Correlation between serum C-peptide-releasing effects and the risk of elevated uric acid in type 2 diabetes mellitus

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Abstract. Our study aimed to investigate the C-peptide-releasing effect associated with the risk of elevated serum uric acid (SUA) levels in patients with type 2 diabetes mellitus (T2DM). In the cross-sectional study, 345 patients with T2DM hospitalized at the First Affiliated Hospital of Harbin Medical University were consecutively enrolled, and their baseline data were collected. The study design used two parameters for C-peptide releasing effects: the multiplication effect of 1 h postprandial C-peptide to fasting C-peptide ratio (1hCp/FCp) and 2hCp/FCp; the incremental effect of 1hCp minus FCp (1hΔCp) and 2hΔCp. The patients with T2DM in the upper quartiles of SUA had higher FCp, 1hCp, 1hΔCp, 2hCp, and 2hΔCp. Multiple linear regression analysis revealed that after adjusting all the confounding factors, the serum C-peptide including 1hCp ($\beta = 5.14$, $p = 0.036$), 1hΔCp ($\beta = 7.80$, $p = 0.010$), 2hCp ($\beta = 4.27$, $p = 0.009$) and 2hΔCp ($\beta = 5.20$, $p = 0.005$) were still positively correlated with SUA levels in patients with T2DM. In female patients, only the 2hCp ($\beta = 4.78$, $p = 0.017$) and 2hΔCp ($\beta = 5.28$, $p = 0.019$) were associated with SUA level; however, in male patients, no C-peptide parameter was associated with SUA levels in T2DM (all $p > 0.05$). Within a certain range, the elevated SUA levels might be associated with the better C-peptide incremental effect of islet β cell function in T2DM, especially in female patients.

Key words: C-peptide, Serum uric acid, Hyperuricemia, Type 2 diabetes mellitus

SERUM URIC ACID (SUA) levels are positively associated with multiple metabolic abnormalities including obesity, hypertension, hyperglycemia, and hyperlipidemia [1]. Elevated SUA levels are independently correlated with the incidences of hypertension and metabolic syndrome (MetS) in some Asian countries including China, Japan, and Korea [2-5]. For patients with type 2 diabetes mellitus (T2DM), higher SUA levels are associated with the lower estimated glomerular filtration rate (eGFR) and higher prevalence of diabetic nephropathy, but not diabetic retinopathy [6]. Moreover, in general, the decline in SUA levels slows the progression of diabetic kidney disease [7]. SUA levels are positively asso-

ciated with a higher cardiovascular mortality risk irrespective of the presence of MetS [8]. A meta-analysis of cohort studies involving 62,834 participants reported that SUA levels were positively associated with the incidence of impaired fasting glucose and T2DM [9]. In patients with T2DM, hyperuricemia was positively correlated with hyperinsulinemia [10], fasting C-peptide (FCp) level [11], and insulin-resistant syndrome [12].

C-peptide, the 31 amino-acid residues peptide formed during cleavage of insulin from proinsulin, is co-secreted from pancreatic β cells in equimolar amounts with insulin [13]. C-peptide may serve as a simple predictor of an insulin resistance condition [14, 15] and exhibits a

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Abbreviations: SUA, serum uric acid; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; FCp, fasting C-peptide; OGTT, oral glucose tolerance test; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide; 1hCp/FCp, 1 h postprandial C-

peptide to fasting C-peptide ratio; 2hCp/FCp, 2 h postprandial C-peptide to fasting C-peptide ratio; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SD, standard deviation; ANOVA, One-way Analysis of covariance; β , beta coefficient

simple correlation with components of MetS [16]. FCp was correlated with SUA level and might be an independent risk factor of elevated SUA level in T2DM [17]. The SUA level was shown to be significantly correlated with C-peptide and also regarded as an independent risk factor of islet β cell functions in female patients with type 2 diabetes [18], but other studies showed there were no significant correlations between SUA level and insulin secretory capacity in the females [19].

The detecting level of serum insulin was particularly interfered by exogenous insulin, internal insulin antibody and proinsulin levels. However, the level of C-peptide assay was not influenced by the above factors and could also reflect the function of islet β cells. Therefore, we usually used the oral glucose tolerance test (OGTT) combined with a C-peptide release assay to evaluate the insulin secretion capacity of pancreatic β cells in patients with diabetes. After OGTT combined with the C-peptide release test, the C-peptide level of the healthy control group increased to the peak at postprandial 0.5–1 h, which was 4–6 times as much as fasting C-peptide, and gradually returned to normal at postprandial 3 h. The C-peptide level of T2DM patients increased to the peak at postprandial 2–3 h, which was generally lower than 5 times of fasting C-peptide [20, 21].

Based on the above mentioned characteristics of C-peptide release in T2DM patients, we applied two C-peptide parameters, the incremental and multiplication effect, to determine which parameter can better predict the long-term risk of serum uric acid: 1) The incremental effect was postprandial C-peptide minus fasting C-peptide, which could quickly determine the extra insulin secretion capacity of islet β cell in postprandial state compared with fasting state. The incremental effect includes 1hCp minus FCp (1h Δ Cp) and 2hCp minus FCp (2h Δ Cp). 2) The multiplication effect was postprandial C-peptide to fasting C-peptide ratio, and its value could also reflect the insulin secretion capacity of islet β cell, which may be more intuitive than the incremental effect. The multiplication effect includes 1 h postprandial C-peptide to FCp ratio (1hCp/FCp) and 2 h postprandial C-peptide to FCp ratio (2hCp/FCp). The cross-sectional study aimed to investigate which C-peptide releasing effect is associated with the risk of elevated SUA levels in patients with T2DM.

Methods

Study population

This cross-sectional study, conducted from August 2019 to June 2020, involved 345 consecutive patients with T2DM who were hospitalized for treatment at the First Affiliated Hospital of Harbin Medical University.

The 1999 World Health Organization criteria were used for T2DM diagnosis (fasting plasma glucose (FPG) ≥ 7.0 mmol/L or 2 h-postprandial plasma glucose ≥ 11.1 mmol/L). Hyperuricemia was defined as the SUA level of 7.0 mg/dL (420 μ mol/L) or higher regardless of sex. Subjects who were pregnant; had diabetic ketoacidosis, ketonuria or acute kidney injury, pancreatitis, or infection, had a malignant disease, or were undergoing dialysis were excluded. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University (Clinical Trials Registry number: ChiCTR2100047648).

Clinical data

All patients underwent a standardized interview to collect the clinical data including diabetes duration; smoking history; alcohol intake; medication treatment history including only insulin, only oral hypoglycemic medicine, oral + insulin hypoglycemic medicine, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB), aspirin and statins and other related variables. Smoking was defined as using >1 cigarette/day for at least one year and still currently smoking; drinking was defined as the consumption of liquor, beer, or wine on two days/week for one year. Blood pressure, body weight, and height were assessed. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). After 10 minutes of rest, blood pressure was measured three times using a mercury sphygmomanometer, with the patient in a seated position. The values of the three measurements were then averaged. Hypertension was diagnosed as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive drugs.

Biochemical measurements

Venous blood samples were collected in the morning after overnight fasting for at least 8–10 h, refrigerated immediately after phlebotomy, and centrifuged within 2 h of collection. SUA, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-C), creatinine, and FPG levels were measured using a Hitachi automated analyzer (NO.87128, Hitachi, 149 Ltd, Tokyo, Japan). Glycated haemoglobin (HbA1c) was measured by high-performance liquid chromatography (VARIANT II, BIO-RAD, Hercules, CA, USA). Serum C-peptide was assessed by chemiluminescence immunoassay (AIA-1800ST, TOSOH, kaisei-machi, Yamaguchi, Japan). The GFR was estimated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). *P*-value was 2-tailed and considered statistically significant at $p < 0.05$. Continuous data are summarized as mean $\pm$ standard deviation (SD) or medians (interquartile ranges) for skewed variables. Categorical variables are presented as percentages (%) and were assessed using chi-square test, as appropriate. One-way analysis of covariance (ANOVA) and an independent-samples *t*-test were applied to compare normally distributed continuous variables. The Mann-Whitney U test and Kruskal-Wallis H test were used for continuous variables not distributed normally.

Pearson's correlation was adopted to identify the correlations among the normally distributed variables. The correlations between the C-peptide-related parameters with SUA were analyzed using Spearman's rank correlation. Multiple linear regression analysis was applied to evaluate the association between the serum C-peptide releasing effects and SUA levels while adjusting for other confounding factors. Three models were constructed to avoid inference: Model 1 was unadjusted; Model 2 included adjustments for sex, age, smoking, drinking, BMI, TG, HDL-c, and eGFR. Model 3 included the variables of Model 2 and the duration of diabetes, HbA1c, oral medicine, oral + insulin, CCB, ACEI/ARB, and FPG.

Results

Baseline characteristics of the study population

The clinical characteristics of the T2DM patients with vs. without hyperuricemia are summarized in Table 1. Compared to patients without hyperuricemia, patients with hyperuricemia were more often male; were young; had a smoking history; took more oral and CCB medicines; and had high BMI, TG, creatinine, and FCp levels as well as lower levels of eGFR (all $p < 0.05$). However, no significant differences were found in diabetes duration, the prevalence of hypertension, drinking status, levels of HbA1c, TC, HDL-c, LDL-c, FPG, and intake of other medicines between both groups (all $p > 0.05$). Furthermore, the serum C-peptide-releasing effects including 1hCp, 1hΔCp, 2hCp and 2hΔCp concentrations in the hyperuricemia group were significantly higher than those in the non-hyperuricemia group (all $p < 0.05$), whereas 1hCp/FCp and 2hCp/FCp did not differ significantly between the groups. All the patients were divided into two groups by gender (Table 2). Compared to the male patients, the female patients tended to be older and have higher HDL-c level and 2hCp/FCp but the lower BMI and lower levels of creatinine, eGFR, SUA, and FCp; the prevalence of smoking and drinking was also lower (all $p < 0.05$).

Characteristics by quartiles of SUA and C-peptide levels

The characteristics of the patients based on SUA quartiles are shown in Table 3. The patients with T2DM in the upper quartiles of SUA are more likely to be males, of younger age, smokers, and drinkers; with a higher prevalence of oral medicine treatment, higher levels of BMI, TG, creatinine, and FCp; but lower levels of HbA1c and HDL-c (all $p < 0.05$). Additionally, the serum C-peptide including 1hCp ($p < 0.001$), 1hΔCp ($p = 0.011$), 2hCp ($p < 0.001$) and 2hΔCp ($p = 0.013$) were obviously elevated together with the increase in SUA quartiles, but not for 1hCp/FCp ($p = 0.753$) and 2hCp/FCp ($p = 0.465$). Moreover, patients turn to have higher SUA levels with elevating quartiles of 1hCp (Q1: 295.77 ± 73.88 , Q2: 328.93 ± 89.51 , Q3: 340.31 ± 93.62 , Q4: 356.54 ± 92.85 , umol/L, $p = 0.003$), 1hΔCp (Q1: 309.47 ± 87.20 , Q2: 320.12 ± 81.70 , Q3: 338.50 ± 94.79 , Q4: 362.37 ± 90.59 , umol/L, $p < 0.001$), 2hCp (Q1: 301.22 ± 83.09 , Q2: 325.77 ± 79.81 , Q3: 336.72 ± 95.43 , Q4: 362.95 ± 92.20 , umol/L, $p < 0.001$), and 2hΔCp (Q1: 311.39 ± 86.87 , Q2: 327.13 ± 87.85 , Q3: 331.23 ± 90.05 , Q4: 357.95 ± 91.26 , umol/L, $p = 0.007$), whereas this was not the case for 1hCp/FCp ($p = 0.804$) and 2hCp/FCp ($p = 0.549$) (Fig. 1).

Associations between parameters of serum C-peptide and SUA

The linear correlation analysis between the C-peptide levels and SUA levels is shown in Fig. 2. As expected, SUA levels was significantly correlated with age ($r = -0.225$), smoking ($r = 0.208$), drinking ($r = 0.184$), BMI ($r = 0.270$), TG ($r = 0.332$), HDL-c ($r = -0.241$), creatinine ($r = 0.469$), FCp ($r = 0.282$), oral medicine ($r = 0.202$), oral + insulin ($r = -0.148$), CCB ($r = 0.117$), and ACEI/ARB ($r = 0.118$). Furthermore, the serum C-peptide levels including 1hCp, 1hΔCp, 2hCp and 2hΔCp were all significantly correlated with SUA level (all $p < 0.001$). However, 1hCp/FCp and 2hCp/FCp were not significantly correlated with SUA level (both $p > 0.05$).

Multiple linear regression analysis revealed that in Model 1 (Table 4), the serum C-peptide-related effects including FCp, 1hCp, 1hΔCp, 2hCp and 2hΔCp were positively associated with SUA levels ($p < 0.001$ for trend). After adjusting for age, BMI, TG, HDL-c, eGFR, sex, smoking, drinking, diabetes duration, HbA1c and FPG, oral medicine, oral + insulin, CCB, and ACEI/ARB in Model 3, the serum C-peptide involved 1hCp, 1hΔCp, 2hCp and 2hΔCp (all $p < 0.05$) were still significantly associated with SUA levels, but FCp ($p = 0.977$), 1hCp/FCp ($p = 0.852$), and 2hCp/FCp ($p = 0.676$) were not significantly associated (Table 4).

Table 1 Baseline characteristics of participants according to the presence or not of hyperuricemia

	Non-Hyperuricemia	Hyperuricemia	All (<i>n</i> = 345)	<i>p</i> -value
	UA <420 (<i>n</i> = 289)	UA ≥420 (<i>n</i> = 56)		
male (<i>n</i> [%])	140 (48.44)	43 (76.79)	183 (53.00)	<0.001
Age (year)	54.92 ± 11.21	50.91 ± 11.55	54.27 ± 11.34	0.015
Duration (year)	8.00 (3.00–14.00)	5.00 (2.00–11.00)	7.00 (3.00–14.00)	0.129
Hypertension (<i>n</i> [%])	113 (39.10)	28 (50.00)	141 (40.87)	0.129
Smoking (<i>n</i> [%])	84 (29.07)	27 (48.21)	111 (32.20)	0.005
drinking (<i>n</i> [%])	82 (28.37)	23 (41.07)	105 (30.4)	0.059
BMI (kg/m ²)	25.57 ± 3.38	26.95 ± 3.75	25.79 ± 3.47	0.019
HbA1c (%)	8.68 ± 1.79	8.59 ± 1.84	8.67 ± 1.80	0.737
TC (mmol/L)	4.94 ± 1.23	5.21 ± 1.07	4.99 ± 1.20	0.128
TG (mmol/L)	1.78 (1.18–2.61)	2.49 (1.47–4.20)	1.81 (1.29–2.89)	0.002
HDL-c (mmol/L)	1.08 (0.92–1.25)	1.02 (0.94–1.20)	1.07 (0.92–1.25)	0.454
LDL-c (mmol/L)	3.04 ± 0.80	3.23 ± 0.75	3.07 ± 0.79	0.101
Creatinine (mmol/L)	57.30 (47.58–67.53)	75.40 (63.40–88.80)	59.40 (48.70–70.90)	<0.001
eGFR (mL·min ⁻¹ ·1.73(m ²) ⁻¹)	105.78 (98.26–115.74)	103.85 (87.62–117.30)	105.18 (97.10–116.15)	0.034
SUA (μmol/L)	303.83 ± 66.49	474.58 ± 53.35	331.54 ± 90.18	<0.001
FPG (mmol/L)	6.80 (5.93–7.80)	6.90 (6.10–7.80)	6.90 (6.00–7.80)	0.688
FCp (ng/mL)	1.50 (1.00–2.00)	2.00 (1.50–3.10)	1.60 (1.10–2.10)	<0.001
1hCp (ng/mL)	3.85 (2.65–5.80)	5.20 (3.60–7.42)	4.00 (2.90–6.10)	<0.001
1hΔCp (ng/mL)	2.30 (1.40–3.80)	3.20 (1.79–4.50)	2.46 (1.50–3.90)	0.026
1hCp/FCp	2.78 (2.12–3.52)	2.57 (2.03–3.25)	2.73 (2.09–3.45)	0.193
2hCp (ng/mL)	5.48 (3.70–8.30)	7.80 (4.90–10.90)	5.70 (3.89–8.60)	<0.001
2hΔCp (ng/mL)	4.10 (2.52–6.33)	5.48 (2.90–8.00)	4.20 (2.60–6.60)	0.011
2hCp/FCp	3.94 (3.00–5.21)	3.29 (2.71–4.50)	3.88 (2.94–5.14)	0.051
Insulin (<i>n</i> [%])	32 (11.07)	3 (5.36)	35 (10.14)	0.195
Oral medicine (<i>n</i> [%])	103 (35.64)	28 (50.00)	131 (37.97)	0.043
Oral + Insulin (<i>n</i> [%])	156 (53.98)	25 (44.64)	181 (52.46)	0.200
CCB (<i>n</i> [%])	56 (19.38)	19 (33.93)	75 (21.74)	0.016
ACEI/ARB (<i>n</i> [%])	69 (23.88)	19 (33.93)	88 (25.51)	0.114
Aspirin (<i>n</i> [%])	87 (30.10)	14 (25.00)	101 (29.28)	0.442
statins (<i>n</i> [%])	183 (63.32)	31 (55.36)	214 (62.03)	0.261

Baseline characteristics of participants according to the presence or not of hyperuricemia. Data were expressed as the mean ± SD, median (interquartile range) or *n* (%) according to the distribution of variables. Comparison between Non-Hyperuricemia and Hyperuricemia group was shown with *p* value. Abbreviations: SUA, serum uric acid; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SD, standard deviation.

Correlations between C-peptide-release levels and SUA levels by sex

According to linear correlation analysis, the levels of SUA and C-peptide parameters including FCp (male, *r* =

0.230; female, *r* = 0.298), 1hCp (male, *r* = 0.242; female, *r* = 0.287), 1hΔCp (male, *r* = 0.201; female, *r* = 0.227), 2hCp (male, *r* = 0.243; female, *r* = 0.313) and 2hΔCp (male, *r* = 0.220; female, *r* = 0.240) were positively

Table 2 Clinical characteristics of participants according to gender

	Male (<i>n</i> = 183)	Female (<i>n</i> = 162)	<i>p</i> -value
Age (year)	52.80 ± 10.89	55.93 ± 11.65	0.010
Duration (year)	8.00 (2.00–15.00)	7.00 (3.00–12.25)	0.729
Hypertension (<i>n</i> [%])	74 (40.44)	67 (41.36)	0.913
Smoking (<i>n</i> [%])	93 (50.82)	18 (11.11)	<0.001
drinking (<i>n</i> [%])	86 (46.99)	19 (11.73)	<0.001
BMI (kg/m ²)	26.31 ± 3.22	25.27 ± 3.64	0.016
HbA1c (%)	8.64 ± 1.84	8.70 ± 1.75	0.775
TC (mmol/L)	4.87 ± 1.07	5.12 ± 1.33	0.052
TG (mmol/L)	1.88 (1.35–3.02)	1.81 (1.15–2.56)	0.090
HDL-c (mmol/L)	1.00 (0.87–1.15)	1.13 (0.99–1.32)	<0.001
LDL-c (mmol/L)	3.02 ± 0.73	3.14 ± 0.86	0.170
Creatinine (mmol/L)	68.20 (60.15–77.40)	48.85 (44.68–57.60)	<0.001
eGFR (mL·min ⁻¹ ·1.73 (m ²) ⁻¹)	107.84 (98.22–119.02)	103.54 (96.02–111.67)	0.016
SUA (umol/L)	362.20 ± 85.77	296.91 ± 82.36	<0.001
FPG (mmol/L)	6.90 (6.05–7.90)	6.80 (5.90–7.70)	0.273
FCp (ng/mL)	1.60 (1.20–2.20)	1.50 (0.90–2.09)	0.023
1hCp (ng/mL)	4.00 (2.94–6.10)	3.99 (2.62–5.94)	0.388
1hΔCp (ng/mL)	2.50 (1.40–3.90)	2.45 (1.60–3.90)	0.706
1hCp/FCp	2.62 (1.88–3.37)	2.83 (2.23–3.51)	0.074
2hCp (ng/mL)	5.70 (3.90–8.30)	5.65 (3.70–9.33)	0.851
2hΔCp (ng/mL)	4.10 (2.45–6.10)	4.58 (2.70–7.40)	0.283
2hCp/FCp	3.54 (2.74–4.68)	4.12 (3.10–5.51)	0.001
Insulin (<i>n</i> [%])	19 (10.38)	16 (9.88)	0.877
Oral medicine (<i>n</i> [%])	77 (42.08)	54 (33.33)	0.095
Oral + Insulin (<i>n</i> [%])	89 (48.63)	92 (56.79)	0.130
CCB (<i>n</i> [%])	42 (22.95)	33 (20.37)	0.562
ACEI/ARB (<i>n</i> [%])	50 (27.32)	38 (23.46)	0.411
Aspirin (<i>n</i> [%])	60 (32.79)	41 (25.31)	0.128
statins (<i>n</i> [%])	117 (63.93)	97 (59.88)	0.438

Clinical characteristics of participants according to gender. Data were expressed as the mean ± SD, median (interquartile range) or *n* (%) according to the distribution of variables. Comparison between male group and female group was shown with *p* value. Abbreviations: SUA, serum uric acid; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SD, standard deviation.

correlated in both male and female groups (all *p* < 0.01). However, 1hCp/FCp and 2hCp/FCp were not significantly correlated with SUA levels (both *p* > 0.05).

Multiple linear regression analysis was used to determine the relationship between SUA and C-peptide levels in male and female groups (Table 5). In Model 1, SUA level was significantly associated with C-peptide level

including FCp, 1hCp, 1hΔCp, 2hCp, and 2hΔCp in both male and female groups unadjusted for any factors (all *p* < 0.01). However, after adjusting for the confounding factors in Model 3, SUA level only remained positively associated with 2hCp ($\beta = 4.78$, *p* = 0.017) and 2hΔCp ($\beta = 5.28$, *p* = 0.019) in the female group. The FCP, 1hCp, 1hΔCp, and the multiplication effect involving

Table 3 Baseline characteristics of participants according to the serum uric acid quartiles

	Q1 (<i>n</i> = 86)	Q2 (<i>n</i> = 87)	Q3 (<i>n</i> = 86)	Q4 (<i>n</i> = 86)	<i>p</i> -value
male (<i>n</i> [%])	22 (25.58)	44 (50.57)	54 (62.79)	63 (73.26)	<0.001
Age (year)	57.0 ± 11.6	55.9 ± 10.3	52.9 ± 10.9	51.3 ± 11.9	0.003
Duration (year)	6.0 (3.0–13.8)	8.0 (4–14.3)	8.0 (3–15)	5.0 (1–12)	0.127
Hypertension (<i>n</i> [%])	33 (23.5)	32 (22.7)	38 (26.9)	38 (26.9)	0.658
smoking (<i>n</i> [%])	15 (13.5)	27 (24.3)	31 (27.9)	38 (34.3)	0.002
drinking (<i>n</i> [%])	12 (11.4)	28 (26.7)	32 (30.5)	33 (31.4)	0.001
BMI (kg/m ²)	24.1 ± 3.1	25.9 ± 3.1	26.6 ± 3.6	26.6 ± 3.5	<0.001
HbA1c (%)	9.2 ± 1.9	8.5 ± 1.6	8.5 ± 1.8	8.5 ± 1.8	.025
TC (mmol/L)	4.97 ± 1.38	4.80 ± 1.01	5.14 ± 1.33	5.05 ± 1.04	0.298
TG (mmol/L)	1.44 (0.94–2.21)	1.69 (1.18–2.45)	1.92 (1.38–2.94)	2.49 (1.48–4.09)	<0.001
HDL-c (mmol/L)	1.17 (1.03–1.42)	1.05 (0.91–1.22)	1.06 (0.90–1.19)	1.00 (0.86–1.14)	<0.001
LDL-c (mmol/L)	2.98 ± 0.91	3.01 ± 0.70	3.20 ± 0.80	3.11 ± 0.76	0.242
Creatinine (mmol/L)	50.10 (44.15–59.88)	56.80 (47.68–67.83)	61.40 (50.00–70.88)	71.70 (59.25–80.20)	<0.001
eGFR (mL·min ⁻¹ ·1.73 (m ²) ⁻¹)	104.98 (96.72–114.98)	107.38 (99.88–116.26)	105.29 (99.88–116.20)	103.85 (90.88–116.72)	0.172
SUA (umol/L)	223.17 ± 33.24	296.11 ± 18.15	357.12 ± 20.23	450.18 ± 54.68	<0.001
FPG (mmol/L)	6.70 (5.90–8.10)	6.85 (5.80–7.93)	7.00 (6.28–7.73)	6.90 (6.10–7.70)	0.935
FCp (ng/mL)	1.45 (0.80–2.00)	1.40 (1.00–1.71)	1.60 (1.06–2.20)	1.90 (1.40–2.60)	<0.001
1hCp (ng/mL)	3.65 (2.13–5.65)	3.60 (2.80–5.15)	4.10 (2.92–7.08)	5.09 (3.50–6.55)	<0.001
1hΔCp (ng/mL)	2.00 (1.18–3.73)	2.21 (1.40–3.40)	2.60 (1.62–4.58)	3.10 (1.71–4.15)	0.011
1hCp/FCp	2.82 (2.09–3.44)	2.63 (2.12–3.50)	2.84 (2.07–3.74)	2.63 (2.04–3.30)	0.753
2hCp (ng/mL)	5.00 (3.10–7.58)	5.43 (3.93–7.90)	5.80 (3.68–9.15)	7.40 (4.70–10.25)	<0.001
2hΔCp (ng/mL)	3.45 (2.15–5.63)	4.20 (2.89–5.93)	4.15 (2.70–6.95)	5.20 (2.85–7.75)	0.013
2hCp/FCp	3.93 (2.89–5.23)	3.99 (3.09–5.50)	3.87 (2.88–5.14)	3.60 (2.84–5.14)	0.465
Insulin (<i>n</i> [%])	13 (15.12)	7 (8.05)	8 (9.30)	7 (8.14)	0.362
Oral medicine (<i>n</i> [%])	22 (25.58)	29 (33.33)	38 (44.19)	42 (48.84)	0.007
Oral + Insulin (<i>n</i> [%])	51 (59.30)	52 (59.77)	41 (47.67)	37 (43.02)	0.062
CCB (<i>n</i> [%])	13 (15.12)	20 (22.99)	18 (20.93)	24 (27.91)	0.235
ACEI/ARB (<i>n</i> [%])	16 (18.60)	21 (24.14)	23 (26.74)	28 (32.56)	0.207
Aspirin (<i>n</i> [%])	28 (32.56)	23 (26.44)	27 (31.40)	23 (26.74)	0.744
statins (<i>n</i> [%])	55 (63.95)	48 (55.17)	61 (70.93)	50 (58.14)	0.150

Data were expressed as the mean ± SD, median (interquartile range), or *n* (%) according to the distribution of variables. Comparison among all the groups was shown with *p* value. Abbreviations: SUA, serum uric acid; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SD, standard deviation.

1hCp/FCp and 2hCp/FCp in the female group and any C-peptide parameters in the male group were not associated with SUA levels in T2DM (all *p* > 0.05).

Discussion

We assessed the association between the long-term risk of elevated SUA levels and serum C-peptide effect obtained clinically. We identified that SUA levels were positively correlated with 1hCp, 2hCp, and the

Fig. 1 Association of different C-peptide quartiles with SUA levels: (A) Serum uric acid with quartiles of 1hCp; (B) Serum uric acid with quartiles of 1hΔCp; (C) Serum uric acid with quartiles of 1hCp/FCp; (D) Serum uric acid with quartiles of 2hCp; (E) Serum uric acid with quartiles of 2hΔCp; (F) Serum uric acid with quartiles of 2hCp/FCp. Abbreviations: SUA, serum uric acid; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide.

Fig. 2 Correlation of serum uric acid with different C-peptide releasing effects: (A) Serum uric acid with 1hCp; (B) Serum uric acid with 1hΔCp; (C) Serum uric acid with 1hCp/FCp; (D) Serum uric acid with 2hCp; (E) Serum uric acid with 2hΔCp; (F) Serum uric acid with 2hCp/FCp. Abbreviations: SUA, serum uric acid; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide.

Table 4 Association of different C-peptide releasing parameters with SUA by multiple linear regression analysis

	Model 1		Model 2		Model 3	
	β (95%CI)	<i>p</i>	β (95%CI)	<i>p</i>	β (95%CI)	<i>p</i>
FCp	26.82 (17.60–36.04)	<0.001	5.61 (–4.26–15.47)	0.264	–0.18 (–12.02–11.67)	0.977
1hCp	9.89 (6.24–13.53)	<0.001	5.51 (1.64–9.37)	0.005	5.14 (0.33–9.95)	0.036
1hΔCp	9.06 (4.34–13.78)	<0.001	7.07 (2.12–12.02)	0.005	7.80 (1.90–13.70)	0.010
1hCp/FCp	–3.36 (–8.17–1.45)	0.17	–0.39 (–5.06–4.29)	0.871	0.47 (–4.50–5.44)	0.852
2hCp	6.86 (4.23–9.48)	<0.001	4.49 (1.92–7.05)	0.001	4.27 (1.09–7.46)	0.009
2hΔCp	6.11 (2.99–9.23)	<0.001	5.27 (2.31–8.23)	<0.001	5.20 (1.63–8.78)	0.005
2hCp/FCp	–2.93 (–6.35–0.49)	0.093	0.31 (–3.04–3.67)	0.86	0.77 (–2.86–4.40)	0.676

In every regression analysis, only one C-peptide parameter was used to analyze the relationship with SUA, but not all the C-peptide parameters. Model 1 was unadjusted; Model 2 was adjusted for age, BMI, TG, HDL-c, eGFR, sex, smoking, drinking; Model 3 was adjusted for the Model 2 variables plus diabetic duration, HbA1c, oral medicine, oral + insulin, CCB, and ACEI/ARB, and FPG. Abbreviations: β , beta coefficient; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide; SUA, serum uric acid; BMI, body mass index; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 5 Multiple linear regression analysis between C-peptide releasing parameters and SUA by sex

		Male		Female	
		β (95%CI)	<i>p</i>	β (95%CI)	<i>p</i>
Model 1	FCp	18.83 (7.12–30.54)	0.002	29.49 (16.21–42.77)	<0.001
	1hCp	8.30 (3.71–12.88)	<0.001	10.66 (5.52–15.80)	<0.001
	1hΔCp	8.51 (2.68–14.33)	0.004	11.21 (4.17–18.25)	0.002
	1hCp/FCp	0.537 (–7.64–8.71)	0.897	–2.95 (–8.32–2.42)	0.280
	2hCp	8.00 (4.05–11.95)	<0.001	7.03 (3.98–10.07)	<0.001
	2hΔCp	8.26 (3.50–13.03)	0.001	6.56 (2.94–10.17)	<0.001
	2hCp/FCp	–0.21 (–6.03–5.61)	0.943	–1.71 (–5.58–2.16)	0.384
Model 2	FCp	0.21 (–13.52–13.95)	0.976	13.56 (0.12–27.01)	0.048
	1hCp	2.73 (–2.95–8.41)	0.343	7.24 (2.31–12.18)	0.004
	1hΔCp	4.06 (–2.90–11.02)	0.250	9.76 (3.02–16.51)	0.005
	1hCp/FCp	0.66 (–12.16–13.48)	0.919	0.44 (–4.12–4.99)	0.850
	2hCp	2.16 (–2.59–6.90)	0.370	4.98 (2.21–7.75)	0.001
	2hΔCp	2.78 (–2.64–8.19)	0.312	5.59 (2.36–8.83)	0.001
	2hCp/FCp	–0.70 (–9.28–7.88)	0.872	1.12 (–2.21–4.45)	0.508
Model 3	FCp	–2.30 (–18.72–14.13)	0.782	3.15 (–14.86–21.17)	0.729
	1hCp	3.92 (–3.04–10.89)	0.267	5.57 (–1.28–12.42)	0.110
	1hΔCp	5.93 (–2.18–14.04)	0.150	8.26 (–0.61–17.13)	0.067
	1hCp/FCp	3.25 (–11.10–17.60)	0.654	1.69 (–3.18–6.56)	0.494
	2hCp	2.70 (–3.07–8.46)	0.356	4.78 (0.86–8.69)	0.017
	2hΔCp	3.66 (–2.71–10.03)	0.258	5.28 (0.88–9.68)	0.019
	2hCp/FCp	0.308 (–9.53–10.15)	0.951	1.89 (–1.73–5.51)	0.303

In every regression analysis, only one C-peptide parameter was used to analyze the relationship with SUA, but not all the C-peptide parameters. Model 1 was unadjusted; Model 2 was adjusted for age, BMI, TG, HDL-c, eGFR, smoking, drinking; Model 3 was adjusted for the Model 2 variables plus diabetic duration, HbA1c, oral medicine, oral + insulin, CCB, and ACEI/ARB, and FPG. Abbreviations: β , beta coefficient; FCp, fasting C-peptide; 1hCp, 1 h postprandial C-peptide; 2hCp, 2 h postprandial C-peptide; SUA, serum uric acid; BMI, body mass index; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

incremental effect of serum C-peptide-releasing effect 1h Δ Cp and 2h Δ Cp in patients with T2DM, but were not significantly associated with FCp and the multiplication effect of C-peptide such as 1hCp/FCp and 2hCp/FCp after adjusting for the confounding variables of age, BMI, TG, HDL-c, eGFR, sex, smoking, drinking, diabetes duration, HbA1c, oral medicine, oral + insulin, CCB, ACEI/ARB, and FPG. After grouping by sex, only the 2hCp and 2h Δ Cp were associated with SUA levels in female patients; but no C-peptide parameters were associated with SUA levels in males with T2DM.

Hyperuricemic patients were older and had higher values of macroalbuminuria, BMI, TC, C-peptide, the prevalence of hypertension, and MetS, but lower values of HDL-c and HbA1c [11]. SUA was also strongly associated with full MetS as well as hypertriglyceridemia [22, 23]. Nevertheless, some prospective and retrospective studies have yielded contrary results. There were no significant association between SUA levels and cholesterol, HDL-c, LDL-C, TG, FPG, HbA1c, and urine microalbumin levels [24]. In subjects with MetS, the average SUA level was higher than that in the subjects without MetS, but this difference was not significant (6.62 vs. 6.28 mg/dL; $p = 0.556$) [25]. A study on 1,381 subjects who constituted a longitudinal health check-up cohort failed to show that increased SUA level was a causal risk factor for MetS or its components [26]. In T2DM, the subjects with higher SUA levels tended to have a higher prevalence of oral medicine treatment; higher BMI, TG, creatinine, and FCp levels; and lower levels of HbA1c and HDL-c (all $p < 0.05$). The serum C-peptide including FCp, 1hCp, 1h Δ Cp, 2hCp and 2h Δ Cp were obviously elevated together with the increase in SUA quartiles, but not for 1hCp/FCp ($p = 0.753$) and 2hCp/FCp ($p = 0.465$). When these C-peptide levels were decreased, the islet β cell function was poorer, thus leading to higher HbA1c (Q1, $9.2 \pm 1.9\%$) at lower SUA levels. The HbA1c mean value of Q4 (8.5%) was significantly lower than Q1 (9.2%), which might be associated with the improved islet β cell function at the upper SUA level.

According to The US Third National Health and Nutrition Examination Survey (1988–1994) involving 14,664 participants, SUA levels increased linearly with FCp and serum insulin levels (multivariate p -values for trend, <0.001) [27]. A study on 164 patients with type 1 diabetes mellitus revealed that C-peptide secretors had higher SUA levels (259 vs. 238 $\mu\text{mol/L}$, $p = 0.048$) compared to subjects with undetectable C-peptide [28]. SUA was found to be positively correlated with FCp, 2hCp, BMI, waist-to-hip ratio, TG, creatinine, smoking, and drinking ($p < 0.05$), and FCp was identified as an independent risk factor for elevated SUA, but sex did not

affect the relationship between FCp and SUA [17]. In males with type 2 diabetes, SUA level also showed significant positive correlations with insulin secretory capacity, including 2hCp, FCPI, PPCPI, Δ C-peptide, and HOMA2%B; however, no such significant correlations were observed among females [19]. The results of our present study are consistent with some of the observations described above involving the significant relationship between uric acid and Δ C-peptide levels. After adjusting for all the confounding factors, the 1hCp, 2hCp, 1h Δ Cp, and 2h Δ Cp of C-peptide-releasing parameters in patients with T2DM were positively associated with SUA levels. However, FCp was not significantly associated with SUA in patients with T2DM which is contrary to most previous findings. Insulin can enhance renal urate reabsorption *via* stimulation of the urate transporter in the human kidneys [29], thus insulin also decreased renal urate excretion [30–32]. Here, in order to reliably observe the insulin-secreting ability of islet β cell, we replaced insulin index with C-peptide. The finding may explain the positive correlation between the above C-peptide parameters and SUA levels. However, an elevated level of uric acid caused β -cell injury *via* the Nuclear factor-kappaB- Inducible nitric oxide synthase- nitric oxide (NF- κ B-iNOS-NO) signalling axis that causes abnormal pancreatic β cells function [33]. Hyperuricemia induced oxidative stress *in vivo* and *in vitro*, thereby leading to insulin resistance and glucose metabolism dysfunction [34]. Hence, we considered that at a certain range, the elevated SUA levels might be associated with the better C-peptide levels of islet β cell function.

Moreover, the level of SUA was positively associated with 2hCp ($\beta = 4.78$, $p = 0.017$) and 2h Δ Cp ($\beta = 5.28$, $p = 0.019$) in female patients with T2DM. Compared with all negative results in the male patients, the positive results between SUA and C-peptide parameters in the females might be associated with better clinical indicators including the higher HDL-c, but the lower BMI, creatinine, SUA, FCp, and prevalence of smoking and drinking (all $p < 0.05$). Females had lesser risk factors and better clinical indicators. Therefore their insulin resistance and metabolic syndrome were milder than male patients with T2DM. The C-peptide release test for type 2 diabetes generally peaks at 2–3 h postprandial. Hence, the level of SUA was positively associated with 2hCp and 2h Δ Cp in female patients with T2DM. However, male patients got the above risk factors, including smoking, drinking, the higher BMI, SUA, FCp and creatinine, but lower mean age and HDL-c, which could exacerbate insulin resistance and metabolic syndrome, decrease renal function and worsen cardiovascular disease. Thus, the SUA and C-peptide parameters do not

show a similar correlation as female patients. The result suggests that male patients should reduce the above risk factors.

The studies have shown that hyperuricemia may mediate insulin resistance, fatty liver, and dyslipidemia in both fructose-dependent and fructose-independent models of MetS [35]. SUA may augment the basal insulin secretion and insulin resistance indexes both in T2DM subjects in a population-based study [36]. After adjustment for age, alcohol, tobacco consumption, creatinine levels, BMI, and menopausal status, individuals with hyperuricemia had a higher prevalence of insulin resistance (OR = 1.84, 95%CI 1.25–2.73). And an increased prevalence of insulin resistance was associated with increasing levels of uric acid (*p* for trend <0.001) [37]. Though the mechanism between SUA and C-peptide-releasing effects remains unclear, we found a linear increase between SUA and islet β cells function in line with the existing data.

Nevertheless, the study has several limitations. First, the present study did not include healthy control subjects, and only inpatients with T2DM were included. Second, there might be a selection bias; the subjects were confined to a single-center or ethnic group; hence, the results could not be representative of other regions or peoples. Third, the causality of Δ C-peptide and SUA levels could not be established in a cross-sectional study, thus, further prospective research is needed to confirm these effects. Fourth, the retrospective study did not collect quantitative data on renal urate excretion that could be associated with SUA levels. Finally, the SUA levels were influenced by many factors including diet [38], genetics [39], race [40], and commonly used drugs such as statins [41] and aspirin [42]. However, we could not

adjust for such confounders in the present study due to the data insufficiency.

In conclusion, our results point out that after adjusting for the confounding factors, the 1hCp, 2hCp, and the incremental effect of serum C-peptide-releasing parameters involving 1h Δ Cp and 2h Δ Cp were still positively correlated with SUA levels in patients with T2DM. However, FCp, 1hCp, 1h Δ Cp, and the multiplication effect of C-peptide involving 1hCp/FCp and 2hCp/FCp in female patients and all C-peptide parameters in male patients were not significantly associated with SUA levels in patients with T2DM. Within a certain range, the elevated SUA levels might be associated with the better C-peptide incremental effect of islet β cell function in T2DM, especially in female patients with T2DM.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

Authors' Contributions Statement

Study design: YY-L, ZQ-Y, and HJ-Z; collection of data: X-Z, SR-W, and C-H; analysis and interpretation of data: YY-L and ZQ-Y; study supervision: X-Z and HJ-Z; writing of the manuscript: YY-L. All authors contributed to the manuscript and approved the submission.

References

1. Zhu C, Cui R, Gao M, Rampersad S, You H, *et al.* (2017) The associations of serum uric acid with obesity-related acanthosis nigricans and related metabolic indices. *Int J Endocrinol* 2017: 5438157.
2. Pingmuangkaew P, Tangvarasittichai O, Tangvarasittichai S (2015) Association of elevated serum uric acid with the components of metabolic syndrome and oxidative stress in abdominal obesity subjects. *Indian J Clin Biochem* 30: 286–292.
3. Ni W, Wang R, Liu Z, Yuan X, Chi H, *et al.* (2020) Association of serum uric acid with metabolic syndrome and its components: a cross-sectional study in chinese coastal population. *Metab Syndr Relat Disord* 18: 103–109.
4. Nagahama K, Inoue T, Kohagura K, Kinjo K, Ohya Y (2015) Associations between serum uric acid levels and the incidence of hypertension and metabolic syndrome: a 4-year follow-up study of a large screened cohort in Okinawa, Japan. *Hypertens Res* 38: 213–218.
5. Jeong J, Suh YJ (2019) Association between serum uric acid and metabolic syndrome in Koreans. *J Korean Med Sci* 34: e307.
6. Xia Q, Zhang SH, Yang SM, Zhu XL, Su S, *et al.* (2020) Serum uric acid is independently associated with diabetic nephropathy but not diabetic retinopathy in patients with type 2 diabetes mellitus. *J Chin Med Assoc* 83: 350–356.
7. Mauer M, Doria A (2020) Uric acid and risk of diabetic kidney disease. *J Nephrol* 33: 995–999.
8. Pugliese NR, Mengozzi A, Virdis A, Casiglia E, Tikhonoff V, *et al.* (2021) The importance of including uric acid in the definition of metabolic syndrome when assessing the mortality risk. *Clin Res Cardiol* 110: 1073–1082.
9. Jia Z, Zhang X, Kang S, Wu Y (2013) Serum uric acid

- levels and incidence of impaired fasting glucose and type 2 diabetes mellitus: a meta-analysis of cohort studies. *Diabetes Res Clin Pract* 101: 88–96.
10. Niskanen L, Laaksonen DE, Lindström J, Eriksson JG, Keinonen-Kiukkaanniemi S, *et al.* (2006) Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabetes Care* 29: 709–711.
 11. Zong J, Sun Y, Zhang Y, Yuan J, Wang X, *et al.* (2020) Correlation between serum uric acid level and central body fat distribution in patients with type 2 diabetes. *Diabetes Metab Syndr Obes* 13: 2521–2531.
 12. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G (2001) Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. *Eur J Clin Invest* 31: 318–321.
 13. Johansson J, Ekberg K, Shafqat J, Henriksson M, Chibalin A, *et al.* (2002) Molecular effects of proinsulin C-peptide. *Biochem Biophys Res Commun* 295: 1035–1040.
 14. Khan HA, Sobki SH, Ekhzaimy A, Khan I, Almusawi MA (2018) Biomarker potential of C-peptide for screening of insulin resistance in diabetic and non-diabetic individuals. *Saudi J Biol Sci* 25: 1729–1732.
 15. Jones AG, Hattersley AT (2013) The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet Med* 30: 803–817.
 16. Kim ST, Kim BJ, Lim DM, Song IG, Jung JH, *et al.* (2011) Basal C-peptide level as a surrogate marker of subclinical atherosclerosis in type 2 diabetic patients. *Diabetes Metab J* 35: 41–49.
 17. Liang Q, Wang XY, Hu HF, Lai JB, Yao WL, *et al.* (2018) Correlation between fasting C-peptide and serum uric acid in patients with type 2 diabetes mellitus. *Nan Fang Yi Ke Da Xue Xue Bao* 38: 490–495 (in Chinese).
 18. Ling Y, Li XM, Gu Q, Gao X (2012) Correlation of serum uric acid and islet beta cell functions in female type 2 diabetes. *Zhonghua Yi Xue Za Zhi* 92: 541–545 (in Chinese).
 19. Zhong X, Zhang D, Yang L, Du Y, Pan T (2019) The relationship between serum uric acid within the normal range and β -cell function in Chinese patients with type 2 diabetes: differences by body mass index and gender. *PeerJ* 7: e6666.
 20. Kang Y, Hua C, Dan L, Feng Y (2014) Characteristics and relevant factors of insulin, C-peptide release after oral glucose test in newly diagnosed type 2 diabetes patients. *Chin J Mod Med* 24: 40–43 (in Chinese).
 21. Wang W, Ding Z, Jian F, Zhong B, Yang X (2019) Study on serum insulin and C-peptide release levels of patients with type 2 diabetes mellitus. *Int J Lab Med* 40: 203–205, 209.
 22. Xu J, Liu C, Fu L, Li L, Wang T (2021) The association of serum uric acid with metabolic syndrome and its components-from a single-clinical centre in China. *Int J Clin Pract* 75: e13845.
 23. Ali N, Miah R, Hasan M, Barman Z, Mou AD, *et al.* (2020) Association between serum uric acid and metabolic syndrome: a cross-sectional study in Bangladeshi adults. *Sci Rep* 10: 7841.
 24. Li L, Song Q, Yang X (2019) Lack of associations between elevated serum uric acid and components of metabolic syndrome such as hypertension, dyslipidemia, and T2DM in overweight and obese Chinese adults. *J Diabetes Res* 2019: 3175418.
 25. Adnan E, Rahman IA, Faridin HP (2019) Relationship between insulin resistance, metabolic syndrome components and serum uric acid. *Diabetes Metab Syndr* 13: 2158–2162.
 26. Wang L, Zhang T, Liu Y, Tang F, Xue F (2020) Association of serum uric acid with metabolic syndrome and its components: a mendelian randomization analysis. *Biomed Res Int* 2020: 6238693.
 27. Choi HK, Ford ES (2008) Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels-the Third National Health and Nutrition Examination Survey. *Rheumatology (Oxford)* 47: 713–717.
 28. Bulum T, Tomić M, Vuković-Rebrina S, Roso V, Vučić Lovrenčić M, *et al.* (2020) Preserved C-peptide secretion in patients with type 1 diabetes and incipient chronic complications is associated with lower serum resistin and higher uric acid levels. *J Diabetes Metab Disord* 19: 1185–1189.
 29. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, *et al.* (2002) Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 417: 447–452.
 30. Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, *et al.* (1997) Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. *Clin Sci (Lond)* 92: 51–58.
 31. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, *et al.* (1996) Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens* 9: 746–752.
 32. Facchini F, Chen YD, Hollenbeck CB, Reaven GM (1991) Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA* 266: 3008–3011.
 33. Jia L, Xing J, Ding Y, Shen Y, Shi X, *et al.* (2013) Hyperuricemia causes pancreatic β -cell death and dysfunction through NF- κ B signaling pathway. *PLoS One* 8: e78284.
 34. Zhu Y, Hu Y, Huang T, Zhang Y, Li Z, *et al.* (2014) High uric acid directly inhibits insulin signalling and induces insulin resistance. *Biochem Biophys Res Commun* 447: 707–714.
 35. King C, Lanaspa MA, Jensen T, Tolan DR, Sánchez-Lozada LG, *et al.* (2018) Uric acid as a cause of the metabolic syndrome. *Contrib Nephrol* 192: 88–102.
 36. Hu Y, Liu J, Li H, Zhu H, Liu L, *et al.* (2018) The association between elevated serum uric acid levels and islet β -cell function indexes in newly diagnosed type 2 diabetes mellitus: a cross-sectional study. *PeerJ* 6: e4515.
 37. Abreu E, Fonseca MJ, Santos AC (2011) [Association between hyperuricemia and insulin resistance]. *Acta Med*

- Port* 24 Suppl 2: 565–574 (in Portuguese).
38. Tang O, Miller ER 3rd, Gelber AC, Choi HK, Appel LJ, *et al.* (2017) DASH diet and change in serum uric acid over time. *Clin Rheumatol* 36: 1413–1417.
 39. Voruganti VS, Nath SD, Cole SA, Thameem F, Jowett JB, *et al.* (2009) Genetics of variation in serum uric acid and cardiovascular risk factors in Mexican Americans. *J Clin Endocrinol Metab* 94: 632–638.
 40. Beydoun MA, Fanelli-Kuczmarski MT, Canas JA, Beydoun HA, Evans MK, *et al.* (2018) Dietary factors are associated with serum uric acid trajectory differentially by race among urban adults. *Br J Nutr* 120: 935–945.
 41. Ogata N, Fujimori S, Oka Y, Kaneko K (2010) Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides Nucleotides Nucleic Acids* 29: 321–324.
 42. Zhang P, Wang H, Chen XH, Liang WY, Liu WW, *et al.* (2020) Effect of low-dose aspirin on serum uric acid levels in Chinese individuals over 60: subanalysis of a multi-centre randomized clinical trial. *Eur Rev Med Pharmacol Sci* 24: 2719–2724.