International Journal of Diabetes in Developing Countries (September–October 2023) 43(5):677–686
https://doi.org/10.1007/s13410-022-01132-w

ORIGINAL ARTICLE

Association between uric acid and renal impairment in non-albuminuric diabetes kidney disease of type 2 diabetes

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Received: 8 September 2021 / Accepted: 21 September 2022 / Published online: 15 October 2022

Abstract

Background Elevated serum uric acid (SUA) is increasingly recognized as a risk factor for diabetic kidney disease (DKD). However, the roles of SUA in the declined renal function of non-albuminuric DKD, the prevailing phenotype, are unclear.

Methods A total of 5285 Chinese inpatients with type 2 diabetes were enrolled in this study. Based on albuminuria and reduced estimated glomerular filtration rate (eGFR), the participants were classified into four DKD phenotypes to assess and compare the influence of SUA levels on renal function. In non-albuminuric DKD, exploratory factor analysis of SUA and other metabolism parameters was performed, and linear regression was used to evaluate the associations between eGFR and SUA, individually and in combination with other covariates.

Results In non-albuminuric DKD, SUA explained 16.0% ($\beta = -0.443$; $p < 0.0001$) of the eGFR variance, which was significantly higher than in the other three DKD phenotypes. The values were 3.1%, 6.1%, and 4.6% in no-DKD, albuminuric DKD with preserved eGFR, and albuminuric DKD with reduced eGFR, respectively. In non-albuminuric DKD, SUA was independently and most strongly associated with eGFR ($R^2 = 18.2\%$; $\beta = -0.426$; $p < 0.0001$), followed by triglyceride ($R^2 = 1.4\%$). In the combination of metabolism parameters, SUA was most strongly associated with eGFR ($R^2 = 19.3\%$; $\beta = -0.442$; $p < 0.0001$). Analysis adjusted for covariates provided similar results, and SUA remained most strongly associated with eGFR ($R^2 = 16.3\%$; $\beta = -0.425$; $p < 0.0001$).

Conclusions The management of hyperuricemia may become an important strategy to safeguard renal function in the patients with DKD, especially in non-albuminuric DKD.

Keywords Diabetes kidney disease · Uric acid · Non-albuminuria · Type 2 diabetes

Introduction

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) worldwide [1], and non-albuminuric renal impairment has been demonstrated to be the prevailing DKD phenotype in type 1 and type 2 diabetes individuals [2–6]. Non-albuminuric rather than albuminuric nephropathies are responsible for the largest share of ESRD burden worldwide [6, 7]. Moreover, despite improvement in glycemic and blood pressure control and the use of renin-angiotensin system blocking (RASB) drugs, the number of persons who develop diabetes-related ESRD is steadily increasing each year [8–10], in parallel with the worldwide epidemic of diabetes [11]. Patients with non-albuminuric DKD were reported to have better controlled glucose level, blood pressure, and lipid profiles, compared with albuminuric DKD [12]. Beside, typical glomerular changes were mainly observed in patients with elevated albuminuria [13]. In non-albuminuric DKD patients, renal biopsy findings indicated that predominant interstitial and vascular changes were more frequent, which likely reflect greater contributions from aging, hypertension, and arteriosclerosis [13, 14]. Above all, it is fair to speculate that there are different clinical characteristics and pathophysiologic feature between non-albuminuric and albuminuric nephropathies. While non-albuminuric renal impairment is the prevailing DKD phenotype, risk factors for this phenotype of

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DKD in type 2 diabetes are a research hotspot which might be one of the keys to reducing the prevalence of DKD [6].

Recently, the incidence of hyperuricemia in China has risen from 1.4% in the early 1980s to 10% in the early twenty-first century [15]. Hyperuricemia is currently considered as an independent risk factor for the occurrence and development of DKD in type 2 diabetic individuals [16, 17]. But at present, there is lack of investigation on the association between non-albuminuric DKD and SUA. A study of 1052 cases revealed that SUA may play an important role in the decrease of eGFR in diabetic patients with normoalbuminuria [18]. Further studies should be conducted on role of SUA in non-albuminuric DKD.

As we all know, SUA level is associated with not only metabolic syndrome [19], but also arteriosclerosis and its risk factors [15], which include high blood pressure, diabetes, dyslipidemia, smoking, and obesity. These metabolism parameters, gender, and age are all involved in the deterioration of renal function [20]. Although individual risk factors can cause renal function decline, whether the contribution of each risk in DKD phenotypes is different and whether risk increases if factors overlap, even if each factor is low?

This cross-sectional study in type 2 diabetes patients aimed to identify the metabolism parameters, which individually and in combination are most strongly associated with estimated glomerular filtration rate (eGFR) decline in non-albuminuric DKD. First, we discussed the different contributions of SUA to renal function decline in each phenotype of DKD. Second, we examined if and how individual metabolism parameters are associated and cluster together, in order to discern whether the various metabolism risk factors represent different underlying metabolism characteristics. Finally, we examined if SUA or other metabolism factors explain most of the variance in eGFR, individually and in concert, in non-albuminuric DKD.

Materials and methods

Study design and participants

A retrospective cross-sectional study was designed and conducted in type 2 diabetic patients who were hospitalized at the Zhongda Hospital affiliated to Southeast University between July 2013 and December 2018. For patients who met all selection criteria and had multiple hospitalization records, only the first hospitalization record was entered.

The inclusion criteria were as follows: (1) type 2 diabetic patients meeting the 1999 World Health Organization's diagnostic criteria for diabetes and (2) have at least one previous inpatient medical record for diabetes.

The exclusion criteria were (1) patients with type 1 diabetes mellitus or other special types of diabetes; (2) patients who had been re-hospitalized; (3) patients with missing data on all key variables; (4) patients with other types of nephropathy such as primary nephrotic syndrome and hypertensive nephropathy and patients with acute kidney injury at admission; (5) patients less than 20 years of age; and (6) pregnant women. A total of 5285 patients were finally enrolled in this study (Supplementary Fig. 1).

Outcome definition

Diagnosis codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, were used to extract cases of type 2 diabetes mellitus, glomerulonephritis, and other associated diagnoses.

DKD was defined as albuminuria, reduced eGFR, or both. The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). The albumin-to-creatinine (ACR) values of <30 and ≥ 30 mg/g SCr were considered as normoalbuminuria and albuminuria, respectively. On the basis of albuminuria (ACR <30 or ≥ 30 mg/g SCr) and eGFR (≥ 60 or <60 ml/min/1.73m^2), individuals were classified into the following four DKD phenotypes: no-DKD, albuminuria alone (albuminuric DKD with preserved eGFR), reduced eGFR alone (non-albuminuric DKD), or albuminuria and reduced eGFR (albuminuric DKD with reduced eGFR).

Measurements

The medical records of all patients were collected, including demographic variables, such as gender, age, ethnicity, height, weight, drinking history, and smoking history, as well as medication information. Body mass index (BMI) was calculated as the body weight divided by the square of the height (kg/m^2). Blood samples, collected in the clinic from the subjects the next morning after their admission to the hospital, were used to determine fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum creatinine (SCr), and SUA. The measurement of urine ACR was performed on spot urine samples. Internal and external quality control of the Laboratory Center of the Affiliated Zhongda Hospital of Southeast University was used in accordance with the Chinese Laboratory Quality Control.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 25.0. Missing data were not imputed.

First, the results are presented as mean (standard deviation) for numerical variables with Gaussian distribution and median (interquartile range) for numerical variables with non-parametric distribution, respectively, as percentage for nominal variables. Comparisons of continuous variables among the four DKD phenotypes were performed by one-way ANOVA. Comparisons between frequencies in the study groups were made by X^2 tests.

Second, the linear regression models of four DKD phenotypes were conducted, respectively, to investigate the relationships between eGFR and SUA, when all other metabolism parameters and confounding or potential covariates were controlled. Results were reported in standardized β coefficients with 95% CIs, p value, and explained variance (R^2 [%]; [explained variance/total variance] × 100), for comparing SUA among the four phenotypes.

Third, in the non-albuminuric DKD group, we performed an exploratory factor analysis to evaluate the association between the different individual metabolism parameters and potential underlying metabolism characteristics (latent variables or constructs; explanatory metabolism variables that are not directly observable). Factor matrixes were extracted using the maximum likelihood method and varimax orthogonal rotations with Kaiser normalization. Scree plot analysis (cutoff of 0.85) was used to determine the appropriate number of factors to retain. The underlying metabolism characteristics were derived from the rotated factor matrix; a factor-loading cutoff of 0.4 was used to discern factor characteristics. Factor analysis was acceptable in this dataset, as indicated by the Kaiser–Meyer–Olkin measure of sampling adequacy (0.474) and Bartlett test of sphericity ($X^2 = 356.899$; df 15; $p < 0.001$).

Finally, in order to assess the metabolism parameters that were most strongly associated with eGFR, we performed linear regression analyses. Results were reported in standardized β coefficients with 95% CIs, p value, and explained variance (R^2 [%]; [explained variance/total variance] × 100), for comparability of model parameters among the individual metabolism factors. Backward stepwise regression analysis was performed in order to assess the combined metabolism factors that were most strongly associated with eGFR. The backward elimination approach involves starting with all candidate metabolism factors, deleting the parameter for which loss gives the least deterioration of the model fit, and repeating the process until no further metabolism parameters can be deleted without a significant loss of fit (i.e., defined as $p < 0.1$ for the individual metabolism factors). Thereafter, we assessed the effects of confounding and potential explanatory covariates (Model 2).

Results

Characteristics of the participants with type 2 diabetes

In this study, the prevalence of DKD phenotypes was 57.0% for no-DKD, 21.9% for albuminuric DKD with preserved eGFR, 6.6% for non-albuminuric DKD, and 14.4% for albuminuric DKD with reduced eGFR (Table 1).

Among the four DKD phenotypes, patients with non-albuminuric DKD were more frequently never smokers, older, and had lower levels of TG and higher prevalence of CVD than patients with no-DKD and albuminuric DKD phenotypes. In addition, patients with non-albuminuric DKD were more frequently female and had longer duration of diabetes and lower levels of HbA1c, HDL, and LDL but higher level of SUA than those with no-DKD or albuminuric DKD with preserved eGFR but similar to those with albuminuric DKD with reduced eGFR (Table 1).

Relationship between eGFR and SUA in four DKD phenotypes

A strong negative association was established between SUA and eGFR in all DKD phenotypes. In the analysis adjusted by variables used for Model 3, SUA explained 16.0% ($\beta = -0.443$, $p < 0.0001$) of the eGFR variance in non-albuminuric DKD, while only 3.1% ($\beta = -0.203$, $p < 0.0001$), 6.1% ($\beta = -0.298$, $p < 0.0001$), and 4.6% ($\beta = -0.239$, $p < 0.0001$) were explained in no-DKD, albuminuric DKD with preserved eGFR, and albuminuric DKD with reduced eGFR, respectively. Therefore, the SUA level was most strongly associated with eGFR in the non-albuminuric DKD group (Table 2).

SUA and risk of non-albuminuric DKD

Distinct characteristics of metabolism parameters

Associations among individual metabolism parameters ranged from $r = 0.002$ ($p = 0.970$) to $r = 0.719$ ($p < 0.001$) (Supplementary Table 1). Factor analysis suggested four underlying metabolic characteristics: factor 1 linking the glucose concentrations (FBG, HbA1c), factor 2 linking the lipid concentrations (TG, CHOL), factor 3 linking lipid ratio (HDL-C/LDL-C), and factor 4 linking SUA concentration (Table 3). These results suggested that SUA is an independent metabolism characteristic.

Table 1 Clinical characteristics of the 5285 Nanjing Chinese T2DM patients as a whole and stratified by DKD phenotypes

	Overall ($n=5285$)	Alb^-eGFR^- ACR < 30,eGFR ≥ 60 ($n=3013$)	Alb^+eGFR^- ACR ≥ 30, eGFR ≥ 60 ($n=1160$)	Alb^-eGFR^+ ACR < 30,eGFR < 60 ($n=350$)	Alb^+eGFR^+ ACR ≥ 30,eGFR < 60 ($n=762$)	*p*
N	5285	3013 (57.0%)	1160 (21.9%)	350 (6.6%)	762 (14.4%)	
Age (yr)	65.52 (14.17), $n=5285$	62.04 (13.22), $n=3013$	65.54 (13.98), $n=1160$	77.32 (11.46), $n=350$	73.85 (12.76), $n=762$	< 0.0001
Male sex	3023/5285 (57.20%)	1793/3013 (59.5%)	673/1160 (58.0%)	171/350 (48.9%)	386/762 (50.7%)	< 0.0001
Diabetes duration (yr)	7.74 (3.54), $n=4486$	7.00 (3.02), $n=2563$	7.82 (3.91), $n=1000$	9.76 (3.48), $n=288$	9.69 (3.80), $n=635$	< 0.0001
Coronary artery disease	1358/5285 (25.69%)	604/3013 (20.0%)	280/1160 (24.1%)	158/350 (45.1%)	316/762 (41.5%)	< 0.0001
Hypertension	3392/5285 (64.18%)	1617/3013 (53.7%)	836/1160 (72.1%)	291/350 (83.1%)	648/762 (85.0%)	< 0.0001
Smoking	1425/5257 (27.11%)	880/3004 (29.3%)	313/1150 (27.2%)	65/349 (18.6%)	167/754 (22.1%)	< 0.0001
Drinking	826/5257 (15.71%)	548/3004 (18.2%)	175/1150 (15.2%)	28/349 (8.0%)	75/754 (9.9%)	< 0.0001
Antiplatelet use	2347/4693 (50.01%)	1215/2664 (45.6%)	513/1025 (50.0%)	208/324 (64.2%)	411/680 (60.4%)	< 0.0001
Statins use	1980/4685 (42.26%)	1062/2664 (39.9%)	429/1022 (42.0%)	168/323 (52.0%)	321/676 (47.5%)	< 0.0001
Insulin use	2958/4704 (62.88%)	1750/2671 (65.5%)	647/1028 (62.9%)	172/324 (53.1%)	389/681 (57.1%)	< 0.0001
Metformin use	1265/4702 (26.90%)	811/2671 (30.4%)	299/1027 (29.1%)	45/323 (13.9%)	110/681 (16.2%)	< 0.0001
ACE inhibitors or ARBs	610/3177 (19.2%)	358/2055 (17.4%)	144/682 (21.1%)	39/160 (24.4%)	69/280 (24.6%)	0.003
Other antihypertensive drugs	959/3177 (30.2%)	487/2055 (23.7%)	258/682 (37.8%)	69/160 (43.1%)	145/280 (51.8%)	< 0.0001
Urate- lowering drugs	46/3177 (1.4%)	21/2055 (1.0%)	13/682 (1.9%)	5/160 (3.1%)	7/280 (2.5%)	0.020
Height (cm)	164.75 (8.63), $n=5285$	165.49 (8.63), $n=3013$	164.70 (8.73), $n=1160$	162.15 (8.03), $n=350$	163.07 (8.26), $n=762$	< 0.0001
Weight (kg)	68.71 (12.66), $n=5285$	69.18 (12.67), $n=3013$	69.00 (13.26), $n=1160$	65.77 (11.41), $n=350$	67.81 (12.00), $n=762$	< 0.0001
BMI	25.25 (3.84), $n=5285$	25.19 (3.75), $n=2453$	25.36 (4.06), $n=1000$	24.98 (3.75), $n=288$	25.45 (3.89), $n=635$	0.136
FBG (mmol/L)	11.53 (5.99), $n=5183$	11.52 (5.74), $n=2962$	12.23 (6.19), $n=1136$	10.75 (6.57), $n=340$	10.88 (6.27), $n=754$	< 0.0001
HbA1c (%, mmol/mol)	8.6, 71 (2.3, 2), $n=5024$	8.7, 72 (2.3, 2), $n=2868$	8.8, 74 (2.2, 1), $n=1107$	8.2, 66 (2.3, 1), $n=329$	8.2, 66 (2.2, 1), $n=720$	< 0.0001
CHOL (mmol/L)	4.72 (1.30), $n=5206$	4.77 (1.23), $n=2961$	4.80 (1.37), $n=1143$	4.32 (1.11), $n=347$	4.58 (1.50), $n=755$	< 0.0001
HDL-C (mmol/L)	1.18 (0.30), $n=5172$	1.19 (0.29), $n=2945$	1.19 (0.32), $n=1135$	1.12 (0.28), $n=345$	1.14 (0.32), $n=747$	< 0.0001
LDL-C (mmol/L)	2.82 (0.90), $n=5172$	2.86 (0.85), $n=2945$	2.87 (0.93), $n=1135$	2.59 (0.81), $n=345$	2.74 (1.03), $n=747$	< 0.0001
TG (mmol/L)	2.06 (2.00), $n=5206$	2.07 (2.13), $n=2961$	2.20 (2.11), $n=1143$	1.78 (1.23), $n=347$	1.92 (1.51), $n=755$	0.001
SUA (umolL)	313.88 (106.69), $n=5285$	289.46 (90.19), $n=3013$	304.58 (99.39), $n=1160$	385.53 (122.92), $n=350$	391.70 (118.14), $n=762$	< 0.0001

Data are number/number assessed (%) or mean (SD) as appropriate. ACR is presented in mg/g Cr, and GFR is presented in ml/min/1.73m^2. *Alb^-GFR*, no-DKD; *Alb^+GFR*, albuminuric DKD without reduced eGFR; *Alb^-GFR^+*, non-albuminuric DKD; *Alb^+GFR^+*, albuminuric DKD with reduced eGFR

BMI, body mass index; *FBG*, fasting blood glucose; *HbA1c*, glycated hemoglobin A1c; *CHOL*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride; *SUA*, serum uric acid; *ACE*, angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers

SUA was proven to be more strongly associated with eGFR than other metabolism parameters in non-albuminuric DKD

SUA and TG were significantly associated with eGFR, while CHOL, FBG, HbA1c, and HDL/LDL were not (Table 4). In unadjusted analysis of individual metabolism factors that were modeled separately, SUA explained most of the variance in eGFR ($\beta = -0.426$; $p < 0.0001$; $R^2 = 18.2\%$) (Table 4), followed by TG ($\beta = -0.118$; $p = 0.028$; $R^2 = 1.4\%$) (Table 4).

Stepwise regression, in which all metabolism parameters were entered in a single model, suggested that SUA was most strongly associated with eGFR ($\beta = -0.442$, $p < 0.0001$), and SUA explained 19.3% of the variance in eGFR (Table 5).

The effects of confounding and potential explanatory factors in non-albuminuric DKD

The following variables were identified as confounding or potential explanatory factors: age, gender, BMI, diabetes

Table 2 The linear association between SUA and eGFR in four DKD phenotypes

DKD phenotypes	Model 1				Model 2				Model 3			
	β	95%CI	*p*	R^2, %	β	95%CI	*p*	R^2, %	β	95%CI	*p*	R^2, %
Alb^-eGFR^-	−0.110	−0.026 to −0.013	< 0.0001	1.2	−0.233	−0.051 to −0.036	< 0.0001	4.5	−0.203	−0.047 to −0.030	< 0.0001	3.1
Alb^+eGFR^-	−0.109	−0.028 to −0.009	< 0.0001	1.2	−0.293	−0.063 to −0.039	< 0.0001	6.7	−0.298	−0.065 to −0.038	< 0.0001	6.1
Alb^-eGFR^+	−0.426	−0.047 to −0.030	< 0.0001	18.2	−0.422	−0.048 to −0.020	< 0.0001	14.7	−0.443	−0.050 to −0.021	< 0.0001	16.0
Alb^+eGFR^+	−0.319	−0.051 to −0.033	< 0.0001	10.2	−0.281	−0.048 to −0.016	< 0.0001	6.7	−0.239	−0.045 to −0.010	< 0.0001	4.6

BMI, body mass index; *FBG*, fasting blood glucose; *HbA1c*, glycated hemoglobin A1c; *CHOL*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride; *SUA*, serum uric acid, *ACE*, angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers

Model 1: unadjusted

Model 2: adjusted by age, gender, BMI, DM duration, hypertension, smoking, drinking, antiplatelet use, statins use, insulin use, metformin use, ACE inhibitors or ARBs, other antihypertensive drugs, urate-lowering drugs

Model 3: adjusted by age, gender, BMI, DM duration, hypertension, smoking, drinking, antiplatelet use, statins use, insulin use, metformin use, ACE inhibitors or ARBs, other antihypertensive drugs, urate-lowering drugs, CHOL, TG, FBG, HbA1c, HDL-C/LDL-C

Table 3 Factor analysis of metabolic parameters in non-albuminuric DKD (factor loadings > 0.4 in bold)

	1	2	3	4
CHOL	−0.044	−0.735	0.469	−0.129
TG	0.057	−0.037	0.950	0.097
SUA	0.012	0.013	0.074	0.991
FBG	0.924	0.010	0.051	0.056
HbA1c	0.929	−0.012	0.007	−0.037
HDL-C/LDL-C	−0.031	0.922	0.120	−0.059

FBG, fasting blood glucose; *HbA1c*, glycated hemoglobin A1c; *CHOL*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride; *SUA*, serum uric acid

duration, hypertension, smoking, drinking, antiplatelet use, statins use, insulin use, metformin use, ACE (angiotensin-converting enzyme), ARBs (angiotensin receptor blockers inhibitors), other antihypertensive drugs, and urate-lowering drugs. When we adjusted for these covariates, associations between individual metabolism parameters and eGFR weakened slightly, suggesting that SUA, as the metabolism parameter, primarily accounted for the variance in eGFR (Model 2, $\beta = -0.420$, $p < 0.0001$, $R^2 = 16.4\%$; Model 3, $\beta = -0.394$, $p < 0.0001$, $R^2 = 18.0\%$) (Table 4).

Stepwise regression analysis, in which all metabolism parameters and confounding or potential covariates were entered in a single model, identified antiplatelet drugs and other antihypertensive drugs as covariates that were associated with eGFR ($\beta = -0.196$, $p = 0.027$; $\beta = -0.183$, $p = 0.039$, respectively) and explained 5.5% of the variance in eGFR. SUA was most strongly associated with eGFR ($\beta = -0.425$, $p < 0.0001$) and explained 16.3% of the variance in eGFR (Table 5). Obviously, variability of SUA remained more strongly associated with eGFR than other metabolism parameters in non-albuminuric DKD when these covariates were adjusted.

Discussion

Non-albuminuric DKD has become the prevailing DKD phenotype [8, 10]. In this study, non-albuminuric DKD accounted for 6.6% of all the type 2 diabetes cases, which was comparable to other Chinese studies of inpatients [21]. Similar to clinical features in previous studies [22], patients with this phenotype of DKD were older and predominantly women.

Moreover, hyperuricemia was associated with reduced eGFR in all DKD phenotypes. While in non-albuminuric DKD, SUA explained 14.7–18.2% of the variance of eGFR in unadjusted or adjusted models, which was stronger than other groups. We also investigated which metabolism

Table 4 Associations between individual metabolic parameters and eGFR in non-albuminuric DKD (parameters of unadjusted and adjusted regression models)

Underlying metabolism variable	Metabolism measure	Model 1				Model 2				Model 3			
		β	95%CI	*p*	R^2, %	β	95%CI	*p*	R^2, %	β	95%CI	*p*	R^2, %
SUA concentration	SUA	−0.426	−0.047 to 0.030	< 0.0001	18.2	−0.420	−0.047 to -0.027	< 0.0001	16.4	−0.394	−0.046 to − 0.021	< 0.0001	18.0
Lipid concentration	CHOL	0.083	−0.220 to 1.852	0.122	0.7	0.087	−0.345 to 2.011	0.165	0.7	0.139	−0.223 to 2.614	0.098	2.0
	TG	−0.118	− 1.979 to -0.1117	0.028	1.4	−0.077	− 1.674to 0.388	0.220	0.5	−0.062	− 1.699 to 0.770	0.458	0.2
Glucose concentration	FBG	−0.087	−0.328 to 0.033	0.108	0.8	−0.056	−0.293 to 0.109	0.367	0.3	−0.029	−0.323 to 0.229	0.736	0.7
	HbA1c	−0.074	−0.873 to 0.162	0.178	0.6	−0.048	−0.822 to 0.363	0.447	0.2	−0.046	−0.946 to 0.546	0.597	1.4
Lipid ratio	HDL-C/LDL-C	−0.011	− 7.361to 6.011	0.843	0.01	−0.023	− 9.256 to 6.340	0.713	0.1	−0.153	− 21.901to − 0.762	0.067	0.7

BMI, body mass index; *FBG*, fasting blood glucose; *HbA1c*, glycated hemoglobin A1c; *CHOL*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride; *SUA*, serum uric acid, *ACE*, angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers

Model 1: unadjusted

Model 2: adjusted by age, gender, BMI, diabetes duration, HBP, smoking, drinking, $R^2 = 1.1\%$

Model 3: adjusted by antiplatelet use, statins use, insulin use, metformin use, ACE inhibitors or ARBs, other antihypertensive drugs, urate-lowering drugs; $R^2 = 10.4\%$

parameters were most strongly associated with eGFR in patients with non-albuminuric DKD of type 2 diabetes. Metabolism parameters included HbA1c, FBG, CHOL, TG, HDL-C/LDL-C, and SUA. Four underlying metabolism factors were identified: glucose concentration, lipid concentration, lipid ratio, and SUA concentration. SUA, which appeared to be an independent metabolism characteristic, was individually most strongly associated with eGFR, explaining 18.2% of the variance in eGFR. SUA was followed by TG (1.4%), which reflected partial lipid concentration. CHOL, FBG, HbA1c, and HDL-C/LDL-C were not associated with eGFR. SUA was most strongly associated with eGFR ($R^2 = 19.3\%$) when all metabolism parameters were entered in a single model of stepwise regression. Analysis adjusted for these covariates provided similar results, although the strength of associations was generally decreased and showed SUA to be most strongly associated with eGFR, explaining 16.3% of the variance in eGFR. The effects by antiplatelet and antihypertensive drugs also partly explain the variance in eGFR ($R^2 = 5.5$).

These findings supported the idea that SUA is an independent risk factor of eGFR decline in non-albuminuric DKD. Observational studies have shown that high level of SUA is associated with the loss of kidney function not only in DKD [16, 23–26] but also in non-albuminuric diabetic patients [18]. In our knowledge, this study might be one of the first time to compare the contribution of SUA and other risk factors in different DKD phenotypes, which proved that the relationship between SUA and eGFR in non-albuminuric DKD was stronger than in other phenotypes. Thus, SUA instead of other metabolism parameters might play a significant role in the development of non-albuminuric DKD, which indicated the different underlying pathogeneses and determinant factors from albuminuric DKD.

The presence of low eGFR in diabetic patients with normoalbuminuria is associated with the presence of metabolic syndrome [27]. Risk factors, including hyperglycemia, hypertension, and dyslipidemia, may trigger a progressive decrease of GFR. However, it is reported that patients of non-albuminuric DKD has lower level of blood pressure, LDL-C, and HbA1c than those of albuminuric diabetes with renal insufficiency [12]. And compared to patients with albuminuric DKD, both vascular lesion and tubulointerstitial injury of individuals with non-albuminuric DKD were more advance. Glomerular lesions were found to be less advanced in those with non-albuminuric DKD [28]. Arteriosclerosis reduces the glomerular blood flow and has been found to be a histological predictor for GFR decline in diabetic patients with normoalbuminuria [29].Hyperuricemia has been proved to induce vascular lesion and tubulointerstitial injury of the kidney [30–32]. In our study, SUA explains more eGFR decline than other metabolism parameters in non-albuminuric DKD. Thus, hyperuricemia,

Table 5 Stepwise regression of metabolic parameters on eGFR in non-albuminuric DKD (parameters of unadjusted and adjusted regression models)

Underlying metabolism variable	Metabolism parameters	Model 1							Model 2						
		Step 1			Final step (step 6)				Step 1			Final step (step 12)			
		β	95%CI	*p*	β	95%CI	*p*	R^2, %	β	95%CI	*p*	β	95%CI	*p*	R^2, %
SUA concentration	SUA	−0.426	−0.046 to 0.028	<0.0001	−0.442	−0.047 to -0.030	<0.0001	19.3	−0.443	−0.050 to -0.021	<0.0001	−0.425	−0.046 to -0.027	<0.0001	16.3
Lipid concentration	CHOL	0.077	−0.416 to 1.956	0.203					0.002	−1.910 to 1.95	0.984				
	TG	−0.089	−1.761 to 0.156	0.102					−0.066	−1.836to 0.911	0.506				
Glucose concentration	FBG	−0.014	−0.259 to 0.212	0.844					−0.020	−0.345 to 0.409	0.867				
	HbA1c	−0.064	−0.993 to 0.381	0.381					−0.034	−1.155 to 0.857	0.769				
Lipid ratio	HDL-C/ LDL-C	0.022	−5.755 to 8.654	0.693					−0.184	−30.035 to 2.778	0.102				
Potential covariates	Age								−0.118	−0.306 to 0.089	0.279				5.5
	Gender								0.055	−2.670 to 4.967	0.552				
	BMI								−0.147	−0.916 to 0.084	0.102				
	Diabetes duration								−0.006	−0.649 to 0.614	0.957				
	Hypertension								0.136	−1.385 to 8.135	0.163				
	Smoking								−0.006	−5.580 to 5.280	0.956				
	Drinking								−0.063	−9.733 to 5.404	0.572				
	Antiplatelet use								0.158	−0.849 to 7.800	0.114	0.196	0.484 to 7.962	0.027	
	Statin use								0.08	−2.315 to 5.655	0.408				
	Insulin use								0.033	−3.224 to 4.593	0.729				
	Metformin use								−0.027	−5.484 to 4.028	0.762				
	ACE inhibitors or ARB use								0.104	−2.033 to 6.944	0.28				

Table 5 (continued)

Underlying metabolism variable	Metabolism parameters	Model 1						Model 2					
		Step 1			Final step (step 6)			Step 1			Final step (step 12)		
		β	95%CI	*p*	β	95%CI	*p*	R^2, %	β	95%CI	*p*	β	95%CI	*p*	R^2, %
	Other antihypertensive drug use								−0.204	−8.501 to −0.061	0.047	−0.183	−7.413 to -0.191	0.039	
	Urate-lowering drugs use								-0.115	-16.446 to 3.249	0.187				

BMI, body mass index; *FBG*, fasting blood glucose; *HbA1c*, glycated hemoglobin A1c; *CHOL*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride; *SUA*, serum uric acid, *ACE*, angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers

Model 1: unadjusted

Model 2: adjusted age, gender, BMI, diabetes duration, HBP, smoking, drinking, antiplatelet use, statins use, insulin use, metformin use, ACE inhibitors or ARBs, other antihypertensive drugs, urate-lowering drugs; $R^2 = 15.5\%$

instead of hyperglycemia, high blood pressure, and dyslipidemia, might explain more part of renal function decline in non-albuminuric DKD.

Nevertheless, the SUA level increases linearly with decreasing GFR also as a result of reduced excretion [33]. Thus, whether elevated SUA level plays a causative role in the progression of kidney disease, is an indirect marker of decreased kidney function, or both, should be investigated in different causes and clinical features of CKD [34]. In type 2 diabetes, SUA is more likely to play a causative role, because hyperuricemia is considered to be a component of metabolic syndrome that is initially involved in the progression of type 2 diabetes [35]. Recently, two pivotal trials have failed to show statistically significant benefit of allopurinol on kidney outcomes [36, 37]. However, type 2 diabetes was not discussed in both trials. Hence, the relationship between SUA and DKD in type 2 diabetes should be further investigated, especially in non-albuminuric DKD.

This study had several limitations. First, we used a cross-sectional study design; therefore, the causal relationship between risk factors and non-albuminuric DKD could not be established. However, a large sample size provided statistical power, which was sufficiently large to identify the significant risk factors for non-albuminuric DKD in type 2 diabetes. Second, assessment of glycemia by HbA1c is hampered by various CKD-associated conditions that can bias the measure either to the low or high range. However, alternative glycemic biomarkers, such as glycated albumin or fructosamine, are even less reliable than HbA1c. Hence, HbA1c remains the preferred glycemic biomarker despite its limitations [38]. Third, serum creatinine and albuminuria were measured only once in each patient. Fourth, this study lacks the generalizability as it focused only one hospital. Hence, multicenter study should be conducted in the future.

In summary, the results indicated that SUA was primarily associated with eGFR decline in non-albuminuric DKD than in other DKD phenotypes. The prevention of hyperuricemia may serve as a primary focus in the management of renal decline of non-albuminuric DKD of type 2 diabetes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-022-01132-w.

Acknowledgment We express our heartfelt gratitude to all participants and staff of the Department of Endocrinology, Affiliated Zhongda Hospital of Southeast University.

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Research design: Shaohua Wang and Xi Huang.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Ethics approval was obtained from the Research Ethics Committee of Zhongda Hospital affiliated to Southeast University (Registration number: 2020ZDSYLL028-P01).

Consent to participate No additional written consent was needed from the participants because all the data were extracted from the computerized data system of hospital authority and no personal data were collected for this study.

Consent for publication The article is the authors' original work. The article has not received prior publication and is not under consideration for publication elsewhere. All authors have seen and approved the manuscript being submitted.

Conflict of interest The authors declare no competing interests.

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