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The triglyceride glucose index can predict newly diagnosed biopsy-proven diabetic nephropathy in type 2 diabetes

A nested case control study

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Abstract

Insulin resistance is usually a key factor in the development of type 2 diabetes. The triglyceride glucose (TyG) index is a marker of insulin resistance which is also implicated in the risk of nephropathy among people with type 2 diabetes. This study aimed to examine associations and potential thresholds between TyG index and the risk of newly diagnosed biopsy-proven diabetic nephropathy in people with type 2 diabetes. A nested case–control study incorporating 950 incident biopsy-proven diabetic nephropathy cases and age, gender matched 4750 patients with treated type 2 diabetes as controls selected by risk-set sampling method was implemented. The dose–response association between TyG index with subsequent risk of newly diagnosed biopsy-proven diabetic nephropathy after adjustment for age, gender, blood pressure, and other major cardiovascular risk factors were examined by conditional logistic regression model. A non-linear relationship was identified between TyG index and the risk of newly diagnosed biopsy-proven diabetic nephropathy with a potential threshold of TyG at 9.05–9.09. Similar relationships with the same threshold were also found in the analyses by fasting glucose and triglyceride levels. TyG index might be a prognostic factor in predicting newly development of biopsy-proven diabetic nephropathy among patients with treated type 2 diabetes. In people with type 2 diabetes, TyG index above 9.05–9.09 could be a prognostic threshold to identify individuals at high risk of diabetic nephropathy. Further replication studies are warranted.

Abbreviations: DN = diabetic nephropathy, eGFR = estimated glomerular filtration rate, HOMA-IR = homeostasis model assessment of insulin resistance, IR = insulin resistance, TyG = triglyceride glucose index, UKPDS = UK Prospective Diabetes Study.

Keywords: diabetes, diabetic nephropathy, insulin resistance, prognosis, TyG index

1. Introduction

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease in patients initialising renal replacement therapy, and is associated with increased cardiovascular mortality.[1,2] In the UK Prospective Diabetes Study (UKPDS), the randomized controlled trial of glycemic management of newly diagnosed type 2 diabetes, the annual incidence of clinically diagnosed DN was 2.0% with a 10-year prevalence of 25%.[3] DN is more common in Asian populations.[4] It has been estimated that in the 1990s, DN doubled as an indication for initializing renal replacement therapy.[5]

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JS and DY are the first authors.

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Insulin resistance (IR) has been reported to be associated with an increased risk of developing progressive DN among patients with diabetes, but only in cross-sectional studies.[6,7] Some prospective studies have also reported that IR may precede and predict microalbuminuria in patients with diabetes.[8] Furthermore, the frequency of factors associated with IR, like hypertension, central obesity, and dyslipidaemia also increase as DN progresses.[6] However, prospective studies demonstrating that IR contributes to the development and progression of DN in type 2 diabetes are yet to be reported, probably due to the cost of insulin measurement and required study duration.

Several recent studies have shown that the triglyceride glucose (TyG) index is associated with IR,[9,10] assessed by both hyperinsulinemic euglycemic clamp testing and homeostasis model assessment of insulin resistance (HOMA-IR). The clamp is considered as the gold standard method for measuring IR.[12] But the clamp method is complex and not used in clinical practice, as it involves a primed-continuous infusion of insulin administered to raise the plasma insulin concentration to a predetermined physiological or pharmacological level. The plasma glucose concentration is then measured at 5-min intervals with a variable infusion of exogenous glucose administered to maintain the plasma glucose concentration constant at the fasting level. Since the plasma glucose concentration remains unchanged, the amount of exogenous glucose infused must equal the amount of glucose utilized in response to the hyperinsulinemia and, thus, provides a direct measure of whole-body sensitivity to insulin.[11]

The other, more widely used HOMA-IR is calculated as (fasting plasma insulin level [in μU/mL] × fasting plasma glucose level [in mmol/L])/22.5. A value of 1.00 is considered normal and higher values indicate progressively severe states of IR. This method is much more variable than the clamp due to the wide range of "normal" values for fasting plasma insulin. Also, it cannot be used in patients with diabetes, where the normal homeostatic relationship between plasma glucose and insulin levels no longer exists. It has theoretical limitations based on the fact that it attempts to measure insulin sensitivity in the fasting state when the majority of glucose uptake is independent of insulin. Thus, the TyG index has shown direct correlation with IR and been proposed as a reliable and simple surrogate marker of IR in clinical practice.[13,14]

Consistent with these data, there is growing evidence to suggest that the TyG index is associated with cardiovascular disease.[15–17] However, to the best of our knowledge, few studies have examined the relationship between the TyG index and the risk of development of DN among patients with type 2 diabetes. Therefore, in the present study, we have investigated the relationship between the TyG index and risk of newly diagnosed biopsy-proven DN among patients with type 2 diabetes.

2. Materials and methods

2.1. Data setting

We conducted this nested case–control study in Zhengzhou, Henan, China, which has 109 million residents. Both cases and controls were enrolled in the First Affiliated Hospital, Zhengzhou University, which is the largest hospital in China and provides both primary and secondary care to Henan residents. Health insurance coverage has been 90% since 2008, allowing most patients with DN to be diagnosed during a hospital admission. As the provincial renal center, most renal biopsies among patients with diabetes were processed in the hospital.

2.2. Case definition

A total of 950 patients with type 2 diabetes who were newly diagnosed with DN at the First Affiliated Hospital, Zhengzhou University between February 1, 2012 and February 28, 2018 were included in this study. The diagnosis of diabetes for cases and controls was based on the American Diabetes Association criteria.[18] The diagnosis of DN was made based on histological characteristics, such as glomerular hypertrophy, thickened capillary basement membranes, diffuse mesangial expansion (sclerosis), nodular mesangial sclerosis, exudative lesions such as capsular drop or fibrin cap, mesangiolysis, mescapillary microaneurysm, or hyalinosis of afferent and efferent arterioles, using appropriate standard for renal biopsy including light microscopy, electron microscopy, and immunofluorescence examination.[9] Patients with other glomerular diseases concomitant with DN were excluded from this study. Renal biopsy was performed for precise diagnosis of renal lesions with the consent of each patient.

2.3. Matched controls

We used the inpatient administration system to select 5 controls for each case, matched for age and gender. Controls were patients with type 2 diabetes who attended outpatient departments or were admitted to the hospital between January 1, 2016 and December 31, 2017. Patients with estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 and urine total protein >30 mg/24 h were excluded.[9,19] Controls were selected using a risk set sampling method,[10] by which the odds ratios estimated the incidence rates ratios. Controls were assigned an index date identical to that of corresponding cases.

2.4. Exposure definition

TyG index was calculated as the ln[fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2].[20] In the dose–response analysis between TyG and risk of DN, TyG was treated as continuous variable. To understand the outcome distribution further, a histogram is shown of incidence rates ratios of outcome by TyG quartile group (Supplemental Figure S1, http://links.lww.com/MD/D371): Group 1 (TyG index <8.60), Group 2 (TyG index in 8.60–9.09); Group 3 (TyG index in 9.09–9.60), and Group 4 (TyG index ≥ 9.60).

2.5. Ethics approval

Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants before inclusion.

2.6. Co-variables and missing information

There was missing information on body mass index (56.2%), systolic blood pressure (37.4%), diastolic blood pressure (38.2%), fasting glucose (6.1%), HbA1c (6.7%), hematocrit (13.6%), mean corpuscular hemoglobin (13.6%), mean platelet volume (13.6%), monocyte (13.6%), red blood cell distribution width (13.6%), magnesium (22.1%), sodium (22.1%), chlorine (22.1%), activated partial thromboplastin time (32.8%), D-Dimer (32.8%), thrombin time (32.8%), fibrinogen (32.8%), and fibrinogen degradation products (32.8%). Multiple imputations were applied to replace missing values by using a chained

equation method based on all candidate predictors and primary outcome. Fifty-six imputed datasets were generated for missing predictors that were then combined across all datasets by using Rubin's rule to generate final model estimates.[21]

2.7. Statistical analysis

In descriptive analyses, differences in participant characteristics by TyG index categories were assessed by logistic regression model for categorical variables, and generalized linear model for continuous variables.

Newly diagnosed biopsy-proven DN was defined as a binary outcome measure. A conditional logistic regression model was used to estimate the crude and adjusted incidence rates ratios of newly diagnosed biopsy-proven DN by TyG index categories. The dose–response relationships between TyG index and risks of newly diagnosed biopsy-proven DN were estimated using a linear model, a natural cubic spline model with three equally spaced knots determined from the levels of TyG index measures, and a quadratic spline model. The natural cubic spline model was chosen as the best fit model for the relationship curve by its minimum Akaike information criterion (AIC) compared with the linear model or quadratic spline model. The linear test was used in the natural cubic spline model to test the linearity of the relationship. The break-point test[22] was carried out to target the potential thresholds (P_5 to P_{95} of TyG index measures) by incorporating the piecewise term into the cubic spline model. The threshold with a significant break in the regression coefficients and achieving the minimum AIC was chosen as the final threshold.[23] The 95% CI of the threshold was obtained from 1000 bootstrap samples. The associations between the TyG index and the risk of newly diagnosed biopsy-proven DN below and above the threshold were analysed such that the TyG index was treated as a continuous variable to observe the risk of DN with each 1 unit increase of the TyG index.

In the sensitivity analyses, the dose–response association between the TyG index and risk of DN was re-analyzed by the level of confounders (glucose and triglyceride) to examine whether the dose–response associations were consistent with those found in the main analyses. At each level of confounders, we also quantified the association between TyG index and risk of DN below and above threshold.

All analyses were performed using STATA (STATA/MP 15.0 StataCorp, College Station, TX). All *P* values were calculated using two-tailed tests and a P value $< .05$ was taken to indicate statistical significance. All methods were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3. Results

Potential prognostic factors measured in cases and controls are shown in Table 1. Cases with newly diagnosed biopsy-proven DN had lower levels of hemoglobin, mean corpuscular hemoglobin, lymphocyte, monocyte, total bile acid, high density lipoprotein cholesterol, calcium, carbon dioxide combining power and eGFR, and higher levels of the remaining factors.

A non-linear ("J-shape") relationship was found between TyG index and risk of development of newly diagnosed biopsy-proven DN (*P*-values for linearity test $< .0001$). The dose–response relationship was derived from the natural cubic spline model with adjustment of covariables in Figure 1. In the sensitivity analysis modeling the associations with fasting glucose and serum triglyceride (fasting glucose <8.0 mmol/L and fasting glucose ≥ 8.0 mmol/L; triglyceride <1.5 mmol/L and triglyceride ≥ 1.5 mmol/L), similar dose–response relationships were identified by fasting glucose level (Figure 1) and by serum triglyceride level (Figure 2). The individual-level incidence rates ratio distribution in four TyG categories based on the quartile of TyG (Group-1: TyG ≤ 8.60; Group-2: TyG $8.60 <$ TyG ≤ 9.09; Group-3: $9.09 <$ TyG ≤ 9.60; and Group-4: TyG > 9.60) were presented in Supplemental Figure S1, http://links.lww.com/MD/D371, which indicated most patients' incidence rates ratio covering the estimated range of risk of DN shown in Figure 1.

A TyG index below 9.07 (95% confidence interval: 9.05–9.09) was estimated to be associated with the lowest risk of newly diagnosed biopsy-proven DN, as tested by linear threshold models. The thresholds were the same with fasting glucose levels and serum triglyceride levels. Table 2 shows that the risks of newly diagnosed biopsy-proven DN increase significantly with each 1 unit increase of TyG index above the TyG threshold (9.07) overall and by glucose and triglyceride levels (except triglyceride <1.5 mmol/L): adjusted incidence rates ratio (IRR) per TyG index unit for risk of newly diagnosed biopsy-proven DN 1.56 (95% CI: 1.27–1.91, $P < .0001$) overall; adjusted IRR for risk of newly diagnosed biopsy-proven DN 1.50 (1.09–2.06, $P < .0001$) in those with glucose <8.0 mmol/L and 2.06 (1.01–4.20, $P < .0001$)) in those with glucose $\geq$ 8.0 mmol/L; adjusted IRR for risk of newly diagnosed biopsy-proven DN 0.99 (0.41–2.40, $P = .3562$) in those with triglyceride <1.5 mmol/L and 1.92 (1.10–3.34, $P < .0001$) in those with triglyceride $\geq$ 1.5 mmol/L. The risks of newly diagnosed biopsy-proven DN did not increase significantly with 1 unit increase of TyG index above the TyG threshold overall and by glucose and triglyceride levels (Table 2).

4. Discussion

Our study was undertaken to relate TyG index, as a measure of insulin resistance, to the risks of newly diagnosed biopsy-proven DN in patients with type 2 diabetes. We focused our investigation on the dose–response relationships assessing the evidence for a nonlinear association, and for the existence of a threshold. In all our analyses, we found evidence that the associations are nonlinear. Threshold analysis provided evidence of a TyG index threshold: 9.07 (9.05–9.09). The significantly higher risks of newly diagnosed biopsy-proven DN were found above 9.07 of TyG index in people with type 2 diabetes.

Our investigation is the first study to explore the association between TyG index, as a surrogate for IR and the risk of newly diagnosed biopsy-proven DN in people with type 2 diabetes. In previous reports, a high TyG index had been found to be associated with the risk of type 2 diabetes in the general population,[24] with subclinical atherosclerosis and arterial stiffness in postmenopausal women[25] and with the risk of other diabetes related complications, such as coronary artery stenosis[26] and Cardiac Autonomic Neuropathy.[27] Consistent with these previous findings, we have found that a high TyG index (in particular TyG index $\geq$ 9.07) is associated with a high risk of DN, which is the leading cause of end-stage renal disease in people with type 2 diabetes.

Non-linear dose–response relationships between TyG index and non-DN outcomes have previously been shown. For example, among patients with type 2 diabetes, a previous study was found that compared with patients with TyG index at 8.2,

Table 1

Clinical measurements among diabetic nephropathy cases and matched controls with type 2 diabetes.

	Case	Control	*P*
N	950	4750	–
Female gender, n (%)	446 (46.91)	2230 (46.91)	–
Age (years)	64 (55–73)	64 (54–72)	–
Body mass index (kg/m^2)	25.4 (23.1–28.6)	23.4 (20.8–25.0)	.0001
Systolic blood pressure (mm Hg)	140.0 (131.5–147.1)	130.7 (123.0–138.9)	.0001
Diastolic blood pressure (mm Hg)	79.0 (74.1–83.5)	76.3 (72.0–80.1)	.0001
Antihypertensive treatment, n (%)	335 (35.3)	798 (16.8)	.0001
Lowering lipid treatment, n (%)	113 (11.9)	508 (10.7)	*.5263*
Insulin treatment, n (%)	797 (83.9)	3268 (68.8)	.0001
HbA1c (%)	7.76 (6.60–9.06)	7.40 (6.27–8.62)	.0001
Alanine transaminase (U/L)	39.90 (22.70–157.71)	35.00 (29.30–40.60)	.0001
Alkaline phosphatase (IU/L)	78.87 (53.00–115.98)	78.50 (60.50–105.33)	.0001
Activated partial thromboplastin time (s)	31.15 (27.60–35.80)	30.10 (26.40–34.68)	.0001
Direct bilirubin (μmol/L)	4.62 (1.30–14.38)	3.60 (2.17–6.90)	.0001
Basophil (%)	0.04 (0.02–0.05)	0.03 (0.02–0.05)	.0001
Cholinesterase (U/L)	8.80 (1.97–33.26)	5.60 (1.58–18.08)	.0001
Calcium (mmol/L)	2.16 (2.05–2.28)	2.24 (2.12–2.34)	.0001
Chlorine (mmol/L)	102.00 (98.50–105.50)	101.88 (98.38–105.00)	.0001
Creatinine (μmol/L)	159.00 (109.40–355.00)	63.00 (11.19–135.59)	.0001
C reaction protein (mg/L)	22.81 (1.49–58.14)	21.06 (3.23–54.39)	.0001
Cysteine proteinase inhibitor	2.18 (1.38–3.34)	0.91 (0.21–1.64)	.0001
D_Dimer (μg/mL)	1.20 (0.69–2.16)	0.46 (0.09–2.22)	.0001
Fibrinogen degradation products (mg/L)	5.72 (1.16–12.03)	3.26 (1.74–4.22)	.0001
Fibrinogen (g/L)	3.90 (3.15–4.66)	3.44 (2.74–4.22)	.0001
Gamma glutamyl transpeptidase (U/L)	35.00 (13.00–91.80)	29.50 (17.00–61.00)	.0001
Globulin (g/L)	26.47 (22.82–30.30)	25.85 (22.20–29.60)	.0001
Glucose (mmol/L)	7.98 (5.51–11.22)	7.89 (5.63–10.90)	.0001
High density lipoprotein cholesterol (mmol/L)	0.97 (0.74–1.21)	1.04 (0.82–1.30)	.0001
Hemoglobin (g/L)	101.00 (84.98–117.00)	119.00 (102.92–134.00)	.0001
Hematocrit (%)	18.94 (3.80–29.00)	11.15 (3.80–2.346)	.0001
Indirect Bilirubin (μmol/L)	5.24 (2.74–8.80)	3.40 (2.00–5.70)	.0001
Potassium (mmol/L)	4.34 (3.95–4.80)	4.20 (3.77–4.62)	.0001
Low density lipoprotein cholesterol (mmol/L)	2.50 (1.75–3.33)	2.47 (1.72–3.26)	.0001
Lymphocyte (%)	1.56 (1.04–2.10)	1.30 (0.83–1.85)	.0001
Mean corpuscular hemoglobin concentration (g/L)	326.75 (320.85–333.00)	329.44 (323.00–337.00)	.0001
Mean corpuscular volume (fL)	90.60 (85.99–95.10)	90.40 (86.30–94.23)	.0001
Magnesium (mmol/L)	0.95 (0.86–1.06)	0.91 (0.81–1.01)	.0001
Mean platelet volume (fL)	8.90 (8.10–9.80)	8.83 (8.00–9.70)	.0001
Monocytes (%)	0.59 (0.25–1.05)	0.56 (0.17–1.07)	.0001
Sodium (mmol/L)	141.45 (138.35–144.37)	140.60 (137.60–143.23)	.0001
Neutrophil (%)	6.70 (4.26–9.68)	5.56 (3.15–8.31)	.0001
Phosphorus (mmol/L)	1.24 (1.05–1.47)	1.11 (0.90–1.31)	.0001
Procalcitonin (ng/mL)	1.19 (0.10–1.42)	1.17 (0.27–1.86)	.0001
Red blood cell (10^{12}/L)	3.89 (1.00–10.99)	3.67 (2.67–10.05)	.0001
Red blood cell distribution width (%)	14.60 (13.60–15.90)	13.94 (13.00–15.37)	.0001
Total cholesterol (mmol/L)	4.12 (3.21–5.13)	4.05 (3.16–5.01)	.0001
Total bile acid (μmol/L)	5.69 (2.37–17.67)	4.10 (1.04–13.82)	.0001
Total bilirubin (μmol/L)	10.14 (4.31–22.45)	7.55 (4.50–13.10)	.0001
Triglyceride (mmol/L)	1.71 (1.06–2.67)	1.63 (0.89–2.62)	.0001
Thyroid-stimulating hormone (μIU/mL)	2.62 (0.38–5.60)	2.25 (0.08–5.31)	.0001
Urine acid (μmol/L)	351.00 (278.40–435.28)	250.99 (179.79–328.00)	.0001
Thrombin time (s)	15.30 (13.58–17.70)	14.60 (12.32–17.32)	.0001
Urea (mmol/L)	11.70 (7.85–18.30)	5.10 (2.45–8.07)	.0001
White blood cell count (10^9/L)	7.99 (5.00–16.14)	6.40 (1.98–21.00)	.0001
estimated glomerular filtration rate (mL/min/1.73 m^2)	35.79 (14.35–53.42)	94.93 (90.17–108.39)	.0001
Carbon dioxide combining power (mmol/L)	23.00 (20.40–25.65)	24.81 (22.20–27.33)	.0001
Urine total protein (mg/24 h)	597.50 (66.90–2255.70)	4.68 (1.28–7.98)	.0001
α-Microglobulin (mg/L)	53.12 (31.00–80.23)	25.88 (5.62–46.74)	.0001
β2-Microglobulin (mg/L)	6.78 (3.75–9.97)	1.74 (0.27–4.00)	.0001

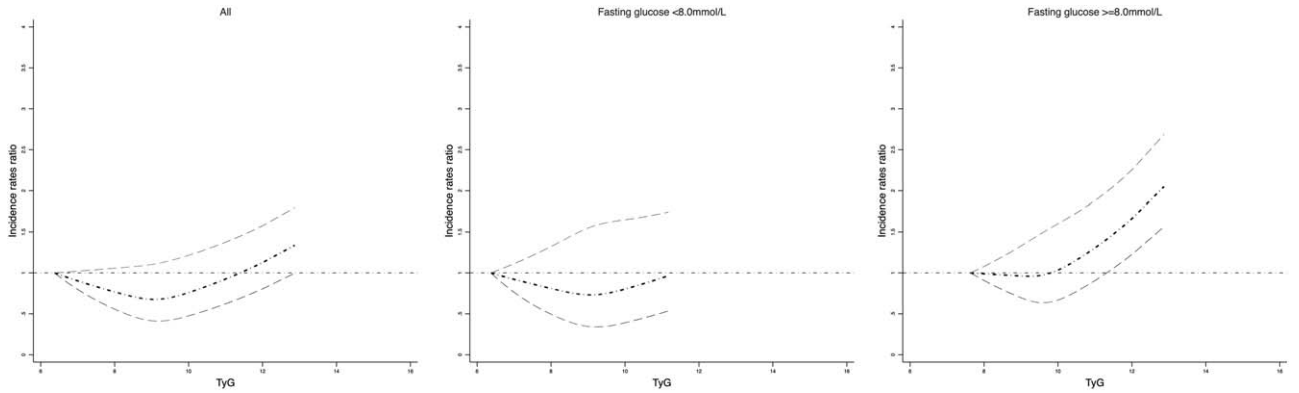

Figure 1. The dose–response association between TyG and risk of biopsy-proven diabetic nephropathy overall and by fasting glucose level. Body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, lowering lipid treatment, insulin treatment, HbA1c, alanine transaminase, alkaline phosphatase, activated partial thromboplastin time, direct bilirubin, Basophil, cholinesterase, calcium, chlorine, creatinine, C reaction protein, cysteine proteinase inhibitor, D_Dimer, fibrinogen Degradation Products, gamma glutamyl transpeptidase, globulin, glucose, high density lipoprotein cholesterol, hemoglobin, hematocrit, indirect Bilirubin, potassium, low density lipoprotein cholesterol, lymphocyte, mean corpuscular hemoglobin concentration, mean corpuscular volume, magnesium, mean platelet volume, monocytes, sodium, neutrophil, phosphorus, procalcitonin, red blood cell, red blood cell distribution width, total cholesterol, total bile acid, total bilirubin, triglyceride, thyroid-stimulating hormone, urine acid, thrombin time, white blood cell count, estimated glomerular filtration rate, carbon dioxide combining power, urine total protein, α-microglobulin, β2-microglobulin were adjusted.

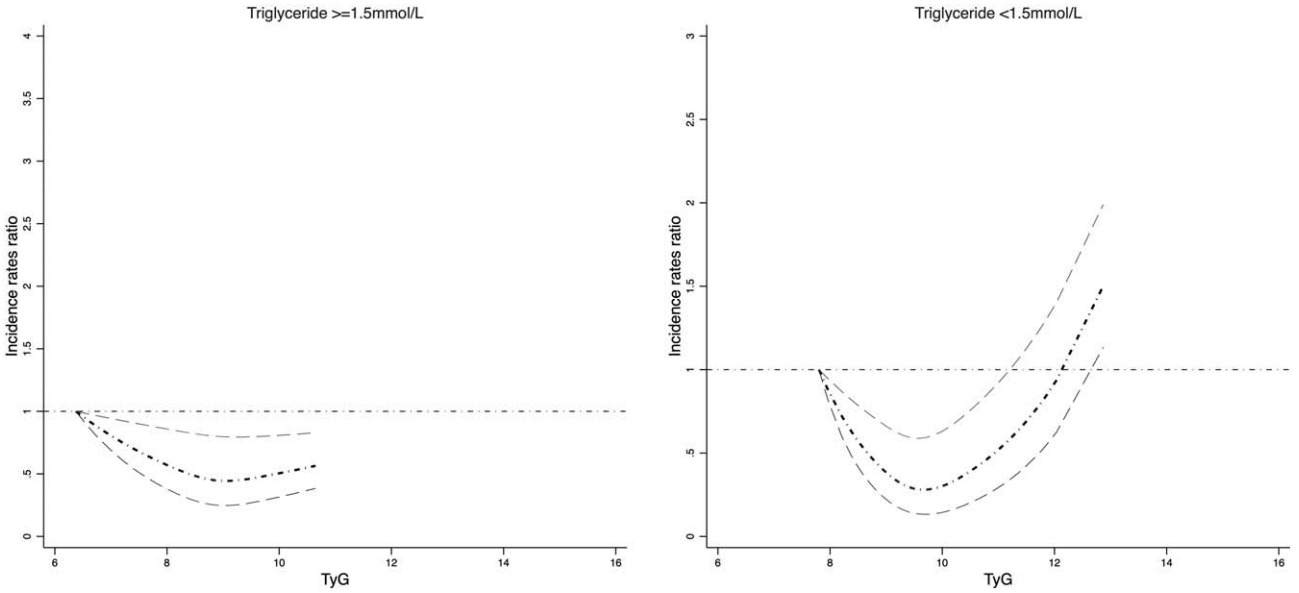

Figure 2. The dose–response association between TyG and risk of biopsy-proven diabetic nephropathy by triglyceride level. Body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, lowering lipid treatment, insulin treatment, HbA1c, alanine transaminase, alkaline phosphatase, activated partial thromboplastin time, direct bilirubin, Basophil, cholinesterase, calcium, chlorine, creatinine, C reaction protein, cysteine proteinase inhibitor, D_Dimer, fibrinogen Degradation Products, gamma glutamyl transpeptidase, globulin, glucose, high density lipoprotein cholesterol, hemoglobin, hematocrit, indirect Bilirubin, potassium, low density lipoprotein cholesterol, lymphocyte, mean corpuscular hemoglobin concentration, mean corpuscular volume, magnesium, mean platelet volume, monocytes, sodium, neutrophil, phosphorus, procalcitonin, red blood cell, red blood cell distribution width, total cholesterol, total bile acid, total bilirubin, triglyceride, thyroid-stimulating hormone, urine acid, thrombin time, white blood cell count, estimated glomerular filtration rate, carbon dioxide combining power, urine total protein, α-microglobulin, β2-microglobulin were adjusted.

people with TyG index at 8.9 had a higher risk of coronary artery stenosis and this risk significantly increased among those with a TyG index of 9.7.[26] In another study, in the general population, compared with people whose TyG index was below 8.21, the risk of incident type 2 diabetes significantly increased with a TyG index of 8.21 to 5.56, plateaued and then increased at a TyG index > 8.97.[24] However, in those studies, the TyG index was modeled as a categorical variable grouped by percentiles, a method no longer recommended as it is found to be less informative.[28] In our study, TyG was modeled as a continuous variable, applying a flexible cubic spline regression model to derive a more accurate dose–response relationship, "J-shape" and a convincible threshold, TyG at 9.05 to 9.09 for future replications and clinical practice.

The mechanism behind the association between TyG index and risk of newly diagnosed biopsy-proven DN could be the

Table 2

Adjusted incidence rates ratio for risk of newly diagnosed biopsy-proven diabetes nephropathy by 1 unit increase in TyG overall and in groups classified by TyG threshold (9.07).

	TyG < 9.07	TyG ≥ 9.07
Overall	0.87 (0.72–1.05)	1.56 (1.27–1.91)
Fasting glucose < 8.0 mmol/L	0.78 (0.233–2.64)	1.50 (1.09–2.06)
Fasting glucose ≥ 8.0 mmol/L	1.00 (0.638–1.56)	2.06 (1.01–4.20)
Triglyceride < 1.5 mmol/L	0.53 (0.185–1.53)	0.99 (0.41–2.40)
Triglyceride ≥ 1.5 mmol/L	0.91 (0.361–2.31)	1.92 (1.10–3.34)

Body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, lowering lipid treatment, insulin treatment, HbA1c, alanine transaminase, alkaline phosphatase, activated partial thromboplastin time, direct bilirubin, Basophil, cholinesterase, calcium, chlorine, creatinine, C reaction protein, cysteine proteinase inhibitor, D_Dimer, fibrinogen Degradation Products, gamma glutamyl transpeptidase, globulin, glucose, high density lipoprotein cholesterol, hemoglobin, hematocrit, indirect Bilirubin, potassium, low density lipoprotein cholesterol, lymphocyte, mean corpuscular hemoglobin concentration, mean corpuscular volume, magnesium, mean platelet volume, monocytes, sodium, neutrophil, phosphorus, procalcitonin, red blood cell, red blood cell distribution width, total cholesterol, total bile acid, total bilirubin, triglyceride, thyroid-stimulating hormone, urine acid, thrombin time, white blood cell count, estimated glomerular filtration rate, carbon dioxide combining power, urine total protein, α-microglobulin, β2-microglobulin were adjusted.

progression of IR in people with type 2 diabetes.[29] Previous findings suggest that the deteriorated IR in people with type 2 diabetes is associated with significantly changed levels of hormone, like parathyroid hormone,[30] cortisol,[31] peptide hormone[32,33] that could lead to microalbuminuria and declined eGFR in people with type 2 diabetes.

Our findings have some potential implications for the clinical practice. First, this dose–response relationship and especially the threshold found in our study could be used as a prognostic index in clinical practice to identify potentially high-risk individuals that could warrant more intensive treatment to postpone the progress of DN. In practical terms, the need to reduce and then cease metformin, an insulin sensitizer, could accelerate progression to end-stage renal disease.[34] The careful use of a thiazolidinedione, while monitoring for and avoiding fluid overload, could be a strategy to reduce progression while maintaining euglycemia.[35] Finally, while the clinical utilisation of HOMA is restricted by its cost and lack of utility in insulin-treated diabetes, the TyG Index, a measurement of fasting glucose and triglycerides, could be used as a marker of IR.[20,36] This index has the advantage of being clinically applicable as both triglyceride and glucose concentrations are inexpensive and routinely measured in those with diabetes.[20]

Our study has some limitations. First, the control population were patients admitted to hospital, and therefore unlikely to be representative of the Chinese type 2 diabetes population. However, those with DN were also hospital patients, partly because there are no distinctive differences between primary and secondary care settings in China. The potential selection bias in our study would therefore be lower than in settings without this continuum. Future validation studies are warranted in other type 2 diabetes populations, including those from ambulatory care (primary and secondary). Secondly, the proportion of people with missing data was significant, particularly for some covariables. Although our analyses were carried out using imputed datasets, further validation studies with datasets with less missing data are also warranted.

In summary, we have identified a non-linear relationship between the TyG index, a proxy for IR, and risk of newly diagnosed biopsy-proven DN in people with type 2 diabetes. The TyG index threshold of 9.05 to 9.09 may be useful for identifying high-risk individuals for further intensive intervention. These findings may suggest a greater role for insulin sensitizers in the prevention of DN. Further replication studies are warranted.

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