Association Between Triglyceride-Glucose Index and Serum Uric Acid Levels: A Biochemical Study on Anthropometry in Non-Obese Type 2 Diabetes Mellitus Patients

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Purpose: The triglyceride–glucose index (TyG) is positively correlated with serum uric acid (SUA) in patients with type 2 diabetes mellitus (T2DM). However, whether this relationship exists in non-obese T2DM patients remains unknown. The study investigated the relationship between TyG and SUA in Chinese non-obese T2DM patients and examined the prognostic value of TyG in hyperuricemia (HUA).

Patients and Methods: In total, 719 T2DM patients who were not obese were enrolled from among those who visited the Hebei General Hospital. The patients were categorized into groups according to their SUA levels. The relationship between TyG and clinical parameters was examined through correlation analysis. To consider covariates and examine the independent impact of TyG on HUA, logistic regression was performed. The receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of TyG and homeostasis model assessment of insulin resistance (HOMA-IR) for HUA.

Results: The HUA prevalence was 12.10%. TyG was statistically different among the four SUA groups, with lower TyG levels in the Q1, Q2, and Q3 groups than that in the Q4 group. TyG was positively correlated with SUA ($r = 0.176$, $P < 0.001$). Logistic regression exhibited that TyG and SUA were independently correlated (OR = 2.427, 95% CI = 1.134-5.195, $P = 0.022$) even after adjustment for confounding factors. The ROC curve showed that the predictive value of TyG for HUA was higher than that of HOMA-IR ($AUROC = 0.613$, $P = 0.001$).

Conclusion: TyG was positively correlated with SUA in non-obese T2DM patients. TyG may better predict HUA in non-obese T2DM patients than HOMA-IR.

Keywords: type 2 diabetes mellitus, insulin resistance, uric acid, hyperuricemia, TyG, HOMA-IR, inflammation

Introduction

In the past decade, the prevalence of both hyperuricemia (HUA) and type 2 diabetes mellitus (T2DM) was increasing, and they are currently major public health concerns globally. T2DM is a chronic disease characterized by hyperglycemia with insulin resistance (IR) and relative insulin deficiency. HUA is a state in which serum uric acid (SUA) levels are elevated because of excessive production or insufficient excretion of uric acid (UA). Studies have shown that T2DM is closely related to HUA. Both these diseases are associated with chronic inflammation. Moreover, IR and obesity are the common risk factors for T2DM and HUA. Thus, understanding the relationship of HUA with IR and T2DM may be beneficial for investigating mechanisms underlying T2DM and HUA development.

The HUA–IR relationship has been investigated in populations with and without diabetes. In 53,477 adults, Tae et al showed that the homeostasis model assessment of IR (HOMA-IR) was independently and positively associated with SUA. In
2016, a meta-analysis of 16 cohort studies on the association between SUA and T2DM revealed that SUA was independently associated with T2DM, and IR developed with an increase in baseline SUA.\textsuperscript{18} Inflammation is considered a crucial link in the IR–HUA relationship.\textsuperscript{19} SUA may influence insulin signaling and induce IR under the action of inflammatory factors.\textsuperscript{20} On the other hand, IR can cause inflammation and indirectly promote HUA. Administration of anti-inflammatory intervention to insulin-resistant individuals reduces SUA levels.\textsuperscript{21} Although obese individuals are more likely to have IR and HUA, non-obese individuals, including those normal-weight and overweight, also have elevated SUA levels.\textsuperscript{22–24} Currently, few studies have investigated the IR–HUA relationship in non-obese people.

Several measurement methods have been used to evaluate IR, with the gold standard being the hyperinsulinemic-euglycemic clamp (HEC) technique. HEC is less used in clinical studies because it is time-consuming, labor-intensive, and invasive. HOMA-IR is the most commonly used clinical surrogate index. HOMA-IR is based on fasting insulin (FINS) and fasting plasma glucose (FPG) levels. HOMA-IR is susceptible to the effect of exogenous insulin, and uniform experimental methods are lacking. Therefore, some non-insulin-dependent IR-related indicators have been developed. In 2008, Simental-Mendía developed the triglyceride–glucose index (TyG) as a proxy for IR evaluation in apparently healthy people.\textsuperscript{25} Numerous investigations have demonstrated that TyG has an outstanding capability to predict IR.\textsuperscript{26,27} Compared with HEC and HOMA-IR, the detection of FPG and triglyceride (TG) levels for TyG calculation is inexpensive and easy to perform. Therefore, TyG has great potential for clinical application. Recent reports have suggested the important role of TyG as an IR indicator in metabolic and inflammatory conditions, such as T2DM and hypertension.\textsuperscript{30} In addition, TyG is used to study the HUA–IR relationship. TyG was discovered as an independent risk factor for elevated SUA in several investigations of the general population and hypertensive patients.\textsuperscript{33,34} Han et al was the first to use TyG to investigate the IR–HUA relationship in T2DM patients. They showed that TyG was positively correlated with SUA levels and that TyG had a predictive value for HUA, with an area under the receiver operating characteristic (ROC) curve (AUROC) of 0.693 and a cut-off value of 9.55.

Different from the Caucasian population, most Asian patients with T2DM are normal-weight and overweight. However, no specific study has explored the connection between TyG and HUA in non-obese T2DM patients. Therefore, we conducted this cross-sectional study to investigate the link between TyG and HUA in non-obese T2DM patients and to evaluate the predictive value of TyG for HUA.

**Methods**

**Participants**

All participants were selected from patients with T2DM who visited the Department of Endocrinology of Hebei General Hospital during December 2020–2021.

The subject inclusion criteria were as follows: 1) the diagnosis of T2DM was based on the latest American Diabetes Association guidelines for the diagnosis and treatment of diabetes;\textsuperscript{36} 2) all patients were aged ≥18 years and ≤80 years; 3) subjects had a body mass index (BMI) <28 kg/m\textsuperscript{2}, which met the Chinese diagnostic standard for non-obesity.\textsuperscript{37}

The subject exclusion criteria were as follows: 1) individuals with other types of diabetes, including type 1 diabetes, gestational diabetes, and other specific types of diabetes; 2) patients with acute complications of diabetes, such as hyperosmolar hyperglycemic syndrome, ketoacidosis, and hypoglycemia; 3) patients with a history of chronic kidney disease, severe hepatic or renal insufficiency, and those undertaking a uric acid-lowering therapy; 4) patients with severe cardiac diseases, acute cerebrovascular diseases, tumor, and psychosis.

The study was conducted in accordance with the Declaration of Helsinki, and the Ethics Committee of the Hebei General Hospital gave its clearance to this study (approval number: No. 387). All participants provided their signed informed consent forms before participating in the study. The participants’ information has been kept private.

**Data Collection**

Basic information about the patients was collected, which included their gender, age, the course of diabetes, medical history, and a history of drug application. The height, weight, and blood pressure (systolic/diastolic blood pressure, SBP/DBP) of the subjects were measured. For all patients, venous blood samples were collected after fasting them for 8–12 h to detect total protein (TP), albumin (ALB), aspartate transaminase (ALT), alanine transaminase (AST), blood urea
nitrIogen (BUN), serum creatinine (Scr), SUA, total cholesterol (TC), TG, high-density lipoprotein (HDL), low-density lipoprotein (LDL), 25-hydroxyvitamin D [25-(OH)D], FPG, glycated hemoglobin (HbA1c), and FINS. All patients underwent abdominal ultrasonography under a fasting state to confirm the presence of fatty liver (FL).

Definition
SUA >420 µmol/L in men and >360 µmol/L in women was used to define HUA. FL was defined as the echo enhancement of liver parenchyma with an attenuation of the posterior liver tissues and poor visualization of intrahepatic ductal structures on ultrasound. The estimated glomerular filtration rate (eGFR) was determined by using the following chronic kidney disease-epidemiology (CKD-EPI) formula.  

\[
BMI = \frac{weight(kg)}{(height(m))^2}
\]

\[HOMA-IR = \frac{FPG(mmol/L) \times FINS(\mu IU/mL)}{22.5}\]

\[TyG = \ln(FPG(mg/L) \times TG(mg/L)/2)\]

\[HOMA-\beta = \frac{FPG(mmol/L) - 3.5}{[FINS(\mu IU/mL)]}\]

\[TG/HDL = \frac{TG(mmol/L)}{HDL(mmol/L)}\]

Study Groups
The study patients were categorized into the following groups: Q1 (SUA <247.50 µmol/L), Q2 (247.50 ≤ SUA < 296.10 µmol/L), Q3 (296.10 ≤ SUA < 350.80 µmol/L), and Q4 (SUA ≥350.80 µmol/L) according to the SUA quartiles. In addition, all participants were split into either the hyperuricemia (HUA) group or the normal uric acid (NUA) group. According to the Chinese BMI classification standards, the patients were classified as non-overweight (BMI <24 kg/m²) or overweight (BMI ≥24 kg/m²).

The patients were also categorized into the FL group and non-FL (NFL) group based on the results of abdominal ultrasonography.

Statistical Analyses
SPSS 26.0 and GraphPad Prism 9.0 were used for the statistical analysis of the data. Continuous variables were tested for conformity to a normal distribution by Shapiro–Wilk test, with normally distributed variables, expressed as the mean ± standard deviation and non-normally distributed variables expressed as a median value (P25, P75). ANOVA test was applied to analyze the differences between groups for variables that conformed to a normal distribution with an equal variance between the groups. The Nonparametric test was applied to analyze the differences for variables that conformed to a normal distribution, but with an uneven variance between the groups and for variables that were not normally distributed. Categorical variables were presented as percentages and Chi-square tests were applied for the analysis of differences between the groups. Correlational analyses were performed to test the correlation between SUA and other indicators. Logistic regression analysis was performed to analyze whether TyG was independently correlated with HUA. The predictive powers of TyG and HOMA-IR for HUA were examined using ROC curves. A two-tailed distribution of \(P < 0.05\) was considered to indicate statistical significance.

Results
In total, 719 patients were included in this study, including 436 men and 283 women (median age: 58 years, BMI: 24.86 kg/m², and diabetes course: 8 years). Of all the participants, 12.10% had HUA.

Comparison of Clinical Parameters Among the Four SUA Groups
According to Table 1, no significant differences in age, BMI, SBP, DBP, diabetes course, TP, eGFR, TC, LDL, 25(OH)D, and HOMA-IR were observed among the SUA subgroups, whereas age, male proportion, BMI, ALB, ALT, AST, BUN, Scr, TG, HDL, FPG, HbA1c, HOMA-β, TyG, TG/HDL, and FL prevalence were different. Further pairwise comparisons of the Q1, Q2, and Q3 groups were made with the Q4 group, which was considered the control. Compared with the Q4 group, HDL and HbA1c in the Q1 group were higher, whereas BMI, ALB, ALT, AST, Scr, BUN, TG, HOMA-β, TyG, and TG/HDL were lower. Compared with the Q2 group, HDL and HbA1c were lower in the Q4 group, whereas BMI, AST, Scr, BUN, TG, TyG, and TG/HDL were higher. Moreover, Scr, BUN, TG, TyG, and TG/HDL were lower in the Q3 group than those in the Q4 group. The proportion of male patients and FL showed an upward trend among the four groups, but statistically significant differences were
### Table 1: Comparison of the Clinical Parameters of the 4 SUA Groups

<table>
<thead>
<tr>
<th>SUA Group</th>
<th>Q1 (SUA &lt;247.50 µmol/L)</th>
<th>Q2 (247.50 ≤SUA &lt;296.10 µmol/L)</th>
<th>Q3 (296.10 ≤SUA &lt;350.80 µmol/L)</th>
<th>Q4 (SUA ≥350.80 µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>179</td>
<td>180</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>Age, year</td>
<td>60.00(53.00, 67.00)</td>
<td>60.00(53.00, 67.00)</td>
<td>60.00(53.00, 67.00)</td>
<td>60.00(53.00, 67.00)</td>
</tr>
<tr>
<td>Male, n/%</td>
<td>79/44.13</td>
<td>101/56.11</td>
<td>134.00(122.00, 147.00)</td>
<td>134.00(122.00, 147.00)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>131.00(119.00, 143.00)</td>
<td>134.00(122.00, 147.00)</td>
<td>134.00(122.00, 147.00)</td>
<td>134.00(122.00, 147.00)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79.00(73.00, 87.00)</td>
<td>80.00(73.25, 88.00)</td>
<td>80.00(73.25, 88.00)</td>
<td>80.00(73.25, 88.00)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.22(22.48, 25.82)</td>
<td>24.45(22.66, 26.22)</td>
<td>24.45(22.66, 26.22)</td>
<td>24.45(22.66, 26.22)</td>
</tr>
<tr>
<td>Duration, year</td>
<td>8.00(3.00, 15.00)</td>
<td>10.00(3.25, 16.00)</td>
<td>10.00(3.25, 16.00)</td>
<td>10.00(3.25, 16.00)</td>
</tr>
<tr>
<td>TP, g/L</td>
<td>68.20(63.20, 72.60)</td>
<td>68.45(64.23, 72.80)</td>
<td>68.45(64.23, 72.80)</td>
<td>68.45(64.23, 72.80)</td>
</tr>
<tr>
<td>ALB, g/L</td>
<td>41.50(38.70, 43.80)</td>
<td>42.10(39.60, 44.20)</td>
<td>42.10(39.60, 44.20)</td>
<td>42.10(39.60, 44.20)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>16.70(13.50, 21.90)</td>
<td>17.20(13.43, 22.60)</td>
<td>17.20(13.43, 22.60)</td>
<td>17.20(13.43, 22.60)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>18.50(14.90, 21.30)</td>
<td>18.50(15.90, 22.43)</td>
<td>18.50(15.90, 22.43)</td>
<td>18.50(15.90, 22.43)</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>5.30(4.38, 6.35)</td>
<td>5.31(4.40, 6.30)</td>
<td>5.31(4.40, 6.30)</td>
<td>5.31(4.40, 6.30)</td>
</tr>
<tr>
<td>Scr, µmol/L</td>
<td>68.20(63.20, 72.60)</td>
<td>68.45(64.23, 72.80)</td>
<td>68.45(64.23, 72.80)</td>
<td>68.45(64.23, 72.80)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>97.80(92.28, 107.08)</td>
<td>96.74(89.48, 104.68)</td>
<td>96.74(89.48, 104.68)</td>
<td>96.74(89.48, 104.68)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.84(4.18, 5.56)</td>
<td>4.71(3.97, 5.62)</td>
<td>4.71(3.97, 5.62)</td>
<td>4.71(3.97, 5.62)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>18.60(13.50, 21.90)</td>
<td>17.20(13.43, 22.60)</td>
<td>17.20(13.43, 22.60)</td>
<td>17.20(13.43, 22.60)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.18(1.00, 1.38)</td>
<td>1.16(0.97, 1.31)</td>
<td>1.16(0.97, 1.31)</td>
<td>1.16(0.97, 1.31)</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.11(2.63, 3.73)</td>
<td>3.12(2.44, 3.83)</td>
<td>3.12(2.44, 3.83)</td>
<td>3.12(2.44, 3.83)</td>
</tr>
<tr>
<td>25(OH)D, ng/mL</td>
<td>17.29(13.30, 25.39)</td>
<td>18.79(14.21, 23.95)</td>
<td>18.79(14.21, 23.95)</td>
<td>18.79(14.21, 23.95)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>9.10(7.50, 11.00)</td>
<td>8.70(7.43, 10.70)</td>
<td>8.70(7.43, 10.70)</td>
<td>8.70(7.43, 10.70)</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>5.66(4.70, 12.31)</td>
<td>8.35(6.62, 11.33)</td>
<td>8.35(6.62, 11.33)</td>
<td>8.35(6.62, 11.33)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>7.25(1.42, 4.42)</td>
<td>2.44(1.34, 4.96)</td>
<td>2.44(1.34, 4.96)</td>
<td>2.44(1.34, 4.96)</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>24.18(10.23, 50.17)</td>
<td>28.81(13.33, 56.56)</td>
<td>28.81(13.33, 56.56)</td>
<td>28.81(13.33, 56.56)</td>
</tr>
<tr>
<td>TyG</td>
<td>7.42(6.74, 7.99)</td>
<td>7.56(7.07, 8.02)</td>
<td>7.56(7.07, 8.02)</td>
<td>7.56(7.07, 8.02)</td>
</tr>
<tr>
<td>TG/HDL</td>
<td>1.01(0.67, 1.43)</td>
<td>1.19(0.72, 1.69)</td>
<td>1.19(0.72, 1.69)</td>
<td>1.19(0.72, 1.69)</td>
</tr>
<tr>
<td>Fatty liver, n/%</td>
<td>76/42.46</td>
<td>95/52.78</td>
<td>95/52.78</td>
<td>95/52.78</td>
</tr>
</tbody>
</table>

(Continued)
observed only between the Q1, Q2, and Q4 groups. With increased SUA levels, the age decreased, and the patients in the Q1 and Q2 groups were noticeably older than those in the Q4 group.

**Comparison of TyG and HOMA-IR Between Male and Female Patients**

In the male patients, while no discernible difference in HOMA-IR was observed between the NUA and HUA groups, a higher TyG was observed in the HUA group than that in the NUA group. In the female participants, the HUA group had higher TyG and HOMA-IR than the NUA group (Figure 1).

**Comparison of SUA Between BMI and FL Subgroups**

Compared with the overweight group, the SUA levels were lower in the non-overweight group (Figure 2A). The SUA levels in the FL group were significantly higher than those in the NFL group (Figure 2B).

### Table 1 (Continued).

<table>
<thead>
<tr>
<th>SUA Group</th>
<th>Q1 (SUA &lt;247.50 µmol/L)</th>
<th>Q2 (247.50 ≤SUA &lt;296.10 µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td>2.80(1.86, 5.13)</td>
<td>3.20(1.86, 5.43)</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>37.96(21.25, 72.20)</td>
<td>34.30(20.22, 66.50)*a</td>
</tr>
<tr>
<td>TyG</td>
<td>7.53(7.08, 8.01)</td>
<td>7.83(7.24, 8.37)*a,b,c</td>
</tr>
<tr>
<td>TG/HDL</td>
<td>1.38(0.90, 2.33)</td>
<td>1.72(1.19, 1.89)*a,b,c</td>
</tr>
<tr>
<td>Fatty liver, n/%</td>
<td>110/61.11</td>
<td>120/66.67*ab</td>
</tr>
</tbody>
</table>

**Notes:** n, the number of patients in the SUA subgroups; *P < 0.05 among the SUA subgroups; ††P < 0.01 among the SUA subgroups; a,b,c Represent statistically significant differences among Q1, Q2, Q3, and Q4 groups, respectively.

**Abbreviations:** SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TR, total protein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; 25(OH)D, 25-hydroxyvitamin D; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta-cell function; TyG, triglyceride-glucose index.
Correlation Analysis of SUA with Other Indicators

According to Spearman correlation analysis, SUA was inversely related to age, HDL, FPG, and HbA1c and positively correlated with DBP, BMI, TP, ALB, ALT, AST, BUN, Scr, TG, HOMA-IR, HOMA-β, TyG, and TG/HDL. However, SUA was not correlated with SBP, diabetes course, eGFR, TC, LDL, and 25(OH)D (Table 2).

Regression Analysis of TyG and HUA

We tested whether TyG was independently associated with HUA by three models (Table 3). TyG was independently associated with HUA in all three models. Model 1 did not adjust for any confounding factors, and a 1-unit increase in

Table 2 Correlation Between the SUA and Other Factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>Variables</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>−0.155**</td>
<td>TC, mmol/L</td>
<td>0.016</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>0.041</td>
<td>TG, mmol/L</td>
<td>0.310**</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>0.081*</td>
<td>HDL, mmol/L</td>
<td>-0.216**</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.188**</td>
<td>LDL, mmol/L</td>
<td>-0.008</td>
</tr>
<tr>
<td>Duration, year</td>
<td>0.005</td>
<td>25(OH)D, ng/mL</td>
<td>0.027</td>
</tr>
<tr>
<td>TP, g/L</td>
<td>0.103*</td>
<td>HbA1c,%</td>
<td>-0.142**</td>
</tr>
<tr>
<td>ALB, g/L</td>
<td>0.139**</td>
<td>FPG, mmol/L</td>
<td>-0.090*</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>0.105*</td>
<td>HOMA-IR</td>
<td>0.161*</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>0.142**</td>
<td>HOMA-β</td>
<td>0.183*</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>0.133**</td>
<td>TyG</td>
<td>0.176**</td>
</tr>
<tr>
<td>Scr, μmol/L</td>
<td>0.339**</td>
<td>TG/HDL</td>
<td>0.337**</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>−0.069</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: *P < 0.05; **P < 0.01.

Abbreviations: SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TP, total protein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; 25(OH)D, 25-hydroxyvitamin D; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta-cell function; TyG, triglyceride-glucose index.
TyG was associated with a 67.40% increase in HUA prevalence (OR = 1.674, 95% CI 1.291–2.170). Age and gender were considered in Model 2, which demonstrated that a 1-unit increase in TyG increased HUA prevalence by 71.80% (OR = 1.718, 95% CI 1.302–2.267). Model 3 was further adjusted for BMI, ALB, ALT, AST, BUN, Scr, TG, HDL, FPG, HbA1c, and fatty liver based on Model 2, with a more than 2-fold increase in HUA prevalence for each unit increase in TyG (OR = 2.427, 95% CI 1.134–5.195).

ROC Curve of TyG and HOMA-IR for HUA

We further analyzed the diagnostic value of TyG for HUA through ROC curve analysis and compared it with that of HOMA-IR. As shown in Figure 3 and Table 4, in all T2DM patients, the AUROC for TyG was 0.613 (95% CI 0.680–7.880) with a cut-off value of 7.880. The AUROC for TyG was 0.619 (95% CI 0.715–7.880) in the male patients, with a cut-off value of 7.880, while in the female patients, the AUROC for TyG was 0.615 (95% CI 0.707–8.040), with a cut-off value of 8.040. The AUROCs for HOMA-IR in all participants and the male patients were 0.574 (95% CI 0.502–0.646) and 0.512 (95% CI 0.410–0.603), respectively, with \( P > 0.05 \). In the female patients, HOMA-IR had a predictive value for HUA, with an AUROC of 0.623 (95% CI 0.523–0.719).

Table 3 Logistic Regression Analysis of TyG and HUA

<table>
<thead>
<tr>
<th>Model</th>
<th>OR</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model1</td>
<td>1.674</td>
<td>1.291</td>
<td>2.170</td>
<td>0.000</td>
</tr>
<tr>
<td>Model2</td>
<td>1.718</td>
<td>1.302</td>
<td>2.267</td>
<td>0.000</td>
</tr>
<tr>
<td>Model3</td>
<td>2.427</td>
<td>1.134</td>
<td>5.195</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Notes: Model 1 was a rough model. Model 2 was adjusted for age and gender. Model 3 was further adjusted for BMI, ALB, ALT, AST, BUN, Scr, TG, HDL, FPG, HbA1c, and fatty liver on the basis of Model 2.

Abbreviations: TyG, triglyceride-glucose index; HUA, hyperuricemia; BMI, body mass index; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine; TG, triglyceride; HDL, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose.
Discussion

This is the first study reporting the correlation between TyG and SUA in non-obese T2DM patients. We found that TyG was considerably greater in the Q4 group than that in the Q1, Q2, and Q3 groups. TyG was also markedly higher in the HUA group than that in the NUA group. Further analysis revealed that TyG was a risk factor for HUA in non-obese T2DM patients, independent of sex, age, BMI, ALB, ALT, AST, BUN, Scr, TG, HDL, FPG, HbA1c, and FL. Moreover, TyG had a predictive value for HUA, with an AUROC of 0.613 and a cut-off value of 7.880.

The association between IR and HUA has been investigated in several studies. In a cross-sectional study involving a population with an average BMI of 28.52 kg/m², Mohsen et al³⁹ revealed that HOMA-IR and TyG were strongly and positively correlated with SUA. Obesity, including higher BMI, waist circumference, and visceral fat, was thought to mediate SUA and IR. Wu et al⁴⁰ explored the relationship between SUA, IR, and insulin secretion in prediabetes individuals. However, they did not collect BMI data. The study showed that HOMA-IR was independently positively correlated with SUA in prediabetes individuals (OR = 2.017, \( P < 0.01 \)). Furthermore, the IR–HUA relationship has been demonstrated in T2DM patients. A case-control study by Li et al⁴¹ enrolled 90 elderly patients with T2DM, 49 of whom had BMI ≥ 25 kg/m². The study revealed that SUA was positively correlated with BMI and HOMA-IR. A Chinese study explored the association of four IR indicators, namely TyG, TyG-BMI, TG/HDL, and METS-IR, with HUA in T2DM patients.³⁵ Based on SUA levels, all participants were divided into three groups and the average BMI of the groups was >25 kg/m². The study reported that the four indicators were all independently correlated with HUA. The AUROC for TyG predicting HUA was 0.693 with a cut-off value of 9.55. However, none of these aforementioned studies specifically investigated non-obese T2DM patients, who are more common among the Asian diabetic population. Therefore, the present study investigated the association of SUA with IR in non-obese T2DM patients. Compared with HOMA-IR, TyG is inexpensive and readily available and is not affected by insulin therapy. Therefore, TyG was used for evaluating IR in our study. According to the results, TyG was independently associated with HUA, which was consistent with Han’s study. However, TyG had a weaker predictive power than that reported in Han’s study. This may be because of the difference in the characteristics of our study population. The participants in Han’s study were mostly overweight or obese, whereas our study focused on non-obese patients with T2DM. Furthermore, we compared the predictive ability of TyG and HOMA-IR for HUA; TyG had a stronger ability to recognize HUA.

The causal relationship between IR and HUA is controversial. Several studies have indicated that HUA may underlie IR, while some studies have shown that HUA can appear before IR.⁴²,⁴³ Krishnan et al followed 5012 young American patients for 15 years and found that those with HUA were 1.36 times more likely to have IR than those without HUA. Zhu et al⁴⁴ examined the effect of HUA on IR using an HUA model mouse and HepG2 cells. According to that study, HUA can inhibit insulin signal transduction and lead to IR, which was associated with inflammation and oxidative stress. However, considerable findings have suggested that IR contributes to HUA. In 2021, McCormick et al⁴⁵ published a two-way Mendelian randomization study on HUA and IR. Through their analysis of single-nucleotide polymorphisms associated with SUA, gout, and insulin, they found that genetically determined FINS was positively and independently correlated with SUA, whereas no correlation was noted between genetically determined SUA and FINS. Moreover, HOMA-IR can independently predict HUA.

### Table 4 The Diagnostic Value of TyG and HOMA-IR for HUA in Non-Obese Patients with T2DM

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>95% CI</th>
<th>( P )</th>
<th>Cut-Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>TyG</td>
<td>0.613</td>
<td>0.547–0.680</td>
<td>0.001</td>
<td>7.880</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.574</td>
<td>0.502–0.646</td>
<td>0.064</td>
<td>2.880</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>TyG</td>
<td>0.552</td>
<td>0.676</td>
<td>0.228</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.627</td>
<td>0.523</td>
<td>0.150</td>
</tr>
</tbody>
</table>

Abbreviations: TyG, triglyceride-glucose index; HOMA-IR, homeostasis assessment of insulin resistance.
incidence within 6 years in young and middle-aged Japanese men.\textsuperscript{46} In Nakamura's study, relative to the lowest quartile of HOMA-IR, HUA incidence in the highest quartile increased by 44%. IR may contribute to elevated SUA levels through several mechanisms. First, UA reabsorption was increased in response to insulin regulation of regulating urate transporter 1 (URAT-1) and ATP-binding cassette subfamily G member 2 (ABCG2).\textsuperscript{47} Second, IR disrupts oxidative phosphate and leads to increased adenosine levels. Adenosine has a sodium retention effect and therefore reduces UA excretion.\textsuperscript{41} Third, under the IR state, intermediates of glycolysis and pentose phosphate processes can be converted to ribose pyrophosphate and 5-ribose phosphate, thereby increasing SUA production.\textsuperscript{48} Moreover, IR can amplify inflammatory cascades and lead to liver dysfunction. Liver dysfunction is associated with high xanthine oxidoreductase activity, which then leads to increased UA production.\textsuperscript{49} Our study results showed that in non-obese individuals with T2DM, TyG was a risk factor for HUA, independent of sex, age, BMI, lipid parameters, FPG, HbA1c, and FL. The finding implies that IR contributes to SUA elevation.

Although obesity is strongly associated with IR, IR is undeniably present in non-obese individuals. This may be because of the underlying visceral obesity. Visceral obesity refers to excess adipose tissue deposited in the abdominal organ. Asians are more likely to develop visceral obesity with only a normal or overweight BMI.\textsuperscript{50} FL is a common manifestation of visceral obesity. In our study, FL incidence increased among SUA quartile groups in non-obese T2DM patients. In addition, the FL group showed higher SUA levels than the NFL group. These results are consistent with those of several previous studies. Liu et al showed that the effect of visceral obesity on SUA was more pronounced than that of general obesity.\textsuperscript{51} In T2DM patients, HUA is positively correlated with central body fat distribution, particularly visceral adipose tissue.\textsuperscript{52} The increased SUA level may be related to visceral adipose inflammation induced IR.\textsuperscript{53} Sun et al\textsuperscript{54} showed that adipose tissue IR (Adipo-IR), HOMA-IR, and SUA were closely related. However, HOMR-IR was not correlated with HUA in men with a normal BMI (18.5 kg/m\textsuperscript{2} ≤ BMI < 24 kg/m\textsuperscript{2}). Interestingly, our results also showed that TyG, but not HOMA-IR, was strongly correlated with SUA in non-obese T2DM patients. This may be because HOMA-IR mainly reflects glucose metabolism, while TyG is an index based on a combination of FPG and TG. Thus, TyG reflects the condition of both glucose and lipid metabolism.

Furthermore, the proportion of men in the Q1, Q2, and Q3 groups was lower than that in the Q4 group, which is consistent with the results of previous studies.\textsuperscript{55-57} Men are more susceptible to HUA than women. First, men and women differ in sex hormone production and skeletal muscle content.\textsuperscript{58,59} Moreover, differences in dietary habits, commuting modes, and physical activities between men and women may act as potential factors affecting HUA prevalence.\textsuperscript{60}

TG levels in our study exhibited an obvious upward trend among the four SUA subgroups. TG was positively associated with SUA; this result is consistent with those of previous studies.\textsuperscript{61,62} Some studies from different geographical regions of China have found higher TG to be associated with higher SUA.\textsuperscript{63,64} Qiu et al\textsuperscript{64} found a 3.3-fold elevated HUA risk in participants with TG ≥ 5.65 mmol/L compared with those with TG < 1.69 mmol/L. Diet may partly mediate the simultaneous elevation of TG and SUA.\textsuperscript{55} In addition, TG synthesis requires NADPH as the reducing molecule of the fatty acid synthase complex, which is mainly produced in the pentose phosphate metabolic pathway. Hypertriglyceridemia may be accompanied by an upregulated pentose phosphate pathway and therefore a concomitant increase in SUA synthesis.\textsuperscript{66}

Our study showed that the Q1 and Q2 groups comprised older adults than the Q4 group. Moreover, SUA was negatively correlated with age in our study. However, most studies suggest a positive correlation between SUA and age, and it is thought to be associated with the deterioration of renal function. The renal function decreases by 10% for every 10 years of age after 40 years of age.\textsuperscript{67} Therefore, older patients are at a significantly higher risk of HUA. Our study result was different from the results of previous research possibly because the patients enrolled in the present study are at the median in the CKD I phase (median eGFR: >90 mL/min/1.73 m\textsuperscript{2}). We excluded patients with severe renal insufficiency when screening the participants. Although the median participant age in all four SUA groups was >50 years, no between-group differences were observed in eGFR. Thus, group differences in SUA may be more related to the UA amount generated in the body, including factors such as diet and metabolism, but not renal function.

This was the first study investigating the relationship between SUA and TyG in non-obese T2DM. In non-obese T2DM patients, TyG was positively correlated with SUA and the predictive value of TyG for HUA was better than that of
HOMA-IR. In addition, because of the lack of stability of HOMA-IR calculation and its susceptibility to exogenous insulin, the clinical value of TyG in disease monitoring and prevention is non-neglectable. Improving IR may be a crucial target for HUA treatment and prevention in non-obese T2DM patients. This study also had some shortcomings. First, the study was cross-sectional and could not provide a definitive causal association between IR and HUA. Second, this study included patients from a single clinical institution, and thus, the results might not apply to other populations. Third, SUA was derived from a single blood sample and only reflects UA levels within an individual at a certain time point. Fourth, factors affecting UA levels, including physical activity and dietary habits, were not considered in our study. Therefore, further investigations are required for a better understanding of the relationship between IR and SUA.

Conclusion
For non-obese T2DM patients, TyG was an independent risk factor for elevated SUA. In addition, TyG was found to be an inexpensive and readily available index for IR evaluation. The predictive value of TyG for HUA was higher than that of HOMA-IR.

Disclosure
The authors report no conflicts of interest in this work.

References


