment. The physicians in charge made efforts to measure blood pressure using the method recommended in the JSH 2009 guidelines. Specifically, the arm cuff was maintained at the heart level, and measurement was then performed 2 or more times at 1- to 2-minute intervals with a standard sphygmomanometer. The mean value of 2 measurements was adopted as the clinic blood pressure value. The following laboratory tests were simultaneously performed: fasting plasma glucose (FPG) levels, 2-hour postprandial plasma glucose levels, HbA1c (National Glycohemoglobin Standardization Program [NGSP] or International Federation of Clinical Chemistry [IFCC]), fasting and 2-hour postprandial C peptide reactivity, serum and urinary albumin (Alb) levels, aspartate and alanine aminotransferase transaminases levels, γ -glutamyl transpeptidase levels, serum Cre levels, total cholesterol levels, high-density lipoprotein cholesterol levels, fasting triglyceride (FTG) and 2-hour postprandial triglyceride levels, and serum UA levels. Considering linearity, NGSP values of HbA1c calculated from JDS values were converted to IFCC values using the following formula: IFCC values (mmol/mol) = 10.19 × NGSP values (%) – 19.9. LDL-C levels were calculated using the Friedewald formula. For the Japanese individuals, eGFR was calculated using the following equation: $eGFR = 194 \times Cre^{-1.094} \times Age^{-0.287}$ (for women, $\times 0.739$).^[14] Each value of the urinary albumin-to-creatinine ratio (ACR) was categorized as follows: normoalbuminuria (ACR <30 mg/gCre), microalbuminuria (ACR ≥30 mg/gCre and ACR <300 mg/gCre), and macroalbuminuria (ACR ≥300 mg/gCre). Δ was defined as the difference between the values at baseline and that after 3 years, which was obtained by subtracting baseline measurement from the measurement after 3 years. The values of C peptide reactivity, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, Cre, FTG, postprandial triglyceride, and ACR were logarithmically transformed.

2.3. Statistical analysis

Data are expressed as mean (standard deviation). Differences between groups were tested using the unpaired Student *t* test for normally distributed variables and the Mann–Whitney *U* test for variables with skewed distributions. Factors influencing ΔeGFR were evaluated using bivariate and multivariable analyses. For the multivariable analyses, the following adjustment models were employed. Model 1: adjusted for sex, age, BMI, and Cre; Model 2: Model 1 plus FPG, HbA1c (IFCC), and Alb; Model 3: Model 1 plus FTG, high-density lipoprotein cholesterol, and LDL-C; Model 4: Model 1 plus systolic blood pressure and ARB or ACEI use; Model 5: adjusted for factors extracted using the stepwise method. Almost all analyses were performed using StatFlex software version 7.0 (Artech, Osaka, Japan). However, receiver operating characteristic analysis in multiple logistic models was performed with JMP13.2 (SAS Institute Inc., Cary, NC). *P* < .05 was considered statistically significant.

3. Results

3.1. Participants' characteristics

The baseline demographics of the participants are presented in Table 1. The mean age of participants was 73.6 years, and the duration of diabetes was, on average, 15.9 years. The proportion of patients with diabetic retinopathy, nephropathy, and

Table 1
Baseline participants' demographics.

Patients' characteristics	Number of subjects concerned or mean (SD)
Female	46 (41.1%)
Age, yrs	73.5 (5.7)
Diabetes durations, yrs	16.3 (10.4)
Family history of diabetes, yes, %	46 (41.1%)
Current smoker, %	7 (6.3%)
Current drinker	36 (32.1%)
Type of diabetic complications	
Retinopathy	29 (25.9%)
Nephropathy	54 (48.2%)
Neuropathy	69 (61.6%)
Ischemic heart disease	15 (13.4%)
Cerebrovascular disease	14 (12.5%)
Hypertension	93 (83.0%)
Dyslipidemia	67 (59.8%)
Anti-diabetic agents, yes	105 (93.8%)
Sulfonylurea	33 (31.4% [*])
Biguanide	39 (37.1% [*])
Thiazolidine	3 (2.9% [*])
DPP-4 inhibitor	42 (40.0% [*])
Insulin	54 (51.4% [†])
Anti-hypertensive agents, yes	51 (45.5%)
ARB	75 (82.4% [†])
ACEI	11 (12.1% [†])
Anti-hyperlipidemic agents, yes	51 (45.5%)
Statin	38 (74.5% [‡])
Fibrate	8 (15.7% [‡])
Anti-hyperuricemic agents, yes	6 (5.4%)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin-II receptor blocker, DPP-4 = dipeptidyl peptidase-4.

^{*} Percentage of users of the appropriate drug to all users of anti-diabetic agents.

[†] Percentage of users of the appropriate drug to all users of anti-hypertensive agents.

[‡] Percentage of users of the appropriate drug to all users of anti-hyperlipidemic agents.

Table 2
Disease characteristics of participants.

Parameter	Baseline	3-year follow-up	<i>P</i> value
BMI, kg/m ²	24.4 (3.4)	24.2 (4.0)	.171
SBP, mmHg	131 (16)	130 (14)	.664
DBP, mmHg	74 (12)	69 (10)	.002 [*]
Hb, g/dL	13.9 (1.5)	13.6 (2.1)	.015 [*]
Alb, g/dL	4.2 (0.3)	4.3 (0.3)	.017 [*]
Cre, mg/dL	0.86 (0.28)	1.02 (0.48)	<.001 [*]
eGFR, mL/min/1.73 m ²	62.0 (18.4)	56.2 (18.5)	<.001 [*]
UA, mg/dL	5.5 (1.3)	5.4 (1.4)	.271
HDL-C, mg/dL	53.8 (13.3)	53.6 (13.3)	.751
LDL-C, mg/dL	109.6 (29.6)	104.9 (28.9)	.036 [*]
FTG, mg/dL	109.9 (46.9)	112.3 (63.1)	.621
FPG, mg/dL	143.7 (35.3)	140.0 (28.1)	.313
PPG, mg/dL	164.0 (52.8)	170.3 (53.6)	.312
HbA1c (NGSP), %	7.1 (0.8)	7.1 (0.7)	.772
HbA1c (IFCC), mmol/mol	53.9 (9.2)	54.1 (7.7)	.772
FCPR, ng/mL	1.81 (0.94)	1.79 (1.15)	.855
ACR, mg/gCre	222.6 (644.1)	377.2 (1409.4)	.255

Date was expressed as mean (SD).

ACR=urinary albumin-to-creatinine ratio, Alb=albumin, BMI=body mass index, Cre=creatinine, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, FCPR=fasting C peptide reactivity, FPG=fasting plasma glucose, FTG=fasting triglyceride, Hb=hemoglobin, HbA1c=hemoglobin A1c, HDL-C=high-density lipoprotein cholesterol, IFCC=International Federation of Clinical Chemistry, LDL-C=low-density lipoprotein cholesterol, NGSP=National Glycohemoglobin Standardization Program, PPG=postprandial plasma glucose, SBP=systolic blood pressure, UA=uric acid.

^{*} Statistically significant (*P* < 0.05).

neuropathy was 25.9% (29/112), 48.2% (54/112), and 61.6% (69/112), respectively. The prevalence of normoalbuminuria, microalbuminuria, and macroalbuminuria was 50.0% (56/112), 33.0% (37/112), and 17.0% (19/112), respectively. Among 97 patients (93.8%) who used anti-diabetic medication, 54 (51.4%) were treated with insulin, 42 (40.0%) were treated with dipeptidyl peptidase-4 inhibitors, 39 (37.1%) were treated with biguanides (metformin), and 33 (31.4%) were treated with sulfonylurea. However, no patients used sodium-glucose cotransporter 2 (SGLT2) inhibitors. In addition, 91 (81.3%) of 112 participants treated with anti-hypertensive agents were prescribed ARBs and/or ACEIs, and 38 (74.5%) of 51 users of anti-hyperlipidemic agents received statin therapy. Only 6 individuals (5.4%) were treated with anti-hyperuricemic agents. Table 2 shows the disease characteristics of the participants. Compared with baseline values, diastolic blood pressure and hemoglobin were significantly lower at the 3-year follow-up (69 vs 74 mmHg, *P* = .004 for diastolic blood pressure; 13.6 vs 13.9 g/dL, *P* = .015 for hemoglobin), whereas serum Alb was slightly elevated (4.3 vs 4.2 g/dL, *P* = .017). Of note, in 3 years, eGFR drastically deteriorated (56.2 vs 62.0 mL/min/1.73 m², *P* < .001) as serum Cre increased (1.02 vs 0.86 mg/dL, *P* < .001). However, blood glucose profile, lipid profile, serum UA, and ACR remained unchanged during this period.

3.2. Bivariate analysis on the change in eGFR

To explore factors influencing ΔeGFR, a bivariate analysis was conducted. As shown in Table 3, ΔeGFR was significantly correlated with baseline Alb (*r* = 0.235, *P* = .014) and eGFR (*r* = -0.196, *P* = .039). In particular, with a focus on UA-related variables, a significant negative correlation was observed

Table 3**Bivariate analysis for Δ eGFR as a dependent variable.**

Variables	r	P	Variables	r	P
Age	0.089	.350	–	–	–
BMI	–0.044	.646	Δ BMI	0.006	.949
SBP	–0.057	.549	Δ SBP	0.109	.256
DBP	0.085	.371	Δ DBP	0.045	.642
Hb	0.141	.138	Δ Hb	0.051	.594
Alb	0.235	.014*	Δ Alb	–0.179	.066
Cre	0.185	.051	–	–	–
eGFR	–0.196	.039*	–	–	–
UA	0.073	.444	Δ UA	–0.491	<.001*
HDL-C	0.026	.788	Δ HDL-C	–0.073	.447
LDL-C	0.103	.279	Δ LDL-C	–0.003	.978
FTG	–0.025	.794	Δ FTG	0.034	.724
FPG	–0.046	.630	Δ FPG	0.090	.347
PPG	–0.032	.745	Δ PPG	0.012	.902
HbA1c (IFCC)	0.055	.564	Δ Hb1c (IFCC)	0.005	.960
FCPR	–0.145	.128	Δ FCPR	0.019	.845
ACR	–0.127	.183	Δ ACR	0.002	.984

ACR = urinary albumin-to-creatinine ratio, Alb = albumin, BMI = body mass index, Cre = creatinine, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FCPR = fasting C peptide reactivity, FPG = fasting plasma glucose, FTG = fasting triglyceride, Hb = hemoglobin, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, IFCC = International Federation of Clinical Chemistry, LDL-C = low-density lipoprotein cholesterol, PPG = postprandial plasma glucose, SBP = systolic blood pressure, UA = uric acid.

* Statistically significant ($P < 0.05$).

between Δ UA and Δ eGFR ($r = -0.491$, $P < .001$), whereas baseline UA was not specifically correlated with Δ eGFR ($r = 0.073$, $P = .444$).

3.3. Multivariable analyses on eGFR decline

Next, based on the results of the bivariate analysis, Δ eGFR-associated factors were examined using a variety of multiple linear regression models, as shown in Table 4. In particular, in Model 5, which incorporated variables such as sex (female), age, BMI, Δ UA, and Alb, the adjusted coefficient of determination

(R^2) was the highest at 0.233. The independent factor associated with increased Δ eGFR was decreased Δ UA alone ($\beta = -3.648$, $P < .001$). Multiple logistic regression analysis showed that Δ UA was found to have a positive association with Δ eGFR < 0 , or eGFR decline over time, in all analytical models. For example, in Model 1, with an Akaike information criterion value of 115.334 and an area under the receiver operating characteristic curve value of 0.768, the odds ratio (95% confidence interval) of Δ UA was 2.374 (1.294–4.357). Receiver operating characteristic analysis also showed that sensitivity and specificity were 0.839, 0.720, respectively (cutoff value 0.722) (Supplementary

Table 4**Multiple linear regression analysis of Δ eGFR as an object variable.**

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	P	β	P	β	P	β	P	β	P
Sex, female	–0.912	.535	–1.044	.507	–1.449	.348	–0.686	.643	–1.088	.478
Age	0.032	.797	0.053	.692	0.023	.858	0.049	.691	0.067	.600
BMI	–0.205	.308	–0.263	.251	–0.194	.350	–0.173	.410	–0.184	.370
SBP	–	–	–	–	–	–	–0.004	.991	–	–
Alb	–	–	3.639	.122	–	–	–	–	3.714	.104
Cre	0.981	.687	1.463	.593	0.662	.791	2.381	.367	0.934	.719
FPG	–	–	–0.020	.431	–	–	–	–	–	–
HbA1c (IFCC)	–	–	0.082	.365	–	–	–	–	–	–
HDL-C	–	–	–	–	1.074	.746	–	–	–	–
LDL-C	–	–	–	–	0.030	.206	–	–	–	–
FTG	–	–	–	–	–0.519	.787	–	–	–	–
ACR	–	–	–	–	–	–	–0.684	.118	–	–
Δ UA	–3.943	<.001*	–3.572	<.001*	–3.934	<.001*	–3.756	<.001*	–3.648	<.001*
Retinopathy, yes	–	–	–0.908	.589	–	–	–	–	–	–
Cerebrovascular disease, yes	–	–	–	–	0.508	.810	–	–	–	–
ARB or ACE-I use	–	–	–	–	–	–	0.738	.653	–	–
Adjusted R^2	0.222		0.206		0.206		0.219		0.233	

ACR = urinary albumin-to-creatinine ratio, Alb = albumin, ARB = angiotensin-II receptor blocker, BMI = body mass index, Cre = creatinine, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, FTG = fasting triglyceride, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, IFCC = International Federation of Clinical Chemistry, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, UA = uric acid.

* Statistically significant ($P < .05$).

Table, Supplemental Digital Content, <http://links.lww.com/MD2/A530>).

4. Discussion

Our cohort study included non-obese older adult patients with relatively long duration of T2D with well-controlled blood glucose levels, blood pressure, and blood lipid levels. In this study population, factors including age, duration of diabetes, BMI, HbA1c, blood pressure, and blood lipids may be difficult to extract as those associated with eGFR deterioration for a particular period, as previously shown.^[10] Instead, we found that an increase in serum UA levels (Δ UA) was a strong independent factor for the change in eGFR (Δ eGFR) and made it possible to predict an eGFR decline over 3 years. To the best of our knowledge, this is the first study showing that Δ UA is a novel predictor of future eGFR decline in older adults with T2DM.

Elevated blood UA levels are recognized as a risk factor for new CKD development independent of established metabolic risk factors. In a meta-analysis of 15 cohort studies, the incidence of CKD was suggested to be more frequent in healthy adults below 60 years.^[15] Furthermore, some recent meta-analyses suggested that urate-lowering treatment could prevent worsening of renal function in individuals with CKD.^[16,17] In a community-based cohort study that enrolled older adult individuals aged ≥ 65 years, serum UA levels ≥ 6.0 mg/dL measured at any time point independently predicted the risk of early eGFR decline $\geq 30\%$ over 2 years, which increased progressively with an elevation of serum UA levels.^[18] A correlation between higher initial serum UA levels and increased risk of worsening of renal function is also indicated in diabetics, including in the older adult.^[10,19–21] Unlike past studies, we could not find a correlation between baseline serum UA levels and eGFR decline over 3 years in our study population. A decrease in eGFR is a major cause of elevated blood UA levels based on reduced excretion of UA in urine, and the severity of hyperuricemia is linked to the magnitude of changes in eGFR. However, hyperuricemia often develops due to other causes, including boosted biosynthesis of UA mediated by excessive fructose ingestion, especially in older people with diabetes who have strong preferences for carbohydrates. This indicates that blood UA levels may not always reflect renal dysfunction.^[22] In that regard, dynamic changes in UA levels for a specific period of time may be considered a more reliable predictor of eGFR deterioration than UA levels measured at a given time point. In fact, a prospective observational 2-year study for robustness showed that changes in serum UA levels, as well as changes in FPG and hemoglobin levels, represented one of the earliest eGFR decline markers because of a significant negative correlation between changes in serum UA levels and changes in eGFR.^[23] A recent randomized clinical trial failed to show a beneficial effect of serum urate-lowering therapy with allopurinol on kidney function in subjects with type 1 diabetes and early to-moderate DKD.^[24] However, it is still unclear whether urate-lowering agents exert favorable effects on renal function in persons with T2DM and DKD due to the absence of applicable clinical trials.

In an Italian, prospective, 10-year observational cohort study that enrolled 1682 individuals with T2DM and baseline eGFR ≥ 60 mL/min/1.73 m², albuminuria was reported to be the strongest predictor of the annual decline in eGFR.^[25] In addition, in the Japanese Diabetes Complication and its Prevention prospective study involving 355 subjects with type 1 diabetes and 5194 subjects with T2DM, albuminemia was one of the significant factors related to renal dysfunction.^[26] Moreover, the

cohort data obtained from 1995 Japanese patients with diabetes indicated that higher ACR was significantly associated with an early decline in eGFR.^[20] However, in the present analysis, albuminuria was not identified as a factor related to either Δ eGFR or Δ eGFR < 0 . Not being identified albuminuria as the related factor may be due to half of the study population comprised diabetic individuals with normoalbuminuria. This result is supported by the finding of a UK retrospective study showing that the progression of DKD in diabetic individuals without albuminuria was much less than that in individuals with albuminuria independent of age.^[27]

There are some limitations to the present study. First, the causal relationship between the explanatory variable Δ UA and dependent variables, including Δ eGFR and Δ eGFR < 0 , was unclear because this was an observational study. An interventional clinical trial on the prevention of renal dysfunction by improving blood UA levels is needed. Second, there may be a selection bias because the study was conducted at a single facility that was mainly responsible for the treatment of severe diabetes. For practical interpretation of the clinically significant decline of eGFR in the present study, it may be required to compare the characteristics of the population in our study with that in the study with more diverse Japanese older subjects with diabetes. However, the comparison is difficult because, to the best of our knowledge, there has been no large study examining eGFR decline over time, specifically in Japanese older adults with T2DM. Therefore, a multicenter study should be planned in the future. Third, data sets obtained from the users of anti-hyperuricemic agents were included in the study. Technically, the data sets should be excluded when the relationship between Δ eGFR and serum UA levels at some point is investigated. However, a small number of patients consumed the agents without any changes in dose over the observation period. In addition, we focused on the changes in eGFR and UA rather than those measured at a given time point. Thus, the effects of the agents were considered to be weak in the analysis. Fourth, none of the participants were treated with SGLT2 inhibitors. The participants were recruited into the study before their first market induction or during the period when drug use was not sufficiently widespread in Japan. It is known that SGLT2 inhibitors can have favorable effects on the preservation of renal function.^[28] A new prospective study with SGLT2 inhibitor-treated individuals is required because they may have better renal outcomes.

In conclusion, the decline in eGFR over 3 years can be predicted according to the change in serum UA levels from the baseline, not by the baseline serum UA levels, in older adults with T2DM. Further research is needed to determine whether lowering the serum UA level can prevent DKD progression, including the decline in eGFR.

Acknowledgment

The authors are grateful to the investigators of the prospective observational study and the participants in the study.

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