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Original article

Coexistence of hyper-uricaemia and low urinary uric acid excretion further increases risk of chronic kidney disease in type 2 diabetes

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ABSTRACT

Aim. – To investigate whether hyper-uricaemia and decreased urinary uric acid excretion (UUAE) are associated with increased risk of chronic kidney disease (CKD), and whether the coexistence of hyper-uricaemia and low UUAE further increases CKD risk in type 2 diabetes mellitus (T2DM).
Methods. – In this cross-sectional study based on serum uric acid (SUA) and UUAE levels, 2846 T2DM inpatients were divided into those with normal SUA and UUAE (group 1), normal SUA and low UUAE (group 2), hyper-uricaemia and normal UUAE (group 3), and hyper-uricaemia and low UUAE (group 4). Hyper-uricaemia was defined as SUA levels $\geq$ 420 μmol/L in men and $\geq$ 360 μmol/L in women. Low UUAE was defined as levels below the first UUAE quintiles (< 2161 μmol/24 h in men, 1977 μmol/24 h in women).
Results. – There were trends for significantly increased prevalences of CKD (4.3%, 12.6%, 18.3%, 47.8%; $P < 0.001$), albuminuria (20.2%, 26.4%, 36.9%, 54.9%; $P < 0.001$) and macroalbuminuria (3.3%, 10.1%, 10.7%, 31.9%; $P < 0.001$) from groups 1 to 4, respectively. After controlling for multiple confounding factors, prevalences of CKD ($P < 0.001$) and urinary albumin levels ($P = 0.013$) showed significantly increasing trends, whereas eGFR levels were markedly decreased from groups 1 to 4 ($P < 0.001$).
Conclusion. – Hyper-uricaemia and low UUAE levels are closely associated with presence of CKD, and the concomitant presence of hyper-uricaemia and decreased UUAE levels further increased CKD risk in T2DM. Thus, the combined consideration of SUA and UUAE levels may help to identify those T2DM patients at higher CKD risk.

Introduction

In recent decades, the epidemic of chronic kidney disease (CKD) has cast a heavy health and economic burden the world over and widely aroused public attention. A cross-sectional survey based on nationally representative samples of Chinese adults estimated that 119.5 million have CKD, amounting to a CKD prevalence of 10.8% in China [1]. Furthermore, it is a noteworthy fact that people with type 2 diabetes mellitus (T2DM) have an increased risk of developing CKD [2,3]. Indeed, a study of the Chinese general population and hospitalized urban population demonstrated that CKD related to diabetes has become more common than glomerulonephritis, with the gap between them progressively increasing [4]. Therefore, it is crucial to identify T2DM patients at high CKD risk early on.

Recently, besides the traditional risk factors for CKD such as hypertension and diabetes, a number of clinical and epidemiological studies have confirmed the positive association between serum uric acid (SUA) and CKD in different populations [5–7]. For example, a prospective observational cohort involving 900 healthy normotensive adults followed for 5 years reported that increased

Abbreviations: CKD, chronic kidney disease; T2DM, type 2 diabetes; SUA, serum uric acid; UUAE, urinary uric acid excretion; DD, diabetes duration; HTN, hypertension; LLDs, lipid-lowering drugs; AHAs, anti-hypertensive agents; ACAs, anti-coagulant agents; IIAs, insulin or insulin analogues; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PPG, post-prandial plasma glucose; FCP, fasting C-peptide; PCP, post-prandial C-peptide; UAE, urinary albumin excretion.

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SUA levels were significantly associated with a greater likelihood of decreased estimated glomerular filtration rates (eGFRs) [8]. Similarly, Ceriello and colleagues [6] conducted a follow-up study of Italian patients with T2DM that revealed that the association between a decline in eGFR and increased SUA levels was particularly strong.

However, while a number of studies focused on the relationship between SUA and CKD, only a few investigated the association of urinary uric acid excretion (UUAE) with the presence of CKD. Thus far, two studies have demonstrated a positive association between UUAE and the presence of CKD [9,10]. McPhaul [9] observed elevated SUA and decreased uric acid clearance in patients with CKD compared with non-CKD subjects, and surmised that the rise in SUA was one of the early functional consequences of CKD and decreased UUAE. Similarly, in a previous study by our group [11], a positive relationship was indicated between reduced UUAE levels and CKD in patients with T2DM even after adjusting for multiple factors.

Nevertheless, although the association of SUA and UUAE with CKD has been reported in previous studies, epidemiological studies are lacking as regards the association between concomitant hyper-uricaemia and low UUAE and CKD. Thus, the aims of the present study were to examine the association between hyper-uricaemia/low UUAE and presence of CKD, and to investigate whether the coexistence of hyper-uricaemia and low UUAE further increases CKD risk in patients with T2DM.

Materials and methods

Subjects and study design

This cross-sectional study was conducted based partly on data from our previous studies [11–13]. Briefly, from January 2007 to June 2009, 3598 consecutive inpatients with T2DM were investigated, although 752 patients were excluded for the following reasons: lack of UUAE data; taking drugs such as losartan, furosemide and allopurinol that may affect uric acid metabolism; and incomplete clinical data. Ultimately, 2846 patients (1508 men and 1338 women) were included in our study. Every patient participated in an interview to obtain information on: diabetes duration (DD); history of hypertension (HTN); use of medications including lipid-lowering drugs (LLDs), antihypertensive agents (AHAs), anticoagulant agents (ACAs) and insulin or insulin analogues (IIAs); alcohol consumption; and smoking habits. Smoking status, alcohol consumption and HTN were defined according to criteria previously described elsewhere [13].

Albuminuria was defined as a urinary albumin excretion (UAE) rate $\geq$ 30 mg/24 h. Macro-albuminuria was defined as a UAE $\geq$ 300 mg/24 h. CKD was defined as an eGFR with the cut-off limit of $<$ 60 mL/min/1.73 m^2 and/or the presence of macro-albuminuria, as described in our previous research [11].

Hyper-uricaemia (high SUA levels) was defined using the cut-off limits of $\geq$ 420 μmol/L in men and $\geq$ 360 μmol/L in women [14]. However, as the definition of low UUAE has not been previously reported, this was defined in the present study as any UUAE level below the first UUAE quintile ($<$ 2161 μmol/24 h in men, $<$ 1977 μmol/24 h in women).

Therefore, according to their SUA and UUAE levels, patients were divided into four groups: group 1, those with normal levels of SUA ($<$ 420 μmol/L in men, $<$ 360 μmol/L in women) and UUAE ($\geq$ 2161 μmol/24 h in men, $\geq$ 1977 μmol/24 h in women); group 2, those with normal levels of SUA and low UUAE ($<$ 2161 μmol/24 h in men, $<$ 1977 μmol/24 h in women); group 3, those with high levels of SUA ($\geq$ 420 μmol/L in men, $\geq$ 360 μmol/L in women) and normal UUAE; and group 4, those with high levels of SUA and low UUAE (as defined above).

The study was carried out in accordance with the Declaration of Helsinki and approved by the human research ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. All patients gave their written informed consent before participating in the study.

Physical examination and laboratory measurements

These examinations and measurements were routinely obtained as per our previous methods, described elsewhere [11,13]. Measurements of weight, height, waist circumference, hip circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were carried out according to standardized protocols. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Body mass index (BMI) was calculated by dividing weight in kilogrammes by height in metres squared (kg/m^2).

Blood samples were collected to measure SUA, fasting plasma glucose (FPG), 2-h post-prandial plasma glucose (PPG), fasting C-peptide (FCP), 2-h post-prandial C-peptide (PCP), glycosylated haemoglobin A_{1c} (HbA_{1c}), total triglycerides (TTG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), creatinine (Cr) and C-reactive protein (CRP). eGFR was derived using the following formula for Chinese subjects: $175 \times (\text{serum creatinine})^{-1.234} \times (\text{age})^{-0.179}$ ($\times 0.79$ if female) [1]. Updated versions of homoeostasis model assessment for insulin resistance (HOMA2-IR) and for insulin sensitivity (HOMA2-%S) using FPG and FCP levels were used to calculate scores with the HOMA2 Calculator version 2.2.3 [15].

Currently, UUAE levels as determined by urinary uric acid output over a 24-h period are the most common and simplest method of measurement [16]. Therefore, based on our previous studies [11,12,17], a single 24-h urine sample was collected to determine UUAE levels using enzymatic methods. In addition, the 24-h UAE was obtained as the mean of three separate early-morning urine sample tests.

Statistical analysis

All data were analyzed using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Normally distributed quantitative data were expressed as means ± standard deviation (SD), and non-normally distributed quantitative data were expressed as medians and interquartile range (IQR, 25%–75%). Qualitative data were expressed as percentages. One-way analysis of variance (ANOVA) with least significant difference (LSD) was applied to determine differences across groups for normally distributed variables. For non-normally distributed variables, the Kruskal–Wallis test was performed, and for prevalence data and frequency differences, the chi-squared test was used. Binary logistic regression was carried out to compare the difference in qualitative data between groups when controlling for age and gender, and also to assess the association between patients' grouping and presence of CKD after adjusting for multiple factors. A general linear model was used to compare the means of continuous variables after controlling for age and gender, and to evaluate the relationships between patients' grouping and levels of eGFR and urinary albumin.

Three models were constructed to assess the association of patients' groupings with the presence of CKD and levels of eGFR and albuminuria. Model 1 included adjustments for age, gender, DD, HTN, smoking, alcohol drinking, and use of LLDs, AHAs, ACAs and IIAs; model 2 included further adjustments for SBP, DBP, WHR and BMI; and model 3 included additional adjustments for

laboratory measures, including ALT, TC, TTG, LDL-C, HDL-C, CRP, HbA_{1c}, FPG, 2-h PPG, FCP, 2-h PCP, HOMA2-IR and HOMA2-%S. Moreover, the prevalences of CKD, albuminuria and macroalbuminuria in the four patients' groups were compared after adjusting for age, gender and DD using binary logistic regression. A *P*-value < 0.05 was considered statistically significant.

Results

Clinical and laboratory data

Patients' clinical and laboratory characteristics are presented in Table 1. After adjusting for gender, age, prevalence of HTN, DD, and use of IIAs, LLDs and AHAs, SBP, DBP, BMI, WHR, 2-h PPG, FCP, 2-h CP, HbA_{1c}, HOMA2-%S, HOMA2-IR, TTG, TC, HDL-C, ALT, Cr, UAE and CRP were all significantly different across the four groups (all $P < 0.05$).

Prevalences of CKD, albuminuria and macroalbuminuria

Fig. 1 illustrates the prevalences of CKD, albuminuria and macroalbuminuria in the four patients' groups after controlling for age, gender and DD. CKD prevalence in our group-1 patients (4.3%) was significantly lower than in the other three groups. Interestingly, compared with group 2 (12.6%) and group 3 (18.3%), the prevalence of CKD in group 4 (47.8%) was markedly further increased (Fig. 1A).

Likewise, this significantly increasing trend was also observed for prevalences of albuminuria and macroalbuminuria across the four groups: 20.2%, 26.4%, 36.9% and 54.9% for albuminuria, respectively ($P < 0.001$ for trend), and 3.3%, 10.1%, 10.7% and 31.9% for macroalbuminuria, respectively ($P < 0.001$ for trend; Fig. 1B, 1C).

eGFR levels

Fig. 2 shows eGFR levels in our patients after adjusting for age, gender and DD. The significantly decreasing trend is evident in all four groups ($P < 0.001$ for trend). Compared with eGFR levels in group-1 patients, levels in group 2 and group 3 were all markedly decreased (all $P < 0.001$). Moreover, eGFR levels were considerably lower in group-4 patients compared with groups 2 and 3 (Fig. 2A; all $P < 0.001$). Interestingly, patients with moderate-to-severe reductions in eGFR levels (using cutoff limits at 30–59, 15–30 and < 15 mL/min/1.73 m^2) were more likely to be in group 4 (Fig. 2B).

Association of patients' groupings with presence of CKD

Table 2 presents the association of patients' groupings with presence of CKD in T2DM. After adjusting for age, gender, DD, HTN, smoking, alcohol drinking, and use of LLDs, AHAs, ACAs and IIAs (model 1), the prevalence of CKD in group 1 compared with groups 2, 3 and 4 showed a clearly increasing trend ($P < 0.001$). After

Table 1
Characteristics of study subjects according to four groupings based on levels of serum uric acid (SUA) and urinary uric acid excretion (UUAE).

Variables	Patients with normal SUA and UUAE (n = 1867)	Patients with normal SUA and low UUAE (n = 435)	Patients with high SUA and normal UUAE (n = 431)	Patients with high SUA and low UUAE (n = 113)	*P*	*P
Male gender (n, %)	793 (42.50%)	341 (43.90%)	284 (51.00%)	90 (41.60%)	0.013	0.004
Age (years)	57 ± 12	63 ± 13	59 ± 13	66 ± 13	< 0.001	< 0.001
*DD (months)	72 (12–120)	98 (36-168)	72 (12–132)	120 (60–180)	< 0.001	< 0.001
Smoking (n, %)	572 (30.6%)	119 (27.4%)	110 (25.5%)	31 (27.4%)	0.142	0.992
Alcohol (n, %)	305 (16.3%)	66 (15.2%)	68 (15.8%)	10 (8.8%)	0.202	0.203
HTN (n, %)	890 (47.7%)	225 (51.7%)	294 (68.2%)	84 (74.3%)	< 0.001	< 0.001
LLDs (n, %)	539 (28.9%)	94 (21.6%)	186 (43.2%)	36 (31.9%)	< 0.001	< 0.001
AHAs (n, %)	794 (42.5%)	209 (48.0%)	273 (63.3%)	75 (66.4%)	< 0.001	< 0.001
IIAs (n, %)	1331 (71.3%)	341 (78.4%)	284 (65.9%)	90 (79.6%)	< 0.001	< 0.001
ACAs (n, %)	869 (46.5%)	209 (50.6%)	273 (44.1%)	75 (53.1%)	0.155	0.261
SBP (mmHg)	131 ± 17	132 ± 18	134 ± 17	136 ± 22	< 0.001	0.008
DBP (mmHg)	80 ± 10	78 ± 9	81 ± 10	78 ± 11	< 0.001	< 0.001
Waist-to-hip ratio	0.91 ± 0.06	0.9 ± 0.06	0.93 ± 0.07	0.93 ± 0.06	< 0.001	< 0.001
Body mass index (kg/m^2)	24.7 ± 3.3	23.4 ± 3.6	26.6 ± 3.4	24.7 ± 3.3	< 0.001	< 0.001
BPC ($\times 10^9$)	189 ± 60	183 ± 51	194 ± 55	190 ± 61	0.053	0.219
WBCC ($\times 10^9$)	6.3 ± 1.8	6.3 ± 1.8	6.8 ± 2.4	6.9 ± 2.3	< 0.001	< 0.001
*FPG (mmol/L)	7.9 (6.3–9.8)	7.3 (5.8–9.6)	7.5 (6.1–9.5)	7.6 (6.2–9.7)	0.003	0.194
*2-h PPG (mmol/L)	13.7 (10.3–16.9)	12.9 (8.7–16.1)	13.1 (9.8–17)	12.8 (9.6–16.8)	0.002	0.003
HbA_{1c} (%)	9.23 ± 2.41	9.38 ± 2.66	8.61 ± 2.16	8.67 ± 2.31	< 0.001	< 0.001
*FCP (ng/mL)	1.61 (1–2.34)	1.25 (0.73–1.97)	2.3 (1.58–3.14)	2.25 (1.05–3.36)	< 0.001	< 0.001
*2-h PCP (ng/mL)	3.59 (2–5.29)	2.56 (1.29–4.48)	4.94 (3.22–5.83)	3.91 (2.39–5.69)	< 0.001	< 0.001
*HOMA2-%S	72 (49.8–115.9)	89 (57.3–160.3)	51.6 (37.7–75.5)	52 (35.5–113)	< 0.001	< 0.001
*HOMA2-IR	1.4 (0.9–2.0)	1.1 (0.6–1.7)	2.0 (1.3–2.7)	1.9 (0.9–2.9)	< 0.001	< 0.001
*TTG (mmol/L)	1.38 (0.98–2.02)	1.19 (0.82–1.68)	2.06 (1.41–2.97)	1.68 (1.2–2.44)	< 0.001	< 0.001
TC (mmol/L)	4.68 ± 1.13	4.54 ± 1.08	4.95 ± 1.28	4.71 ± 1.19	< 0.001	< 0.001
HDL-C (mmol/L)	1.12 ± 0.31	1.17 ± 0.31	1.02 ± 0.25	1.01 ± 0.26	< 0.001	< 0.001
LDL-C (mmol/L)	3.08 ± 0.94	2.97 ± 0.95	3.16 ± 0.95	3.01 ± 0.97	0.026	0.095
*ALT (U/L)	20 (14–31)	17 (12–25)	23 (15–41)	17 (11–25)	< 0.001	< 0.001
*Cr (μmol/L)	65 (54–77)	67 (56–83)	72 (59–91)	92 (73–141)	< 0.001	< 0.001
*UAE (mg/24 h)	10.3 (6.5–22.7)	10.2 (5.6–37.1)	17.3 (7.9–64.6)	45.0 (10.5–479.8)	< 0.001	< 0.001
*CRP (mg/L)	1.03 (0.46–2.52)	1.02 (0.41–2.4)	1.57 (0.81–3.84)	1.91 (0.74–5.43)	< 0.001	0.006

Values are expressed as means ± SD, medians (interquartile range) or percentages; * non-normally distributed continuous variables.
P-values not adjusted for age and gender for trend.
DD: diabetes duration; HTN: hypertension; LLDs: lipid-lowering drugs; AHAs: antihypertensive agents; IIAs: insulin or insulin analogues; ACAs: anticoagulant agents; SBP/DBP: systolic/diastolic blood pressure; BPC: baseline platelet count; WBCC: white blood cell count; FPG: fasting plasma glucose; PPG: post-prandial plasma glucose; FCP: fasting C-peptide; PCP: post-prandial C-peptide; HOMA2-%S/-IR: updated homoeostasis model assessment of insulin sensitivity/insulin resistance; TTG: total triglycerides; TC: total cholesterol; HDL-C/LDL-C: high-density/low-density lipoprotein cholesterol; ALT: alanine aminotransferase; Cr: creatinine; UAE: urinary albumin excretion; CRP: C-reactive protein.
* *P*-values adjusted for age and gender for trend.

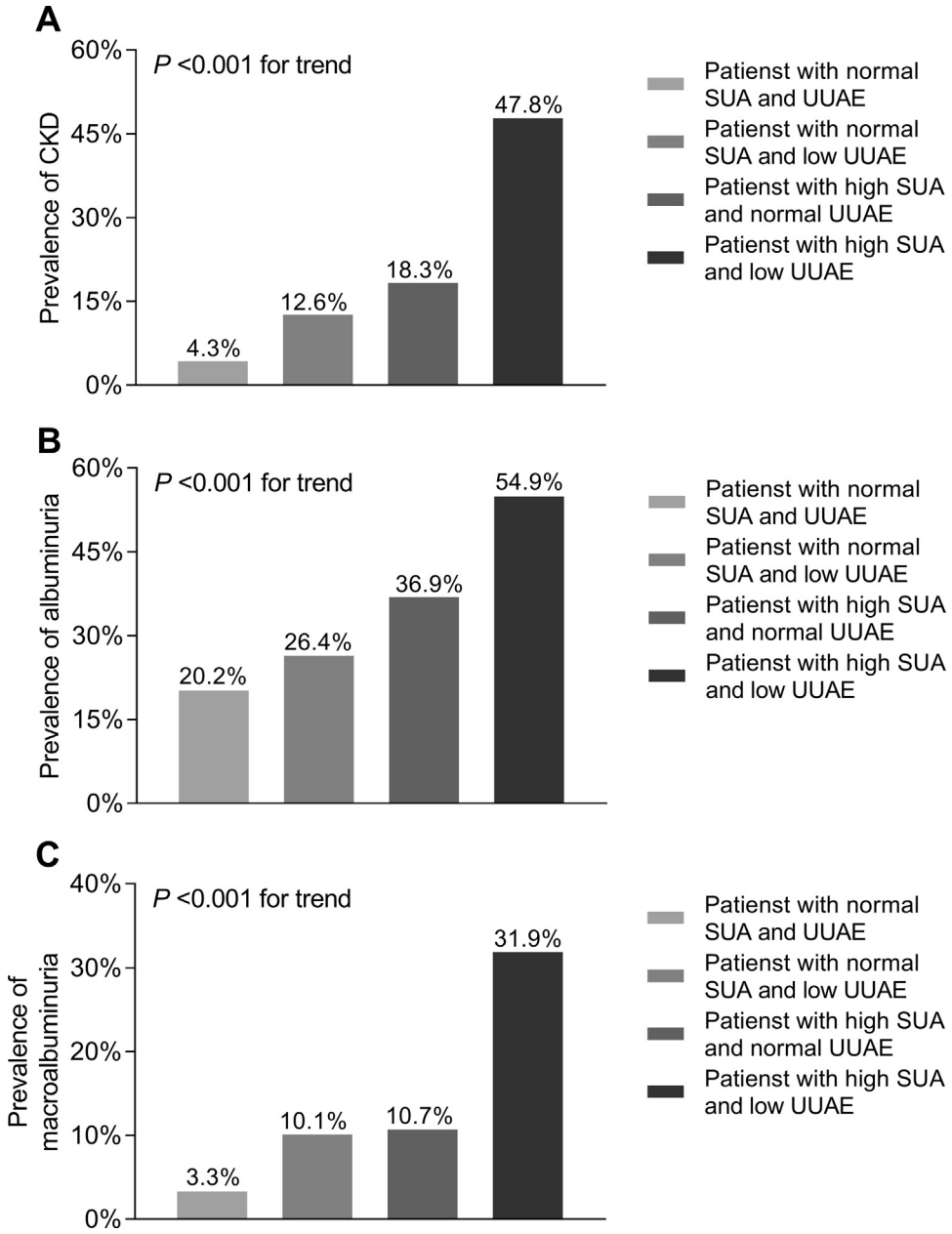

Fig. 1. Prevalences of chronic kidney disease (CKD), albuminuria and macroalbuminuria in four groups of patients: A. CKD after adjusting for age, gender and diabetes duration (DD; $P < 0.001$ for trend); B. Albuminuria after adjusting for age, gender and DD ($P < 0.001$); and C. macroalbuminuria after adjusting for age, gender and DD ($P < 0.001$). SUA: serum uric acid; UUAE: urinary uric acid excretion.

additional adjustments for SBP, DBP, WHR and BMI (model 2) and for ALT, TC, TTG, LDL-C, HDL-C, CRP, HbA_{1c}, FPG, 2-h PPG, FCP, 2-h PCP, HOMA2-IR and HOMA2-%S (model 3), the prevalence of CKD was still independently correlated with patients' groupings ($P < 0.001$ for models 2 and 3). In addition, compared with group 1, the odds ratio (OR) for CKD in group 2 was 2.346 [95% confidence interval (CI): 1.423–3.866], and 3.229 (95% CI: 2.036–5.121) in group 3. Intriguingly, the OR for CKD in group 4 significantly increased even further up to 13.391 (95% CI: 7.186–24.955).

Association of patients' groupings with eGFR and albuminuria

Table 3 presents the associations between our patients' groups and eGFR and albuminuria levels. After controlling for multiple confounding factors, eGFR levels in group 1 were clearly decreased compared with groups 2, 3 and 4 (all $P < 0.001$ for trend in models 1, 2 and 3). Also, after adjusting for age and other factors (model 1), urinary albumin levels in group 1 were significantly increased compared with groups 2, 3 and 4 ($P < 0.001$ for trend). After additional adjustments for other factors (models 2 and 3), albuminuria levels were still independently correlated with patients' groups in T2DM ($P < 0.001$ and $P = 0.013$ for models 2 and 3, respectively).

Discussion

Recently, studies have reported positive associations between hyper-uricaemia and both low UUAE levels and CKD [6,9,18,19]. Also, both high SUA and low UUAE levels have evidence to suggest they are potential predictors of CKD morbidity and mortality in various populations [9,20]. Yet, only a few investigations have

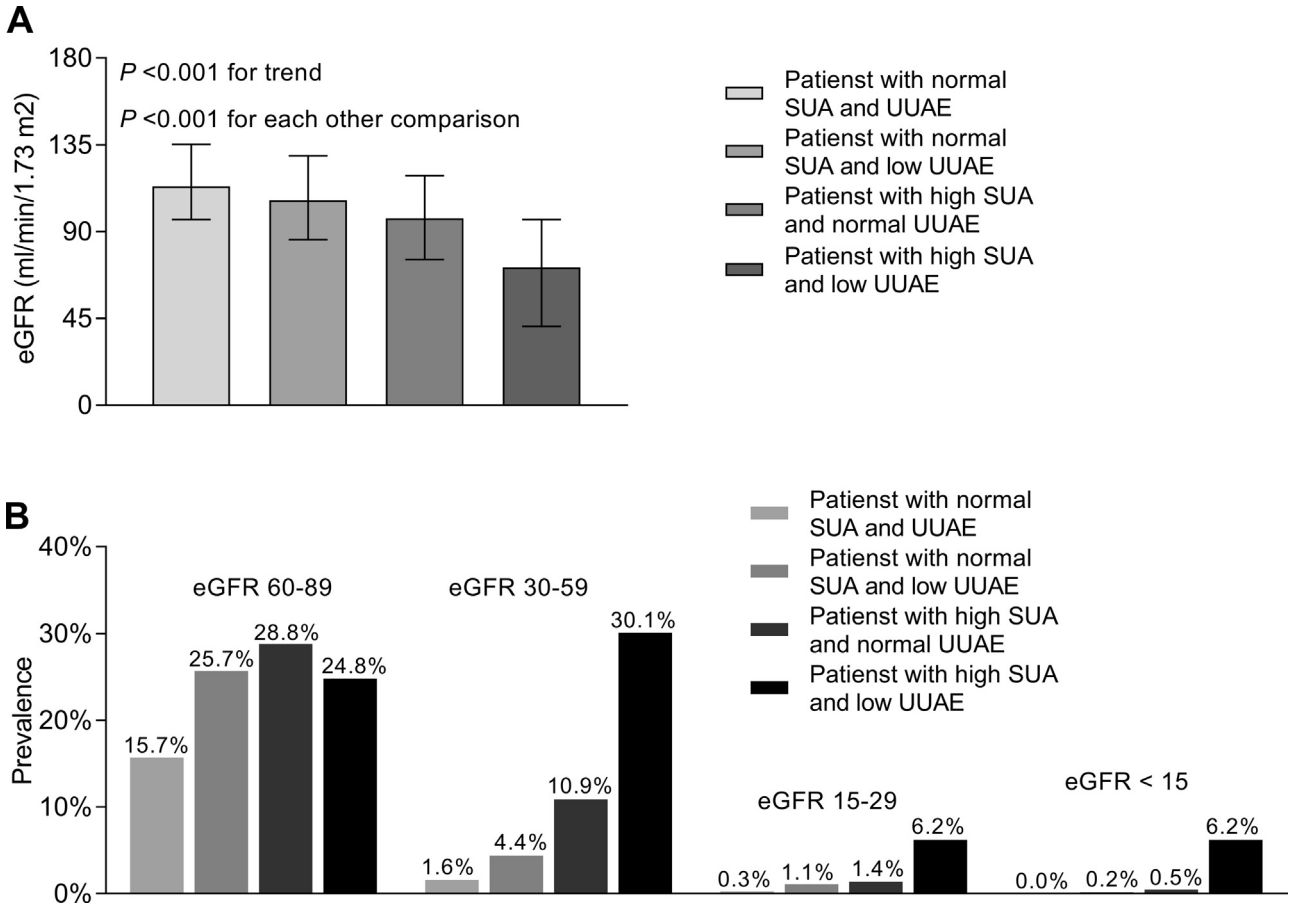

Fig. 2. Estimated glomerular filtration rates (eGFRs) in four groups of patients: A. After adjusting for age, gender and diabetes duration (DD; $P < 0.001$ for trends and for every other comparison); and B. Prevalences of different levels of eGFR after adjusting for age, gender and DD. SUA: serum uric acid; UUAE: urinary uric acid excretion.

Table 2
Association of patients' groupings with chronic kidney disease based on serum uric acid (SUA) and urinary uric acid excretion (UUAE) levels.

	Odds ratios (95% CI)				*P* for trend
	Patients with normal SUA and UUAE	Patients with normal SUA and low UUAE	Patients with high SUA and normal UUAE	Patients with high SUA and low UUAE	
Model 1	1	2.652 (1.803–3.9)	4.512 (3.147–6.468)	15.084 (9.312–24.434)	< 0.001
Model 2	1	2.674 (1.765–4.051)	4.772 (3.250–7.006)	16.143 (9.442–27.599)	< 0.001
Model 3	1	2.346 (1.423–3.866)	3.229 (2.036–5.121)	13.391 (7.186–24.955)	< 0.001

Model 1: adjusted for age, gender, diabetes duration, hypertension, smoking, alcohol drinking, and use of lipid-lowering drugs, antihypertensive agents, insulin or insulin analogues, anticoagulant agents.
Model 2: further adjusted for systolic and diastolic blood pressure, waist-to-hip ratio and body mass index.
Model 3: additionally adjusted for alanine aminotransferase, total cholesterol, total triglycerides, high-density and low-density lipoprotein cholesterol, C-reactive protein, HbA_{1c}, fasting plasma glucose, 2-h post-prandial plasma glucose, fasting C-peptide, 2-h post-prandial C-peptide, and updated homoeostasis model assessment of insulin sensitivity and insulin resistance.

focused on the relationship between the coexistence of high SUA and low UUAE levels and CKD in patients with T2DM. However, our present study has demonstrated that both hyper-uricaemia and low UUAE levels are closely related to the prevalence and severity of CKD in patients with T2DM, even after adjusting for other CKD risk factors. More importantly, the coexistence of high SUA and low UUAE levels could further increase the risk of CKD in patients with T2DM.

Consistent with our present observations, numerous other studies have also revealed positive relationships between raised SUA levels and prevalence of CKD [19,21–24]. For example, Zoppini and colleagues [19] noted that hyper-uricaemia was independently related to the development of incident CKD throughout a 5-year follow-up study. Furthermore, the positive relationship between uric acid and CKD was not only found in adults, but was also observed in children and adolescents. Indeed, a cohort study confirmed that uric acid was an independent risk factor for more rapid progression of CKD in the latter two populations [25].

In fact, many studies have reported that uric acid concentration is an independent risk factor for more rapid progression of CKD [20,25–27], and demonstrated that lowering SUA levels might slow CKD progression and prevent kidney failure [28,29]. One prospective randomized trial found decreased eGFR levels in the control group receiving standard therapy, whereas no change or only slight improvement in eGFR levels was observed in subjects taking allopurinol (100 mg daily) for 2 years [29]. On the other hand, a systematic review showed that therapy to lower uric acid made no difference in the incidence of end-stage kidney disease in the short

Table 3
Association of patients' groupings based on serum uric acid (SUA) and urinary uric acid excretion (UUAE) levels showing estimated glomerular filtration rates (eGFRs) and albuminuria levels.

	β (95% CI)				*P* for trend
	Patients with normal SUA and UUAE	Patients with normal SUA and low UUAE	Patients with high SUA and normal UUAE	Patients with high SUA and low UUAE	
eGFR					
Model 1	0 (Ref)	−1.84 (−5.26–1.57)	-19.01 (−22.47–15.55)	−33.05 (-39.29–-26.82)	< 0.001
Model 2	0 (Ref)	−1.41 (−4.97–2.15)	-18.95 (−22.57–15.34)	−32.93 (-39.54–-26.31)	< 0.001
Model 3	0 (Ref)	−0.76 (−4.61–3.10)	-15.18 (−19.08–11.27)	−29.73 (-36.7–-22.76)	< 0.001
Albuminuria					
Model 1	0 (Ref)	100.28 (38.06–162.50)	141.01 (77.96–204.05)	418.52 (304.97–532.06)	< 0.001
Model 2	0 (Ref)	105.31 (41.81–168.81)	163.73 (99.22–228.25)	452.14 (334.03–570.25)	< 0.001
Model 3	0 (Ref)	137.13 (69.76–204.50)	107.62 (39.32–175.93)	395.85 (274.00–517.69)	0.013

Model 1: adjusted for age, gender, diabetes duration, hypertension, smoking, alcohol drinking, and use of lipid-lowering drugs, antihypertensive agents, insulin or insulin analogues, anticoagulant agents.
Model 2: further adjusted for systolic and diastolic blood pressure, waist-to-hip ratio and body mass index.
Model 3: additionally adjusted for alanine aminotransferase, total cholesterol, total triglycerides, high-density and low-density lipoprotein cholesterol, C-reactive protein, HbA_{1c}, fasting plasma glucose, 2-h post-prandial plasma glucose, fasting C-peptide, 2-h post-prandial C-peptide, and updated homoeostasis model assessment of insulin sensitivity and insulin resistance.

term [30]. These conflicting results may be attributed to their small sample sizes, short investigation periods and different observation endpoints. However, our present study has found that hyper-uricaemia is closely associated with decreased eGFR and urinary albumin levels in T2DM patients even after controlling for other CKD risk factors. Similarly, in their 6-year follow-up study, Ficociello et al. [24] found that the risk of early GFR loss increased linearly across increased baseline uric acid concentrations. In addition, a study of Taiwanese patients with T2DM revealed that increased SUA levels were significantly correlated with severity of albuminuria [31], which is consistent with our present findings.

In general, uric acid homoeostasis rests on the balance between uric acid production and excretion, and kidneys reabsorb about 90% of filtered urate and excrete approximately 70% of total uric acid [32]. However, very few studies have focused on the association between UUAE and CKD [9]. Yet, our present study has found that low UUAE levels are closely associated with the presence of CKD. Similarly, our previous study found that the prevalence of CKD significantly decreased across UUAE quartiles in T2DM [11]. Moreover, in the present study, a reduced UUAE was closely related to eGFR and albuminuria levels in T2DM patients. Likewise, other studies have demonstrated that patients with either higher UAE rates or lower eGFRs tend to have lower UUAE levels, which suggests that low UUAE levels might be related to severity of CKD [11,33]. Consistent with previous studies, our present study has also demonstrated that a decreased UUAE is clearly associated with the presence of CKD and could be an independent risk factor for CKD in Chinese patients with T2DM. Compared with T2DM patients with normal UUAE levels, those with low UUAE levels are at higher CKD risk.

Moreover, our study not only found that hyper-uricaemia or low UUAE levels is significantly associated with decreased eGFR values, but also that patients with either high hyper-uricaemia or low UUAE levels had significantly higher levels of albuminuria and macro-albuminuria. Consistent with our findings, Tseng [34] reported that SUA independently correlates with urinary albumin-to-creatinine ratios in Taiwanese patients with T2DM. Interestingly, another study not only showed that SUA concentration was positively related to albuminuria, but also revealed that a reduced UUAE could lead to increased SUA in patients with albuminuria [33].

More importantly, compared with patients with either normal SUA and low UUAE levels or high SUA and normal UUAE levels, patients with hyper-uricaemia and low UUAE levels have a markedly greater prevalence of CKD. Therefore, the coexistence of hyper-uricaemia and low UUAE levels could further increase the risk of CKD in T2DM. However, unlike our study, most other studies have focused on the relationship between elevated SUA levels and CKD [5,20,25] or the association between decreased UUAE levels and CKD [9,11], whereas investigations into the links between the concomitant presence of hyper-uricaemia and low UUAE levels and CKD risk are extremely rare in various patient populations, including those with T2DM. Nevertheless, a previous study revealed that the prevalence of CKD was 29.5% in diabetes patients with high SUA levels [19], whereas our present study yielded a much greater prevalence of CKD than that, which might be partially explained by our examination of both SUA and UUAE levels and our more limited study population. It is worth noting that the detection of UUAE is non-invasive, and that the combination of both SUA and UUAE levels may help to identify T2DM patients at higher CKD risk.

Nevertheless, the mechanism behind the coexistence of hyper-uricaemia and low UUAE levels to further increase CKD risk has yet to be uncovered. As the end product of the metabolism of purine compounds, renal excretion of uric acid is regulated by genes and the environment [35,36], and elevated levels can result from excessive urate production or decreased UUAE, or both. Several studies have reported that uric acid could contribute to CKD through several mechanisms, including endothelial dysfunction and inflammation [37–39]. Also, SUA might lead to a reduction of nitric oxide bioavailability, activation of oxidative stress and the renin–angiotensin system, and endothelial dysfunction. In rat models, hyper-uricaemia has resulted in systemic and glomerular hypertension, with the resultant kidney hypoperfusion and fibrosis [40]. It is important to note that a reduced UUAE could indicate local accumulation of uric acid in the kidney, where it can then exert direct effects on renal tubules, rather than its entering the blood circulation. When kidney disease is present, decreased glomerular filtration may cause an increase in SUA levels, thereby providing an additional risk for progressive decline of kidney function. Moreover, a decreased UUAE could induce kidney dysfunction, thereby further aggravating the diminishing UUAE. Thus, these findings indicate that uric acid may play a role in the pathogenesis of CKD.

Our present study has several potential limitations. First of all, as it was conducted in hospitalized patients with T2DM, it is uncertain whether similar conclusions could be drawn in other populations. In addition, the single-centre cross-sectional nature of our data may have unavoidably brought about some hidden, unmeasured biases, and can also not identify any causal

relationships between increased SUA, decreased UUAE and CKD. Thus, prospective studies are now needed to verify our present findings.

Nevertheless, to the best of our knowledge, this study is the first to systematically investigate the association between concomitant high SUA and low UUAE levels and CKD with a large sample in Chinese patients with T2DM.

In summary, both hyper-uricaemia and low UUAE levels were found to be closely associated with an increased CKD risk in Chinese inpatients with T2DM. In addition, the concomitant presence of high SUA and low UUAE levels might further increase the risk of CKD in patients with T2DM, which suggests that the combination of SUA and UUAE measurements may improve the identification of T2DM patients at high CKD risk and lead to early interventions, which should prove useful for reducing future prevalences and progression of CKD in T2DM patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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