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RESEARCH ARTICLE

Uric acid, renal function and risk of hypoglycaemia in Chinese type 2 diabetes patients

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Abstract

Background This study aimed to explore independent associations between serum uric acid and hypoglycaemia, and whether mildly increased serum uric acid exacerbated the association between mild decline in estimated glomerular filtration rate (eGFR) and hypoglycaemia.

Methods A cross-sectional survey of 6713 inpatients with type 2 diabetes and eGFR ≥60 mL/min/1.73 m^2 and admitted to 81 tertiary care hospitals in China was conducted. Self-reported asymptotic hypoglycaemia with plasma glucose ≤3.9 mmol/L, hypoglycaemia episodes with symptoms in 1 month or hypoglycaemia that needed assistance from other people in 3 months before hospitalization was used to define hypoglycaemia. Binary logistic regression was used to estimate odds ratios of serum uric acid for hypoglycaemia. Three measures, that is, relative excess risk due to interaction (RERI), attributable proportion due to interaction and synergy index (S) were used to estimate the effect of mildly decreased eGFR on the association of serum uric acid with hypoglycaemia.

Results Serum uric acid was associated with hypoglycaemia in an ordinal manner (P for trend <0.01) with an odds ratio of top quartile *versus* the lowest quartile up to 3.03 (95% confidence interval: 2.13–4.32). The odds ratio of serum uric acid levels ≥ *versus* <283 μmol/L (i.e. the median) was 1.98 (95% confidence interval:1.58–2.48). Serum uric acid levels ≥ *versus* <283 μmol/L greatly enhanced the association between mild decline in eGFR (eGFR < 90 mL/min/1.73 m^2) and hypoglycaemia from 0.94 (0.36–2.43) to 3.90 (2.55–5.95), with a significant additive interaction ($P < 0.05$ for RERI, AP and S).

Conclusions Mildly increased serum uric acid was associated with increased risk of hypoglycaemia and enhanced the association between mildly decreased eGFR and hypoglycaemia in type 2 diabetes.
Keywords serum uric acid; estimated glomerular filtration rate; type 2 diabetes; hypoglycaemia; Chinese

Introduction

Uric acid formed in the liver is a metabolic end product of purine metabolism in humans and possesses both antioxidant and pro-oxidant properties [1]. This dual role was described as the 'uric acid paradox', that is, playing an antioxidant role or a pro-oxidant role contingent upon micro-environment and interactions with other factors as well as upon the level of serum uric acid

(SUA) itself [2]. An elevated concentration of SUA can result from the excessive intake of purine-rich diet or alcohol, decreased renal and intestinal excretion or increased reabsorption in the kidney tubule [1,3].

Renal disorders used to be considered as an important consequence of hyperuricemia [4], and even high-normal SUA is also associated with the increased risk of development of chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM) [5]. A recent study reported a graded increase in the risk of renal dysfunction by increasing SUA levels in patients with T2DM [6]. In addition to CKD, some studies reported that elevated levels of SUA were associated with hypertension, coronary heart disease and stroke in addition to metabolic abnormalities [7,8]. The association between the elevated levels of SUA and the severity of metabolic syndrome was in a dose–response manner [8]. In connection with T2DM, SUA was reported to increase insulin resistance, fasting plasma glucose, postprandial 2-h plasma glucose, glycated haemoglobin (HbA_{1c}) and also to increase risks of diabetes complications including micro-vascular and macro-vascular complications [7,9].

Hypoglycaemia was considered as one of the most common acute complications of type 2 diabetes and a main limiting factor for the optimal glucose control. Moderate hypoglycaemia may lead to a series of neurologic symptoms [10] while severe hypoglycaemia was associated with increased risk of cardiovascular and cerebrovascular emergencies possibly because of a surge of adrenergic activity [11]. In a meta-analysis of population-based studies in 532 542 people with type 2 diabetes on oral antidiabetes drugs (OADs) and insulin, the prevalence of moderate and severe hypoglycaemia was up to 45% and 6%, respectively, and the annualized incidences of moderate and severe hypoglycaemic episodes were, respectively, 19 and 0.80 per person-year [12]. Episodes of hypoglycaemia affected many aspects of life of patients (e.g. social interactions, employment, driving, sleep, leisure activities etc).

Chronic kidney disease was an established risk factor for hypoglycaemia. One study from the Hong Kong Diabetes Registry found that CKD was associated with hypoglycaemia in patient with type 2 diabetes [13], and another retrospective cohort study also demonstrated that CKD was associated with increased risks of hypoglycaemia among subjects with or without diabetes [14]. It is noticed that mildly decreased glomerular filtration rate (eGFR), that is, eGFR < 90 mL/min/1.73 m^2 but ≥ 60 mL/min/1.73 m^2, is common, occurring almost in half of patients with T2DM [15] and was reported to be associated with metabolic disorders and morbidities [16]. Given to the higher prevalence of mildly decreased eGFR and its close links with high SUA and hypoglycaemia, it is worthwhile to investigate whether increased SUA, especially mildly increased SUA, and mildly decreased eGFR had an interactive effect to increase the risk of hypoglycaemia in the patients with T2DM.

The current study used the data from a large cross-sectional survey of Chinese inpatients with type 2 diabetes from 81 top tertiary care hospitals in China to explore associations of SUA with hypoglycaemia episodes and to test whether mildly increased SUA enhanced the association between mildly decreased eGFR and hypoglycaemia in patients with type 2 diabetes.

Methods

Participants

Chinese Hospital Association conducted a survey of inpatients with type 2 diabetes who were admitted to top tertiary hospitals (3A hospitals) in China from May 2013 to August 2013. The study method was described in details previously [17]. Briefly, a total of 81 top tertiary hospitals from 27 cities in 21 provinces in China were invited and agreed to participate in the survey. The inclusion criteria of the patients were (1) with type 2 diabetes and admitted to the department of endocrinology, (2) aged between 18 to 80 years and (3) agreed to use a basal bolus plus meal time insulin insensitive management scheme after admission to hospital. The exclusion criteria were (1) with liver dysfunction defined as alanine aminotransferase or aspartate aminotransferase ≥ 2.5 folds of the upper limits of the normal range, 0–40 U/L, (2) with renal dysfunction defined as serum creatinine ≥ 110 μmol/L in women and ≥ 125 μmol/L in men or CKD, (3) during pregnancy or lactation and (4) unable to communicate in a normal way.

A total of 6713 inpatients with type 2 diabetes were consecutively recruited from the department of endocrinology of the 81 top tertiary hospitals during the survey period. Written informed consent was obtained before the data collection and analysis, and the survey was conducted in accord with the Declaration of Helsinki Principles. The study was approved by the ethics committee of the People's General Army (PLA) Hospital Clinical Research Ethics Committee.

Data collection and clinical measurements

The postgraduate medical students and research nurses were chosen as the fieldworkers, who retrieved and recorded the demographic information, the results of

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clinical measurements and laboratory essays by reviewing case notes of the inpatients. The measured parameters included body height, body weight, sitting blood pressure, self-monitoring of blood glucose, HbA_{1c}, SUA, and liver and renal functions. The fasting blood was collected to measure HbA_{1c} and SUA. The first morning urine was used to measure the albuminuria, and then urinary albumin to creatinine ratio was calculated. The abbreviated Modification of Diet in Renal Disease Study formula recalibrated for Chinese was used to eGFR by the following equation: estimated GFR = $186 \times [SCR \times 0.011]^{-1.154} \times [age]^{-0.203} \times [0.742$ if woman$] \times 1.233$, where SCR is serum creatinine expressed as μmol/L (original mg/dL converted to μmol/L) and 1.233 is the adjusting coefficient for Chinese [18].

Drug usage was documented in details, including antihypertensive drugs (renin angiotensin system inhibitors, calcium antagonists and β-receptor antagonists), lipid lowering drugs (statins and other lipid lowing drugs) and antidiabetes drugs (OADs, glucagon-like peptide-1 based drugs and insulin and combinations of these drugs). Diabetes complications including micro-vascular and macro-vascular complications, sensory neuropathy, diabetes foot and hypertension were also documented in details.

Definition of hypoglycaemia

As in the previous study [17], asymptomatic hypoglycaemia was defined as plasma glucose $\leq$3.9 mmol/L but without any symptoms in 1 month before hospitalization. Mild hypoglycaemia was defined as having one or more episodes of hypoglycaemia with symptom in 1 month prior to the hospitalization. Severe hypoglycaemia was defined as having one or more episodes of hypoglycaemia that needed assistance from other people in 3 months before hospitalization. In this analysis, hypoglycaemia was defined as having asymptomatic hypoglycaemia, mild hypoglycaemia or severe hypoglycaemia.

Statistical analysis

The Statistical Analysis System (SAS, version 9.2; SAS Institute Inc., Cary, NC, USA) was used to analyse the data. All categorical variables were expressed as numbers and percentages. Continuous variables were expressed as medians and interquartile ranges. Q–Q plots were used to check the normality of distribution of continuous variable. Categorical variables between patients with hypoglycaemia and without hypoglycaemia were compared using chi-square test or Fisher's exact test where appropriate. Student *t*-test was used to compare continuous variables between two groups if the variables followed normal distribution. Otherwise, two-sample Wilcoxon rank test was used. Binary logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs) of SUA for hypoglycaemia. SUA was stratified into four groups by quartiles in logistic models. The cut-off points of 25th, 50th and 75th percentiles of SUA were 223 μmol/L, 283 μmol/L and 340 μmol/L, respectively. As there was no clear threshold effects detected, SUA was further stratified into high and low SUA at its median to test possible additive interaction with mildly decreased eGFR for hypoglycaemia (normal eGFR: $\geq$90 mL/min per 1.73 m^2; mildly decreased eGFR: $\geq$60–$<$90 mL/min per 1.73 m^2). Both univariable and multivariable analyses were performed with adjusting for demographic and clinical factors, complications of diabetes, antidiabetes treatment and use of lipid lowing drugs and antihypertensive drugs in the multivariable analysis.

As the level of SUA and morbidities were different between man and woman [19], we further did a subgroup analysis to test the consistence of the association between SUA and hypoglycaemia. Additive interaction was used to test synergistic effects. Three measures of additive interaction, that is, relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy interaction (S) were used to estimate additive interaction between mildly decreased eGFR and SUA on hypoglycaemia. RERI refers to the excess risk due to interaction relative to the risk without exposure; AP is the attributable proportion of disease due to interaction in persons with both exposures; and S is the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without interaction. RERI and AP are more robust than S in some conditions [20,21], and S uses a different method to estimate its confidence interval from RERI and AP [22]. As before [23,24], we defined significant additive interaction as any of the three measures being significant in this analysis, that is, RERI >0, AP >0 or S >1. In this analysis, *P* values less than 0.05 from two-tailed tests were considered to be statistically significant unless specified.

Results

Characteristics of the study patients

Among 6713 patients with type 2 diabetes, 409 reported to have hypoglycaemia (asymptomatic

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hypoglycaemia only: 25, mild hypoglycaemia only: 296, severe hypoglycaemia only: 4 and overlaps of any two or three: 84). Mean age of the patients in the survey was 56.38 (standard deviation: 10.55) years, and median duration of diabetes was 3.00 (interquartile range: 0.41 to 6.05) years. Male patients accounted for 56.56%. Patients in the group with SUA ≥ 283 μmol/L were more likely to have a longer duration of diabetes, higher HbA_{1c}, SBP and DBP, lower eGFR and urinary albumin to creatinine ratio and less frequent uses of self-monitoring of blood glucose than the patients in the other group with SUA < 283 μmol/L. The group with SUA at high level was more likely to have coronary heart disease and less likely to have hypertension as compared with patients with a low level of SUA. The patients at levels of high SUA were also more likely to use hypoglycemic drugs including OADs, glucagon-like peptide-1 based drugs and insulin and renin-angiotensin system inhibitors (Table 1).

Independent associations of SUA and mildly decreased eGFR with hypoglycaemia

Elevated SUA was associated with increased risk of hypoglycaemia (*P* for trend <0.0001). Patients with SUA in the highest quartile were at greatly increased risk of hypoglycaemia in univariable analysis (OR: 2.71, 95%CI: 1.95–3.75) and multivariable analysis (OR: 3.03, 95%CI: 2.13–4.32) as compared with those with SUA in the lowest quartile. As no clear SUA cut-off points detected, its median value (283 μmol/L) was used to stratify SUA into the high and low SUA group. High SUA was associated with 1.98 (95%CI: 1.58–2.48) fold-risk of hypoglycaemia compared with low SUA in multivariable analyses (Table 2).

Patients with mildly decreased eGFR had increased risk of hypoglycaemia in univariable analysis (1.46, 95%CI: 1.04–2.06) and in multivariable analysis (in multivariable

Table 1. Demographic, clinical and biochemical characteristics of subjects by median of SUA

	SUA < 283 μmol/L (*n* = 3352)	SUA ≥ 283 μmol/L (*n* = 3361)	
Variable	Median (25th to 75th) or n(%)	Median (25th to 75th) or n(%)	*P* value
Age, years	57(50–64)	56(50–64)	0.3131*
Male gender	1845(55.04)	1952(58.08)	0.0121*
Duration of diabetes, years	2.01(0.28–5.85)	3.64(0.99–6.75)	<.0001*
Body mass index, kg/m^2	23.80(21.92–25.59)	23.87(21.70–25.78)	0.6354*
HbA_{1c}, %	9.90(9.50–11.50)	10.50(10.00–11.00)	<.0001**
Systolic blood pressure, mmHg	125(121–133)	132(129–137)	<.0001*
Diastolic blood pressure, mmHg	76(73–80)	84(80–87)	<.0001*
SUA, μmol/L	223(192–251)	340(311–383)	<.0001**
eGFR, mL/min per 1.73 m^2	157.76(120.68–174.66)	134.52(114.84–159.32)	<.0001**
eGFR < 90 mL/min per 1.73 m^2	189(5.64)	285(8.48)	<.0001*
ACR, mg/mmol	0.18(0.16–0.19)	0.15(0.15–0.19)	<.0001**
SMBG, yes	1229(36.66)	886(26.36)	<.0001*
Complications			
Prior coronary heart disease	129(3.85)	228(6.78)	<.0001*
Prior stroke	53(1.58)	53(1.58)	0.9889*
Peripheral arterial disease	99(2.95)	117(3.48)	0.2206*
Sensory neuropathy	231(6.89)	199(5.92)	0.1044*
Diabetic nephropathy	100(2.98)	120(3.57)	0.1767*
Diabetic retinopathy	131(3.91)	150(4.46)	0.2564*
Diabetic foot	32(0.95)	34(1.01)	0.8131*
Hypertension[a]	228(6.80)	198(5.89)	0.0317*
Drug abuse			
Statins	176(5.25)	168(5.00)	0.6395*
Other lipid lowering drugs	33(0.98)	31(0.92)	0.7933*
Renin-angiotensin system inhibitors	174(5.19)	224(6.66)	0.0106*
Other antihypertensive drugs	98(2.92)	107(3.18)	0.5360*
OADs only	1124(33.53)	1517(45.14)	<.0001*
GLP-1 based drugs alone or combined with OADs	8(0.24)	19(0.57)	0.0345*
Insulin alone or combined with OADs	1251(37.32)	1035(30.79)	<.0001*

Abbreviations: SUA, serum uric acid; HbA_{1c}, glycated haemoglobin; eGFR, estimated glomerular filtration rate; ACR, urinary albumin to creatinine ratio; SMBG, self monitoring of blood glucose; OADs, oral antidiabetes drugs; GLP, glucagon-like peptide.
[a]Hypertension was defined as SBP/DBP ≥140/80 mmHg.
**P* values were derived from chi-square test or *t*-test.
***P* values were derived from Wilcoxon rank test.

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Table 2. Odds ratios of SUA and mildly decreased eGFR for hypoglycaemia

	N (%)	OR (95%CI)	*P* value
Univariable models[a]			
SUA in category by percentile			<0.0001*
<25th	51(12.47)	1	
25th–50th	95(23.23)	1.78(1.26–2.52)	0.0012
50th–75th	118(28.85)	2.49(1.78–3.49)	0.0008
≥75th	145(35.45)	2.71(1.95–3.75)	<0.0001
SUA in category by median			
<283 μmol/L	146(35.70)	1	
≥283 μmol/L	263(64.30)	1.86(1.51–2.29)	<0.0001
eGFR in category			
≥90 mL/min per 1.73 m^2	369(90.22)		
<90 mL/min per 1.73 m^2	40(9.78)	1.46(1.04–2.06)	0.0276
Multivariable model 1[b]			
SUA in category by percentile			<0.0001*
<25th	51(12.47)	1	
25th–50th	95(23.23)	1.66(1.16–2.38)	<0.0001
50th–75th	118(28.85)	2.44(1.72–3.47)	0.0032
≥75th	145(35.45)	3.03(2.13–4.32)	<0.0001
eGFR in category			
≥90 mL/min per 1.73 m^2	369(90.22)	1	
<90 mL/min per 1.73 m^2	40(9.78)	1.49(1.02–2.21)	0.0404
Multivariable Model 2[b]			
SUA in category by median			
<283 μmol/L	146(35.70)	1	
≥283 μmol/L	263(64.30)	1.98(1.58–2.48)	<0.0001
eGFR in category			
≥90 mL/min per 1.73 m^2	369(90.22)	1	
<90 mL/min per 1.73 m^2	40(9.78)	1.59(1.09–2.33)	0.0172

Abbreviations: SUA, serum uric acid; eGFR, estimated glomerular filtration rate; *N* (%), number of cases (% of number at risk); OR, odds ratios; CI, confidence interval.
[a]Univariable models, not adjusted for any other variables.
[b]Multivariable model, age, gender, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, glycated haemoglobin, self-monitoring, log-transformed urinary albumin to creatinine ratio, and drug use and complications listed in Table 1, was adjusted in multivariable analysis.
**P* for trend.

model 1: 1.49, 95%CI: 1.02–2.21; and in multivariable model 2: 1.59, 95%CI: 1.09–2.33) (Table 2).

Additive interaction between mildly increased SUA and mildly decreased eGFR for hypoglycaemia

Mildly increased SUA (i.e. ≥its median) was associated with higher ORs for hypoglycaemia than those with low SUA in the univariable model (OR: 5.15, 95%CI: 1.98–13.40) and in multivariable model (OR: 3.31, 95% CI: 1.16–9.46) in patients with eGFR at ≥60–<90 mL/min per 1.73 m^2. To a lesser extent, mildly increased SUA was also associated with increased risk for hypoglycaemia in both univariable (OR: 1.71, 95%CI: 1.38–2.13) and multivariable analyses (OR: 2.08, 95%CI: 1.63–2.64) in patients with GFR ≥ 90 mL/min per 1.73 m^2 (Table 3).

On the other hand, mildly decreased eGFR was not associated with hypoglycaemia in both univariable analysis (OR: 0.58, 95%CI: 0.23–1.43) and multivariable analysis (OR: 0.93, 95%CI: 0.34–2.52) among patients with low SUA, that is, less than 283 μmol/L. Conversely, among patients with high SUA, mildly decreased eGFR was significantly associated with increased risk for hypoglycaemia in both univariable analysis (OR: 1.74, 95%CI: 1.19–2.55) and multivariable analysis (OR: 1.99, 95%CI: 1.28–3.09) (Table 3).

Mildly increased SUA greatly increased the OR of mildly decreased eGFR for hypoglycaemia from 0.58 (95%CI: 0.23–1.43) to 3.00 (95%CI: 2.02–5.01) with significant additive interaction in univariable analysis (RERI: 1.70, 95%CI: 0.49–2.91; AP: 0.56, 95%CI: 0.31–0.81; S: 6.70, 95%CI: 0.71–62.53). After adjusting for confounders, mildly increased SUA still greatly increased the risk of mildly decreased eGFR for hypoglycaemia, that is, from 0.94 (95%CI: 0.36–2.43) to 3.90 (95%CI: 2.55–5.95), with significant additive interaction (RERI: 2.11, 95%CI: 0.42–3.81; AP: 0.54, 95%CI: 0.25–0.82; S: 3.71, 95%CI: 1.01–13.69) (Tables 3 and 4).

In addition, subgroup analysis showed that the effect size of SUA for hypoglycaemia was similar in male and female patients in univariable analysis (male: 1.76, 95% CI: 1.33–2.34; female: 2.00, 95%CI: 1.47–2.72) and in

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Table 3. Subgroup analyses of synergistic effects of SUA with mildly decreased eGFR on hypoglycaemia

Exposures	*N* (%)	OR (95% CI)	*P* value
Independent models			
Among patients with eGFR ≥ 90 mL/min per 1.73 m^2			
Model 1[a]: SUA≥ vs. <283 μmol/L	228(61.79):141(38.21)	1.71(1.38, 2.13)	<0.0001
Model 2[b]: SUA≥ vs. <283 μmol/L	228(61.79):141(38.21)	2.08(1. 63, 2.64)	<0.0001
Among patients with eGFR < 90 mL/min per 1.73 m^2			
Model 1[a]: SUA≥ vs. <283 μmol/L	35(87.50):5(12.50)	5.15(1.98, 13.40)	0.0008
Model 2[b]: SUA≥ vs. <283 μmol/L	35(87.50):5(12.50)	3.31(1.16, 9.46)	0.0252
Among patients with SUA < 283 μmol/L			
Model 1[a]: eGFR< vs. ≥90 mL/min per 1.73 m^2	5(3.42): 141(96.58)	0.58(0.23, 1.43)	0.2413
Model 2[b]: eGFR< vs. ≥90 mL/min per 1.73 m^2	5(3.42): 141(96.58)	0.93(0.34, 2.52)	0.8893
Among patients with SUA ≥ 283 μmol/L			
Model 1[a]: eGFR< vs. ≥90 mL/min per 1.73 m^2	35(13.13):228(86.69)	1.74(1.19, 2.55)	0.0038
Model 2[b]: eGFR< vs. ≥90 mL/min per 1.73 m^2	35(13.13):228(86.69)	1.99(1.28,3.09)	0.0021
Additive interactive effect models			
Model 1[a]			
SUA < 283 μmol/L & eGFR ≥ 90 mL/min per 1.73 m^2	141(34.47)	1	
SUA ≥ 283 μmol/L & eGFR ≥ 90 mL/min per 1.73 m^2	228(55.75)	1.71(1.38–2.13)	<0.0481
SUA < 283 μmol/L & eGFR < 90 mL/min per 1.73 m^2	5(1.22)	0.58(0.23–1.43)	0.2460
SUA ≥ 283 μmol/L & eGFR < 90 mL/min per 1.73 m^2	35(8.56)	3.00(2.02–4.44)	<0.0001
Model 2[b]			
SUA < 283 μmol/L & eGFR ≥ 90 mL/min per 1.73 m^2	141(34.47)	1	
SUA ≥ 283 μmol/L & eGFR ≥ 90 mL/min per 1.73 m^2	228(55.75)	1.83(1.45–2.31)	<0.0001
SUA < 283 μmol/L & eGFR < 90 mL/min per 1.73 m^2	5(1.22)	0.94(0.36–2.43)	0.1341
SUA ≥ 283 μmol/L & eGFR < 90 mL/min per 1.73 m^2	35(8.56)	3.90(2.55–5.95)	<0.0001

Abbreviations: SUA, serum uric acid; eGFR, estimated glomerular filtration rate; *N* (%), number of cases (% of number at risk); OR, odds ratios; CI, confidence interval.
[a]Model 1, not adjusted for any other variables.
[b]Model 2, age, gender, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, glycated haemoglobin, self-monitoring, log-transformed urinary albumin to creatinine ratio, and drug use and complications listed in Table 1, was adjusted in multivariable analysis.

Table 4. The interaction between SUA and mildly decreased eGFR for the risk of hypoglycaemia

Measures of interaction	Estimated value	95%CI	*P* value
Model 1[a]			
RERI	1.70	0.49–2.91	0.0059
AP	0.56	0.31–0.81	0.0000
S	6.70	0.71–62.53	0.8140
Model 2[b]			
RERI	2.11	0.42–3.81	0.0150
AP	0.54	0.25–0.82	0.0002
S	3.71	1.01–13.69	0.0488

Abbreviations: SUA, serum uric acid; eGFR, estimated glomerular filtration rate; CI, confidence interval; RERI, relative excess risk of interaction; AP, attributable proportion; S, synergy index; Any of significant RERI, AP or S signifies a significant additive interaction.
[a]Model 1, not adjusted for any other variables.
[b]Model 2, age, gender, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, glycated haemoglobin, self-monitoring, log-transformed urinary albumin to creatinine ratio, and drug use and complications listed in Table 1, was adjusted in multivariable analysis.

multivariable analysis (male: 1.91, 95%CI: 1.41–2.60; female: 2.05, 95%CI: 1.47–2.58). The additive interaction between SUA and gender for hypoglycaemia was also non-significant (data not showed).

Discussion

In Chinese inpatients with type 2 diabetes, we found that both mildly decreased eGFR and mildly increased SUA were associated with increased risk of hypoglycaemia, and co-presence of mildly increased SUA and mildly decreased eGFR had an additive interactive effect towards increasing the risk of hypoglycaemia in Chinese patients with type 2 diabetes. These findings were robust after adjusting for multiple traditional risk factors for hypoglycaemia.

Previous epidemiological or experimental studies reported that SUA was positively correlated with disorders of lipid metabolism, hemodynamic abnormalities [25], cardiovascular disease [26], pre-diabetes (i.e. impaired fasting glucose, mildly elevated HbA_{1c}, hyperinsulinemia and insulin resistance) [9,27] and diabetes [4,19]. Some studies demonstrated that there were gender differences on the association between SUA and pre-diabetes and diabetes, but their findings were inconsistent [19,27]. A Chinese study in Taiwan ($n = 7483$) revealed that elevated SUA levels were associated with hyperinsulinemia and homeostasis model assessment-insulin resistance index, and the association was stronger in women than in men [27]. In addition, a

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study in Indian and Creole populations presented that elevated SUA was an independent risk marker for future diabetes in Mauritian men, whereas the association was weak in women [19]. Consistently, our study further found that high SUA was independently associated with increased risk of hypoglycaemia. However, although our data showed that SUA levels differed by gender, the subgroup analysis showed that the association between SUA and hypoglycaemia was similar in man and woman, without a detectable additive interaction between SUA and gender for hypoglycaemia.

Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2) was relatively rare in the general population, for example, 2.45% as reported in a community-based cross-sectional survey [28]. However, CKD among patients with type 2 diabetes was quite common, for example, 16% in Hong Kong Chinese patients with type 2 diabetes [29] and mildly reduced eGFR even affected up to 30–50% of patients with type 2 diabetes [15,29]. In the general populations, mildly reduced eGFR was associated with metabolic abnormalities, cardiovascular disorders and even mortality [16,30,31]. In patients with type 2 diabetes, mildly reduced eGFR increased the risk of micro-vascular and macro-vascular complications [29]. In connection with hypoglycaemia, a study form Taipei reported that per 1 mL/min/1.73 m^2 increase in eGFR was associated with a 3% decrease in the risk of severe hypoglycaemia in patients with type 2 diabetes [32]. Our study further found that mildly decreased eGFR was not only associated with increased risk of hypoglycaemia but also to exaggerate the association of SUA with hypoglycaemia.

Although the biological mechanisms underlying interplays among hyperuricemia, CKD and hypoglycaemia have been investigated [2,33–35], the associations of mildly increased SUA and mildly reduced renal function with hypoglycaemia and their interplays are poorly understood. In this regard, hypoglycaemia was able to increase ATP breakdown, and therefore uric acid production [36] and mildly decreased eGFR were associated with metabolic disorders [16]. Therefore, it is plausible that some metabolic disorders due to mildly decreased eGFR may be responsible for the increased risk of hypoglycaemia while mildly increased SUA may be one of the manifestations of these underlying metabolic disturbances. Indeed, this is an area that deserves further investigations including the molecular links.

Our study has important clinical implications. Good glycemic control plays a pivotal role in management of type 2 diabetes while hypoglycaemia is one of the major factors that hinder achievement of good glycemic control. Our findings suggest that elevated SUA and mildly decreased eGFR may be useful indictors for an increased risk of hypoglycaemia. In practice, SUA and renal function are routinely measured in many parts of the world as their usefulness in management of patients with T2DM. If our findings can be confirmed by cohort studies, especially in low-risk patients with type 2 diabetes, high SUA may be a useful marker to alert clinicians the high risk of hypoglycaemia, especially when co-presence with mildly decreased eGFR.

Our study has several limitations. First, our study was a cross-sectional study and cannot establish causality between SUA and hypoglycaemia. Further prospective studies are needed to confirm our findings. Second, the present study was a hospital-based study of inpatients admitted for intensive insulin management and thus cannot be extrapolated to general populations with type 2 diabetes, especially low-risk patients with type 2 diabetes. Third, not all patients had their blood glucose measured, and some patients with asymptomatic hypoglycaemia may have been missed. Fourth, lifestyle and socio-economic status such as smoking, alcohol drinking habits, income, education attainment and so on were not collected in our survey and could not be adjusted in the analysis. Fifth, patients with abnormal liver function were excluded in present study. We do not ascertain whether these associations were also established among patients with these conditions. Sixth, patients with clinical renal impairment, that is, eGFR < 60 mL/min per 1.73 m^2, were not invited to participate, and this analysis cannot examine the full association between renal dysfunction and hypoglycaemia.

In conclusion, we found that both mildly increased SUA and mildly decreased eGFR increased the risk of hypoglycaemia, and these two risk factors had an additive interactive effect towards increasing the risk of hypoglycaemia in Chinese patients with type 2 diabetes. Given to the importance of prevention of hypoglycaemia in the management of type 2 diabetes, further follow-up studies are warranted to confirm our findings, especially among low-risk patients with type 2 diabetes, and mechanistic investigations are also needed to understand these observational findings.

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Conflicts of interest

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