

Elevated Blood Glucose Can Promote Uric Acid Excretion: A Cross-Sectional Study Involving Urinary Glucose and Urinary Uric Acid in China

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Purpose: Uric acid and blood glucose are important indicators of metabolic disorders. Numerous studies have elucidated the association between them, but the focus on their relationship through examination of urinary glucose and uric acid excretion has been limited. In this study, we conducted a comprehensive analysis on these indicators to explain the relationship.

Patients and Methods: This study involved the recruitment of 2498 patients who underwent fractional excretion of uric acid (FEUA) testing during their hospitalization at the Health Department of Qilu Hospital (Qingdao), Shandong University, between January 2017 and November 2023, with 1416 subjects being included in the final analysis. The included subjects were analyzed based on different genders. One-way analysis of variance, multiple linear regression analysis, and restricted cubic spline were adopted for data analysis.

Results: Higher FEUA and lower serum uric acid (SUA) levels were observed in diabetic patients with urinary glucose than in diabetic patients without urinary glucose and the nondiabetic population. FEUA exhibited a proportional increase with elevated blood glucose levels, even including cases that lacked urinary glucose. After adjustment for potential confounding factors, SUA levels did not increase with the increase in fasting blood glucose (FBG) levels, and once FBG levels surpassed a certain threshold leading to glucosuria, FEUA was further elevated, accompanied with a subsequent reduction in SUA levels. There is a stronger linear relationship between SUA or FEUA and FBG levels in women than that in men after adjusting for confounding factors.

Conclusion: Hyperglycemia is not considered a risk factor for hyperuricemia. Regardless of the presence of urinary glucose, elevated blood glucose levels can stimulate renal excretion of uric acid. Upon reaching a threshold that induces glucosuria, the SUA levels decrease substantially. Meanwhile, there are some differences in the relationship between SUA or FEUA and FBG among different genders.

Keywords: FEUA, serum uric acid, diabetes, glycosuria, non-linear relationship

Introduction

Uric acid and blood glucose are pivotal indicators of metabolic disorders. Patients with metabolic syndrome normally present elevated levels of serum uric acid (SUA), with insulin resistance and hyperglycemia serving as essential diagnostic criteria. Hyperuricemia shows an association with insulin resistance¹ and represents an independent risk factor for impaired fasting glucose and type 2 diabetes.^{2,3} However, despite the rise in blood glucose levels, the increase in uric acid levels is inconsistent. Instead, a nonlinear relationship has been observed between fasting blood glucose (FBG) and SUA, and it is characterized by an inverted U-shape.⁴ In addition, individuals with overt diabetes exhibit decreased levels of SUA. This phenomenon can be attributed to glycosuria.⁵ Clinical studies have demonstrated the SUA-lowering effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors, which facilitates urinary glucose excretion.⁶ Further assessment of urinary glucose and the excretion capacity of uric acid may contribute to the comprehensive understanding of this phenomenon.

Uric acid is the final oxidation product of purine catabolism, and the kidney accounts for more than 70% of urate excretion. Under normal conditions, 5% to 10% of filtered urate, which is usually expressed as fractional excretion of uric acid (FEUA), is excreted in urine.⁷ FEUA is widely used in the evaluation of the excretion capacity for uric acid. SUA levels vary considerably between genders, with higher levels observed in males.⁸ Therefore, gender should be considered in the evaluation of the relationship between uric acid and blood glucose.

Thus, for the comprehensive elucidation of the association between blood glucose and SUA levels, a cross-sectional study utilizing parameters, such as SUA, FBG, FEUA, and urinary glucose, was performed on individuals with either normal blood glucose levels or diabetes, with consideration for gender differences.

Materials and Methods

Study Population

This study involved the recruitment of 2498 han Chinese patients who underwent FEUA testing upon admission at the Health Department of Qilu Hospital (Qingdao), Shandong University between January 2017 and November 2023. Data collection involved a thorough review of the medical history of subjects. Patients who met any of the following criteria were excluded: (1) The blood and urine samples were not collected on the same day; (2) use of medications known that affect uric acid excretion or metabolism, such as loop diuretics, thiazide diuretics, losartan, alisartan, sacubitril valsartan, allopurinol, febuxostat, benzbromarone, probenecid, fenofibrate; (3) moderate or severe renal insufficiency with an estimated glomerular filtration rate (eGFR) less than 60 mL/min \times 1.73 m²; (4) acute infection or fever or acute phase of gout; (5) diabetes ketoacidosis and diabetes hyperosmolar coma; (6) drinking a lot of alcohol with more than 40 grams of pure alcohol per day for men or 20 grams per day for women; (7) serum sodium levels below 135 mmol/L or above 150 mmol/L; (8) FBG levels below 3.0 mmol/L; (9) pregnant women; (10) below the age of eighteen. The final analysis included a cohort of 1416 subjects (Figure 1). We categorized included subjects into three groups: nondiabetes, diabetes without urinary glucose, and diabetes with urinary glucose groups. The Ethics Committee of Qilu Hospital (Qingdao), Shandong University granted ethical approval for this study, and all procedures were carried out according to the guidelines specified in the Declaration of Helsinki. The data were anonymous, and the study posed no adverse effects on patients. Therefor the ethics committee granted approval for waiver of informed consent requirement.

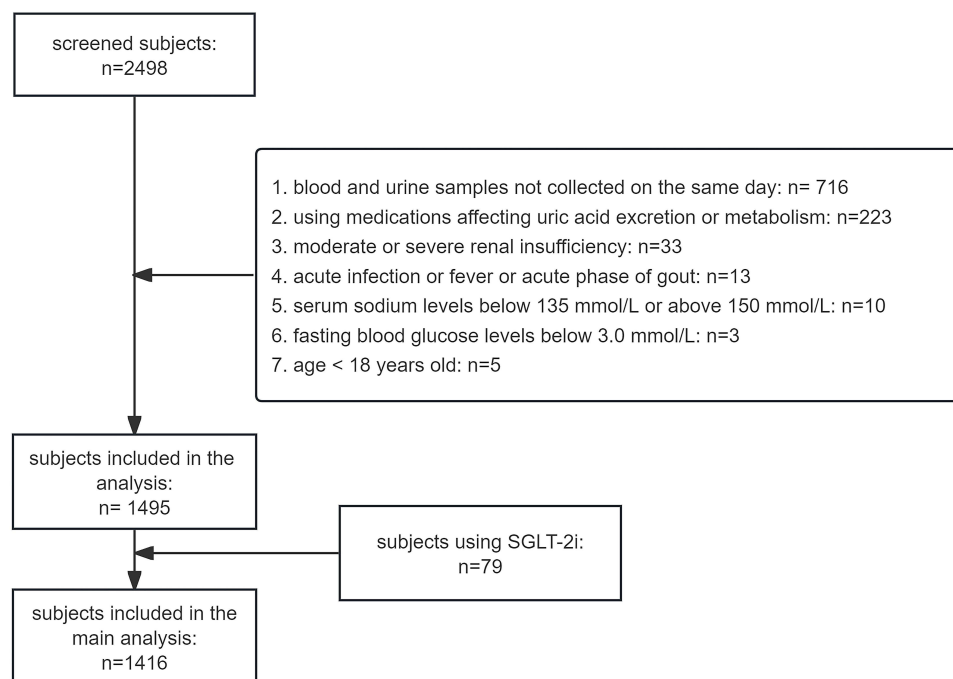


Figure 1 Study flow chart.

Clinical and Laboratory Measurements

The medical record system provided access to demographic information of the subjects, including gender, age, height, and weight, and their comprehensive medication history, previous medical records, and laboratory test results. The subjects underwent overnight fasting for at least 8 h before their blood and urine samples were collected. All indicators were tested in the hospital's central laboratory. These indicators comprised the glycosylated hemoglobin (HbA1c) levels (turbidimetric inhibition immuno assay), FBG levels (hexokinase method), SUA levels (Uricase colorimetric method), total cholesterol levels (cholesterol oxidase method), high-density lipoprotein cholesterol (HDL-C) levels (direct method - selective inhibition method), low-density lipoprotein cholesterol (LDL-C) levels (direct method - surfactant removal method), triglyceride (TG) levels (glycerol phosphate oxidase - peroxidase method), serum creatinine (SCR) levels (picric acid method), serum electrolyte levels (ion selective electrode method), urinary uric acid (UUA) levels (Uricase colorimetric method), urinary glucose levels (dry chemical method), urine pH (dry chemical method), and urinary creatinine (UCR) levels (sarcosine oxidase method). Urinary glucose levels were categorized as follows: “-” (0 mmol/L), “±” (< 5.5 mmol/L), “+” (< 14 mmol/L), “++” (< 28 mmol/L), “+++” (< 55 mmol/L), and “++++” (≥ 55 mmol/L). The eGFR was calculated using the Chronic Kidney Disease Epidemiology equation.⁹ FEUA was derived using the following formula: $(\text{UUA/UCR}) \times (\text{SCR/SUA})$. The corrected serum sodium (CNa) was used in the analysis due to the influence of blood glucose on blood sodium levels:¹⁰ $\text{corrected serum sodium (mmol/L)} = \text{measured serum sodium (mmol/L)} + 2.4 \times \frac{\text{serum glucose (mmol/L)} - 5.5 \text{ mmol/L}}{5.5 \text{ mmol/L}}$

Irrespective of their plasma glucose levels, the diabetes group comprised subjects with a documented history of diabetes and undergoing treatment with antidiabetic agents. Other individuals were diagnosed with diabetes based on FBG levels ≥ 7 mmol/L, HbA1c levels ≥ 6.5%, or blood glucose levels during the 2 h post glucose tolerance test ≥ 11.1 mmol/L.

Statistical Analysis

Data analysis was completed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and R software program version 3.2.2 (<http://www.R-project.org>). Continuous variables with an approximately normal distribution were expressed as means ± standard deviation, and those with a skewed distribution were expressed as medians with interquartile ranges. During the comparison of differences between groups, one-way analysis of variance was used for normally distributed data and Kruskal–Wallis rank-sum test for nonnormally distributed data. Moreover, group comparisons required multiple linear regression analysis to adjust for confounding factors.

The associations between FBG and SUA or FEUA were evaluated via univariate and multiple linear regression analyses, and the potential nonlinear association between them was investigated using restricted cubic spline (RCS). The number of knots was determined based on the lowest value of Akaike information criterion, which ranged from 3 to 5. After the calculation, four knots at the 5th, 35th, 65th, 95th percentiles were used to flexibly model the association of FBG and SUA or FEUA. Initial analyses were conducted without any adjustment (model 1), followed by adjustments for factors, including age, body mass index (BMI), TG, HDL-C, LDL-C, urine pH, eGFR, CNa in model 2. In addition to the aforementioned indicators, the adjustment was made for urinary glucose in model 3. A *p*-value of <0.05 was considered statistically significant.

Results

Differences in FEUA and SUA Based on Diabetes and Urinary Glucose

The cross-sectional study included 1495 subjects, which consisted of 802 men and 693 women. Among the subjects, 79 (24 women and 55 men) were using SGLT2 inhibitors. Then 1416 subjects were included in the final analysis. We categorized them into three groups: nondiabetes, diabetes without urinary glucose, and diabetes with urinary glucose groups. Table 1 presents the main characteristics of the included subjects. Among men in the three groups, significant differences were observed in their age, HDL-C, urine pH and eGFR. The results obtained for the women revealed differences in age, TG, HDL-C, LDL-C, urine pH, and eGFR.

Table 1 Characteristics of Subjects Grouped by Diabetes and Urinary Glucose and by Gender

Variable	Women			p Value	Men			
	Nondiabetes	Diabetes without Urinary Glucose	Diabetes with Urinary Glucose		Nondiabetes	Diabetes without Urinary Glucose	Diabetes with Urinary Glucose	p Value
Number	380	213	76	N/A	365	231	151	N/A
Age (year)	62.2 ± 11.3	67.0 ± 9.6	65.3 ± 10.6	<0.001	59.7 ± 12.7	62.0 ± 11.0	59.1 ± 12.7	0.034
BMI (kg/m ²)	25.2 ± 3.5	25.7 ± 3.7	25.8 ± 3.6	0.135	26.4 ± 3.7	26.4 ± 3.4	26.1 ± 3.4	0.559
HbA1C (%)	4.9 ± 1.9	7.1 ± 1.1	9.3 ± 1.9	<0.001	5.1 ± 1.6	7.1 ± 1.4	8.9 ± 1.8	<0.001
FBG (mmol/L)	4.83 ± 0.52	6.43 ± 1.32	9.68 ± 3.06	<0.001	4.95 ± 0.62	6.37 ± 1.26	9.23 ± 2.71	<0.001
Triglycerides (mmol/L)	1.17 (0.86, 1.59)	1.37 (0.97, 1.96)	1.54 (1.18, 2.16)	<0.001	1.26 (0.89, 1.78)	1.29 (0.95, 1.92)	1.42 (0.94, 2.09)	0.088
TC (mmol/L)	4.96 ± 1.03	4.55 ± 1.03	4.77 ± 1.39	<0.001	4.33 ± 1.01	4.21 ± 1.11	4.44 ± 1.09	0.116
HDL-C (mmol/L)	1.43 ± 0.30	1.31 ± 0.29	1.24 ± 0.30	<0.001	1.20 ± 0.29	1.14 ± 0.28	1.17 ± 0.27	0.046
LDL-C (mmol/L)	3.10 ± 0.85	2.82 ± 0.88	3.01 ± 1.11	0.001	2.78 ± 0.87	2.71 ± 0.89	2.85 ± 0.87	0.289
SUA (μmol/L)	289.1 ± 61.6	298.0 ± 71.5	273.7 ± 64.0	0.018	372.0 ± 82.0	356.1 ± 86.2	315.5 ± 81.1	<0.001
Urine pH	5.9 ± 0.7	5.8 ± 0.7	5.6 ± 0.6	0.003	6.0 ± 0.7	5.8 ± 0.7	5.8 ± 0.6	0.006
CNa (mmol/L)	141.7 ± 2.2	142.0 ± 2.3	142.0 ± 2.2	0.136	141.4 ± 2.2	141.4 ± 2.3	141.6 ± 2.2	0.598
eGFR (mL/min/1.732m ²)	95.6 ± 11.8	92.8 ± 11.0	96.0 ± 11.5	0.013	96.3 ± 12.7	95.9 ± 13.7	100.5 ± 14.5	0.002
FEUA(%)	6.2 ± 2.2	6.8 ± 2.7	7.9 ± 2.9	<0.001	5.2 ± 1.8	6.0 ± 2.3	7.0 ± 2.6	<0.001

Notes: Data are presented as mean ± standard deviation or median (25th percentile, 75th percentile).

Abbreviations: BMI, body mass index; HbA1C, glycosylated hemoglobin; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; CNa, corrected serum sodium; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid.

Table 2 Comparison of FEUA and SUA Among the Three Groups

Variable	Women						Men					
	B versus A	p	C versus A	p	C versus B	p	B versus A	p	C versus A	p	C versus B	p
Unadjusted FEUA(%)	0.57±0.21	0.021	1.70±0.30	<0.001	1.13±0.32	0.002	0.81±0.18	<0.001	1.78±0.21	<0.001	0.96±0.23	<0.001
Adjusted FEUA (%)	0.72±0.20	<0.001	2.49±0.29	<0.001	1.77±0.30	<0.001	0.97±0.16	<0.001	2.15±0.19	<0.001	1.18±0.20	<0.001
Unadjusted SUA (mmol/L)	8.9±5.6	0.336	−15.5±8.2	0.178	−24.3± 8.7	0.016	−16.0±7.0	0.068	−56.6±8.0	<0.001	−40.6±8.7	<0.001
Adjusted SUA(mmol/L)	−1.0±5.1	1.000	−37.0±7.6	<0.001	−36.0± 7.8	<0.001	−14.8±6.1	0.048	−55.9±7.1	<0.001	−41.1±7.6	<0.001

Notes: Data are presented as mean ± standard deviation. Adjusted factors include age, body mass index, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, corrected serum sodium, urine pH and estimated glomerular filtration rate. Multiple comparisons were corrected by Bonferroni method. A, group of nondiabetes; B, group of diabetes without urinary glucose; C, group of diabetes with urinary glucose.

Abbreviations: SUA: serum uric acid; FEUA, fractional excretion of uric acid.

Men in the diabetes with urinary glucose group showed significantly higher FEUA than their counterparts in the diabetes without urinary glucose group. In addition, the FEUA of both groups were significantly higher than that of the nondiabetes group. These differences remained statistically significant after adjustments for age, BMI, TG, HDL-C, LDL-C, urine pH, eGFR, and CNa. Prior to adjustment, the diabetes with urinary glucose group exhibited the lowest levels of SUA and no statistically significant difference was observed between the other two groups. After adjustment, the SUA levels were still the lowest in the group of diabetes with urinary glucose, followed by that in the diabetes without urinary glucose group. The statistical significance was observed in the comparison among different groups. The results are shown in Table 2.

The FEUA of women exhibited a descending order: diabetes with urinary glucose, diabetes without urinary glucose, and nondiabetes groups. Statistically significant differences were observed between each pair of groups. And these differences remained statistically significant after adjustment for age, BMI, TG, HDL-C, LDL-C, urine pH, eGFR, and CNa. Diabetes patients with urinary glucose presented lower SUA levels than diabetes patients without urinary glucose when the factors were not adjusted. However, no statistically significant difference was found between the remaining groups. After adjustment, the SUA levels of diabetes with urinary glucose group remained lower, whereas similar results were observed in the other two groups. Table 2 showed the detailed results.

Association Among FBG, FEUA, and SUA

The analysis included 1416 patients as well and three models were used to conduct multiple analyses as stated earlier.

In men, multiple linear regression analysis revealed a significant positive correlation between FBG and FEUA in all three models (models 1, 2, and 3), the results were shown in Table 3. Moreover, when RCS with four knots was employed to investigate the nonlinear relationship between FBG and FEUA, we observed curves with gradually decreasing slopes in models 1 (Figure 2A) and 2 (Figure 2B). However, model 3 showed the shift in association from positive to slightly negative at a cut point of around 9.2 mmol/L (Figure 2C). Multiple linear regression analysis of the relationship between FBG and SUA identified negative correlations in models 1 and 2 and no correlation was found in model 3. When RCS with four knots was used, Model 1 (Figure 2D) exhibited inverted U-shaped curves while model 2 (Figure 2E) and 3 (Figure 2F) showed inverted L-shaped curves. The turning point occurred at approximately 5.1 mmol/L of serum glucose. Furthermore, the SUA levels in models 1 and 2 gradually decreased with the increase in FBG levels. Conversely, model 3 presented slightly increased SUA levels after exceeding a threshold of 8.8 mmol/L.

For women, multiple linear regression analysis of the relationship between FBG and FEUA revealed a positive correlation in model 1, which was also evident in models 2 and 3. We also employed RCS with four knots to investigate the nonlinear association between FBG and FEUA. Models 1 (Figure 3A) and 2 (Figure 3B) exhibited a nearly linear relationship, with a steeper slope observed in model 2. However, in model 3, when the FBG levels exceeded 9.3 mmol/L, the trend shifted from an upward trajectory to a plateau (Figure 3C). Multiple linear regression analysis was performed to determine the relationship between FBG and SUA in the female subjects. Models 1 and 3 showed no significant correlation between FBG and FEUA, but model 2 exhibited a negative correlation. To explore non-linear relationships via RCS analysis, we identified an approximate inverted U-shaped curve with a turning point at a serum glucose level of 7.8 mmol in model 1 (Figure 3D). The nonlinear relationships were not significant in models 2 (Figure 3E) and 3 (Figure 3F). Notably, a negative correlation was observed in model 2, but no correlation was detected in model 3.

Comparison of FEUA and SUA Between the Hyperglycemia-Induced and SGLT2-Inhibitors-Used High-Urinary-Glucose Groups

The analysis included 78 diabetics using SGLT2 inhibitors and 165 diabetics without using that, all of whom had a minimum urinary glucose level of “+++”. One subject using SGLT2 inhibitors was excluded with urinary glucose level of “++”. After the adjustment for sex and other confounding factors including age, BMI, TG, HDL-C, LDL-C, urine pH, eGFR, and CNa, the two groups showed no significant differences in terms of FEUA ($-0.0975\% \pm 0.3473\%$, $p=0.779$) and SUA ($13.884 \text{ mmol/L} \pm 9.728$, $p=0.155$).

Table 3 Correlations Between FBG and FEUA, SUA in Different Models of Multiple Linear Regression and RCS

	Association Between FEUA (%) and FBG (mmol/L)						Association Between SUA (ummol/L) and FBG (mmol/L)					
	Multiple Linear Regression			RCS with Four Knots			Multiple Linear Regression			RCS with Four Knots		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Men												
AIC	3284.6	3106.0	3087.7	3281.7	3094.6	3071.9	8754.9	8533.4	8515.5	8743.1	8527.7	8510.7
Nonlinear <i>p</i>	N/A	N/A	N/A	0.0319	<0.001	<0.001	N/A	N/A	N/A	<0.001	0.0084	0.0133
β (SE)	0.278 (0.036)	0.367 (0.033)	0.216 (0.047)	N/A	N/A	N/A	-6.489 (1.416)	-8.120 (1.121)	-2.460 (1.772)	N/A	N/A	N/A
P of β	<0.001	<0.001	<0.001	N/A	N/A	N/A	<0.001	<0.001	0.165454	N/A	N/A	N/A
Women												
AIC	3100.558	2974.013	2962.565	3102.9	2977.2	2961.0	7497.6	7343.5	7328.5	7493.7	7344.0	7330.9
Nonlinear <i>p</i>	N/A	N/A	N/A	0.4383	0.6614	0.0655	N/A	N/A	N/A	0.0195	0.1773	0.4533
β (SE)	0.184 (0.047)	0.324 (0.046)	0.173 (0.061)	N/A	N/A	N/A	1.102 (1.248)	-3.837 (1.192)	0.632 (1.602)	N/A	N/A	N/A
P of β	<0.001	<0.001	<0.001	N/A	N/A	N/A	0.3776	0.00135	0.693280	N/A	N/A	N/A

Notes: Model 1: not adjusted; model 2: adjusted for age, body mass index, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, corrected serum sodium, urine pH and estimated glomerular filtration rate; model 3: adjusted for model 2+urinary glucose.

Abbreviations: FBG, fasting blood glucose; FEUA, fractional excretion of uric acid; SUA, serum uric acid; RCS, Restricted cubic spline; SE, Standard error; AIC, Akaike information criterion.

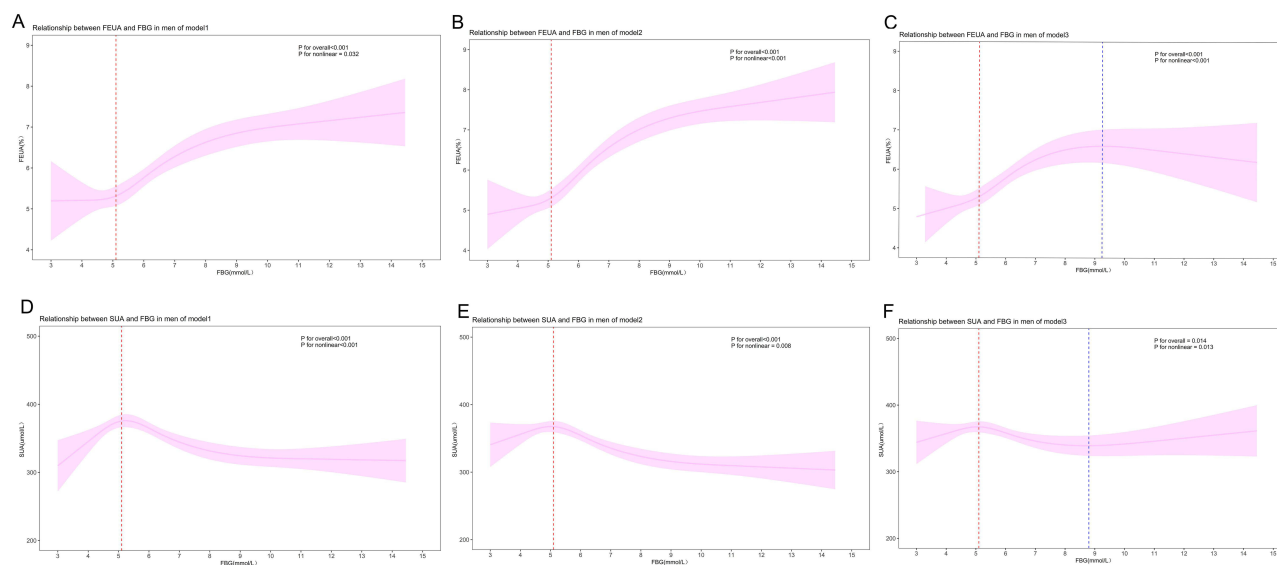


Figure 2 Association between FBG and FEUA or SUA in different models using RCS in men.

Notes: (A) relationship between FEUA and FBG in men of model 1; (B) relationship between FEUA and FBG in men of model 2; (C) relationship between FEUA and FBG in men of model 3; (D) relationship between SUA and FBG in men of model 1; (E) relationship between SUA and FBG in men of model 2; (F) relationship between SUA and FBG in men of model 3; Model 1: not adjusted; model 2: adjusted for age, body mass index, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, corrected serum sodium, urine pH and estimated glomerular filtration rate; model 3: adjusted for model 2+urinary glucose. RCS was functioned with four knots.

Abbreviations: FBG, fasting blood glucose; SUA, serum uric acid; FEUA, fractional excretion of uric acid; RCS, restricted cubic spline.

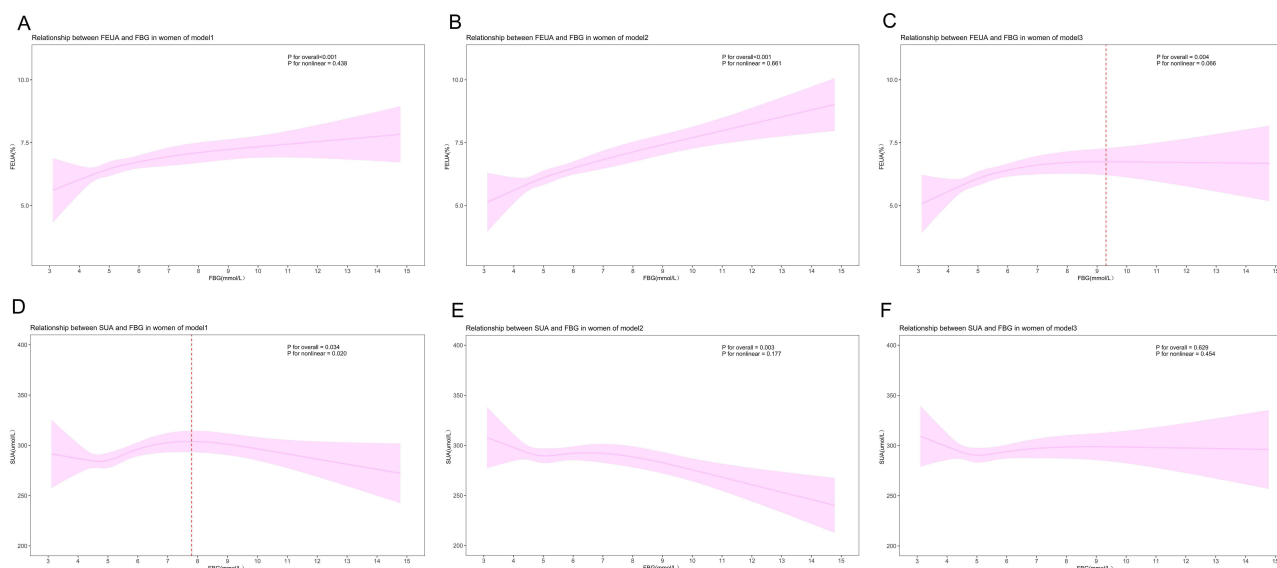


Figure 3 Association between FBG and FEUA or SUA in different models using RCS in women.

Notes: (A) relationship between FEUA and FBG in women of model 1; (B) relationship between FEUA and FBG in women of model 2; (C) relationship between FEUA and FBG in women of model 3; (D) relationship between SUA and FBG in women of model 1; (E) relationship between SUA and FBG in women of model 2; (F) relationship between SUA and FBG in women of model 3; Model 1: not adjusted; model 2: adjusted for age, body mass index, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, corrected serum sodium, urine pH and estimated glomerular filtration rate; model 3: adjusted for model 2+urinary glucose. RCS was functioned with four knots.

Abbreviations: FBG, fasting blood glucose; SUA, serum uric acid; FEUA, fractional excretion of uric acid. RCS, restricted cubic spline.

Discussion

Blood glucose and SUA are crucial indicators of human metabolism. The relationship between these factors has been extensively investigated. Studies^{4,11–14} suggest that with the increase in FBG levels, SUA levels rise until a certain threshold, after which they start to decrease. This inverted U-shaped pattern shows an association with urinary glucose

production. However, these studies did not analyze urinary glucose and the capacity for uric acid excretion, which can provide a comprehensive understanding of the relationship between uric acid and blood glucose.

After the exclusion of drugs affecting uric acid production and excretion and adjustment for related confounding factors, this cross-sectional study revealed that compared with other groups, men and women with diabetes exhibited the highest FEUA and the lowest SUA in the presence of urinary glucose after controlling for potential confounders. This finding aligns with those of previous research highlighting the pivotal role of urinary glucose in the promotion of uric acid excretion.^{5,11} Nevertheless, in cases lacking noticeable amounts of urinary glucose, the diabetes group retained a higher FEUA compared with the nondiabetes group. Furthermore, gender disparities were observed in relation to uric acid concentrations between these two groups. Without adjusting for confounders, the men and women cohorts both showed no statistically significant difference in terms of SUA between nondiabetes and diabetes without urinary glucose groups. After adjustments, the female subjects exhibited no substantial variation, whereas males with diabetes but without urinary glucose displayed significantly lower uric acid concentrations compared with their nondiabetic counterparts. These findings contest those of prior research that revealed a positive correlation between blood glucose elevation and increased uric acid concentrations in the absence of urinary glucose.^{4,12,13}

Additional regression and RCS analyses revealed that when the blood glucose reached about 9 mmol/L, urinary glucose was the main influencing factor of FEUA. At this point, the urinary glucose determined the increase in FEUA and the decrease in SUA levels. And after the adjustment for urinary glucose as a confounding factor, only minimal changes were observed in FEUA or SUA levels after this point. When blood glucose levels were insufficient to produce urinary glucose, FEUA still increased with the increase in FBG levels, but SUA levels showed a different trend. Before adjustment, an inverted U-shaped correlation between FBG and SUA levels was observed, with lower and higher glucose turning points detected in men and women, respectively, similar to the previous study.⁴ However, this inverted U-shaped relationship became less pronounced after the adjustment for confounding factors.

Over four decades ago, rat renal microperfusion tests revealed the improvement of uric acid excretion via glucose infusion.¹⁵ Recent genome-wide association studies have identified various uric acid transporters involved in its resorption and excretion processes.⁷ The majority of these transporters are predominantly located within the proximal renal tubule, with urate transporter 1 (URAT1) and glucose transporter 9 being particularly prominent. Glucose reabsorption primarily occurs within proximal renal tubules through transportation mediated by SGLT2 and SGLT1.¹⁶ However, no research has established any substantial correlation between glucose transporters and uric acid transporters. Instead, they revealed that elevated glucose levels within the renal tubules may hinder URAT1 receptor-mediated uric acid reabsorption.^{17,18} Our findings revealed a positive correlation between the presence of glucose in urine and an increase in FEUA and a decrease in uric acid levels, consistent with these results. Furthermore, our study unveiled that in the absence of glucosuria, the elevation in FEUA still showed an association with the rise in blood glucose levels, which highlights a previously overlooked aspect. This phenomenon can be plausibly explained by the unimpeded passage of glucose and uric acid through the glomerulus, with primary reabsorption occurring within the proximal tubule.⁷ Elevated blood glucose concentrations inevitably lead to heightened glucose levels within the renal tubule. Glucose reabsorption transpires in proximal renal tubular segments S1, S2, and S3,¹⁶ and the presence of glucose in the tubular fluid while awaiting absorption possibly influences uric acid reabsorption. Thus, the mechanism underlying increased uric acid excretion due to elevated blood glucose levels aligns with that in the presence of glucose in urine.

Prior to urinary glucose production, despite an increase in the FEUA with the rise in blood glucose levels, SUA levels revealed no significant decrease. This phenomenon can be attributed to the concurrent elevation in uric acid production. According to the analysis without adjusting for confounding factors, during the initial rise in blood glucose, the rate of uric acid production surpassed that of its excretion, which resulted in an upward branch on the inverted U-shaped curve. However, after adjustment, this upward trend was attenuated, which indicated the presence of additional variables that influence uric acid production among these confounders and the role of blood glucose in promoting uric acid production and excretion reached a balance. Furthermore, adjusting for confounding variables, the steeper slope between changes in FBG and FEUA suggests a simultaneous influence of these confounders on uric acid excretion. Previous studies have demonstrated higher SUA levels among individuals with diabetes or prediabetes without significant glucosuria compared with healthy subjects and these individuals often exhibit varied metabolic or dietary influences on the production and

excretion of uric acid.^{12,19–21} Commonly observed metabolic factors such as BMI, TG levels, and cholesterol levels were thought to interfere with the effect of FBG on SUA in our analysis. All above imply that elevated blood glucose plays no important role in increasing SUA levels.

SGLT2 inhibitors is widely utilized in clinical practice and has demonstrated efficacy in the treatment of type 2 diabetes, chronic kidney disease, and heart failure.²² In addition, these inhibitors exhibit a considerable uric acid-lowering effect primarily through glycosuria. This study compared diabetic patients with urinary glucose using SGLT2 inhibitors to those with urinary glucose due to hyperglycemia. The two groups exhibited no significant difference regarding FEUA and SUA levels, which indicates that the uric acid-lowering effect of SGLT2 inhibitors mainly comes from glycosuria. To date, no relevant studies have shown a direct effect of SGLT2 inhibitors on uric acid transporters.²³

This study encountered several limitations. First, this work is a cross-sectional observational research, and as such, the population's underlying disease characteristics and dietary patterns may show inconsistency. Despite efforts to exclude the influence of certain diseases and medications, the potential effects of other confounding factors cannot be completely eliminated. Second, the calculation of FEUA utilized morning urine samples rather than 24 h urine collections, which possibly introduced some instability. Moreover, this study encompassed a substantial time frame, and all test data were obtained daily from the clinical laboratory of the hospital center. These results were derived from single tests, which may be susceptible to potential laboratory errors. However, our medical testing center maintains stringent quality control measures and employs fully automated testing procedures, which mitigates such errors to a certain extent. Furthermore, we observed gender disparities in the association between blood glucose and SUA levels. Female patients have higher FEUA and lower SUA levels and there is a stronger linear relationship between SUA or FEUA and FBG levels in women after adjusting for confounding factors. However, these discrepancies remained inadequately elucidated. Consequently, separate analyses stratified by gender were performed to address this issue.

Conclusions

In summary, this study revealed higher FEUA and lower SUA levels in diabetic patients with urinary glucose compared with diabetic patients without urinary glucose and the nondiabetic population. Urinary glucose was a significant factor influencing urinary excretion of uric acid and SUA levels in the body. Furthermore, FEUA increased proportionally with elevated blood glucose levels, including cases where urinary glucose was absent. After the adjustment for potential confounding factors, the increase in blood glucose levels did not result in a corresponding rise in uric acid concentrations. Hyperglycemia is not considered a risk factor for hyperuricemia. However, once blood glucose levels surpassed a certain threshold leading to glucosuria, further elevation in FEUA was observed, accompanied with a subsequent reduction in SUA levels. Additionally, gender factors also have a certain impact on the relationship between SUA or FEUA and FBG levels. There is a stronger linear relationship between those indicators in women after adjusting for confounding factors.

Ethics Approval

Ethical approval was obtained from Qilu Hospital (Qingdao) of Shandong University ethical committee approval number KYLL-KS-2023163.

Disclosure

The authors declare no competing interests in this work.

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