JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Association between the triglyceride–glucose index and diabetic nephropathy in patients with type 2 diabetes: A cross-sectional study

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Keywords
Diabetic nephropathy, Insulin resistance, Triglyceride–glucose index

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J Diabetes Investig 2021; 12: 557–565

doi: 10.1111/jdi.13371

ABSTRACT

Aims/Introduction: The triglyceride–glucose (TyG) index has been proposed as a reliable and simple marker of insulin resistance. We investigated the association between TyG index and diabetic nephropathy (DN) in patients with type 2 diabetes.

Materials and Methods: A consecutive case series of 682 adult patients with type 2 diabetes hospitalized in the Department of Endocrinology at the Tongji Hospital (Wuhan, Hubei, China) from January 2007 to December 2009 was included in this cross-sectional analysis. Receiver operating characteristics curve analysis, correlation analysis and multiple logistic regression analysis were carried out.

Results: A total of 232 (34.0%) participants were identified with DN. Compared with the non-DN group, the DN group had longer disease duration, and higher bodyweight, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, triglycerides, total cholesterol, serum uric acid, 24 h-urinary albumin, TyG index and homeostasis model assessment 2 estimates for insulin resistance (HOMA2-IR; $P < 0.05$ for each). The TyG index with an optimal cut-off point >9.66 showed a higher area under the receiver operating characteristic curve of 0.67 ($P = 0.002$) than HOMA2-IR (area under the curve 0.61, $P = 0.029$) on receiver operating characteristic curve analysis for DN identification. Additionally, the TyG index positively correlated with the levels of metabolic indicators (bodyweight, glycated hemoglobin, triglycerides, total cholesterol, serum uric acid, fasting glucose and HOMA2-IR) and natural logarithmic 24 h-urinary albumin ($P < 0.05$ for each), but not natural logarithm of estimated glomerular filtration rate. On multiple regression analysis, an increased TyG index was shown to be an independent risk factor (odds ratio 1.91, $P = 0.001$) for DN.

Conclusions: The TyG index was independently associated with DN in patients with type 2 diabetes, and was a better marker than HOMA2-IR for identification of DN in type 2 diabetes patients.

INTRODUCTION

Diabetic nephropathy (DN), as assessed by the development of albuminuria or a reduction in the glomerular filtration rate, increases cardiovascular morbidity and mortality in patients with type 2 diabetes, and remains the most important cause of end-stage renal disease[1]. There is a high prevalence of DN among Asian patients with type 2 diabetes (China 26–41%, Japan 22–32%, Singapore 53%)[2–5]. Owing to the large population of patients with diabetes in the Asia–Pacific region, the number of patients with DN is a tremendous burden on the healthcare system. Clinical trials have established that the development and progression of DN are closely associated with glycemic control[6]. However, the timing and severity of DN vary in type 2 diabetes patients with poor glycemic control, and DN might also occur in patients with well-controlled blood glucose levels. Therefore, hyperglycemia might not be the only risk factor for renal damage, suggesting that other factors are also involved in the clinical manifestation of DN.

Received 12 March 2020; revised 27 June 2020; accepted 17 July 2020

In the context of renal disease, patients with diabetes or microalbuminuria are often more insulin resistant (IR), suggesting insulin resistance might lead to accelerated progression of DN[7–10]. Increased albuminuria is a strong predictor for the development of overt DN. Although the role of insulin resistance in the pathogenesis of increased albuminuria is well illustrated in type 1 diabetes[11], its contribution in type 2 diabetes is controversial. Both positive[10,12–14] and negative associations[15,16] between insulin resistance and albuminuria have been reported in different studies. These conflicting findings might be attributable to the small number of patients included in the aforementioned studies, and in some circumstances, by studying different markers of insulin resistance[17,18]. Exploring the relationship between insulin resistance and DN will help us further understand the pathogenesis of DN, and potentially identify new intervention points to improve the outcomes in type 2 diabetes.

Most methods of evaluating insulin resistance, such as the hyperinsulinemic euglycemic glucose clamp (HEGC)[19], are costly and difficult to operate. Alternatively, the homeostasis model assessment for insulin resistance (HOMA-IR) index is widely used in clinical practice to evaluate insulin resistance using fasting state measurements[20]. However, the plasma insulin or C-peptide assay is expensive, or it is not easily available in all laboratories and has poor reproducibility. Thus, there is a need for new biomarkers that are easier to detect and more affordable. The triglyceride–glucose (TyG) index is the product of fasting plasma glucose and triglycerides levels, and has shown an excellent predictive performance to determine the insulin resistance when compared with HOMA-IR[21,22] and HEGC[23].

However, few studies have investigated the association between the TyG index and DN. Thus, the aim of the present study was to investigate the association between the TyG index, as a simple surrogate measure of insulin resistance, and DN in patients with type 2 diabetes.

METHODS

Participants

This was a retrospective collection of a consecutive case series including 682 patients with type 2 diabetes hospitalized in the Department of Endocrinology at the Tongji Hospital of Huazhong University of Science and Technology (Wuhan, Hubei, China) from January 2007 to December 2009. Inclusion criteria for analysis included: (i) diagnosis of type 2 diabetes according to the World Health Organization[24] and Chinese Diabetes Society criteria[25]; (ii) age ≥18 years; (iii) patients diagnosed with diabetes for at least 1 year; and (iv) no documented ketosis or ketoacidosis in the 3 months before enrolment. Individuals with any febrile or infectious illness, obstructive uropathy, severe heart failure, stroke, liver disease, cancer, autoimmune disease, changed lifestyle and pharmacological treatment during the past 3 months, and pregnant woman were excluded. DN was defined as an albumin excretion rate (AER) of ≥30 mg/day or an AER of ≥20 μg/min in at least two of three consecutive overnight urine collections. For patients with DN, any evidence of albuminuria in non-diabetic renal disease was an additional exclusion criterion. The study was approved by the ethics committee of Tongji Hospital of Huazhong University of Science and Technology, and was carried out in accordance with the Declaration of Helsinki. Appropriate consent and assent were obtained from all participants.

Clinical and biochemical measurements

Anthropometric measurements included bodyweight and blood pressure assessments. Blood pressure was measured using a mercury sphygmomanometer after the participants sat at rest for 5 min. Fasting blood specimens were obtained from the participants in the early morning after refraining from eating, drinking and smoking for at least 8 h. All blood and urine specimens were tested immediately after collection. Glycated hemoglobin (HbA_{1C}) was measured using high performance liquid chromatography (D-10™; Bio-Rad Laboratories, Hercules, CA, USA). Fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, uric acid and creatinine were measured using an automatic analyzer (Cobas8000; Roche Diagnostics Ltd., Basel, Switzerland). Insulin and C-peptide levels were measured with a chemiluminescent immunometric assay (Cobas e601; Roche Diagnostics Ltd.). Urinary albumin was measured using the immunoturbidimetric method (Cobas8000; Roche Diagnostics Ltd.). Evidence of fatty liver and vessel plaque were analyzed with a medical ultrasonic apparatus.

Definition

The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine and cystatin C using the CRIC Study equation[26]. The homoeostasis model assessment 2 estimates of insulin resistance (HOMA2-IR) and β-cell function (HOMA2-B) based on fasting C-peptide concentrations (which performs better than insulin in patients with diabetes) were calculated using the HOMA calculator (University of Oxford, Oxford, UK, available online from http://www.dtu.ox.ac.uk)[27]. The TyG index was calculated as follows: TyG = ln(fasting triglycerides [mg/dL] × fasting glucose [mg/dL] / 2)[21]. Diabetic retinopathy was diagnosed by an ophthalmologist based on fundus photographs[28]. Diabetic peripheral neuropathy was assessed by neurologists according to the Toronto criteria[29]. Macrovascular complications were identified by clinical evaluation of coronary, cerebral and peripheral artery diseases, and aortic aneurysms[30]. Smokers were defined as those with a daily or occasional smoking habit at the time of recruitment. Drinkers were also defined as those with a daily or occasional drinking habit at the time of recruitment. Normo-, micro- and macroalbuminuria were defined as AER <30, 30–300 and >300 mg/24 h[31], respectively.

Statistical analysis

Data were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Data are presented as the mean ± standard

error or median (interquartile range) for continuous variables, and as percentages for categorical variables. Comparisons between the two groups (DN vs non-DN) were carried out using the Student's *t*-test, Mann–Whitney *U*-test or χ^2-test. One-way ANOVA was used to compare the difference in TyG levels between the three groups of macroalbuminuria, microalbuminuria and normoalbuminuria. The general linear model was used to calculate and compare the corrected means. Pearson's correlation and partial correlation analyses were carried out for correlation analysis of TyG with other variables. HbA_{1C}, HOMA2-IR, AER and eGFR were natural logarithmic (ln) transformed in the correlation analysis. Receiver operating characteristic curve (ROC) analysis was constructed to evaluate the discriminatory performance for DN presence according to the value of the area under the ROC curve (AUC). A binary logistic regression multivariable analysis with DN categorized as a binary variable (presence or absence of DN) was used to evaluate the associations between the measured risk factors and DN. Statistical significance was defined by a *P*-value <0.05.

RESULTS

Characteristics of type 2 diabetes patients with and without DN

A total of 375 men and 307 women, aged 58.0 ± 0.5 years, with a median disease duration of 7 years (interquartile range 4–11 years) were included. A total of 34% (232/682) of patients with type 2 diabetes were identified with DN. Table 1 shows the participant characteristics stratified by groups (non-DN and DN). Compared with the patients without DN, patients with DN had a longer disease duration, and were more likely to have hypertension, fatty liver disease, diabetic retinopathy and diabetic peripheral neuropathy ($P < 0.05$ for each). Of note, the DN group had greater bodyweight, systolic blood pressure, diastolic blood pressure, HbA_{1C}, triglycerides, total cholesterol, serum uric acid and 24h-AER ($P < 0.05$ for each), showing a greater burden of metabolic syndrome. Similarly, there was more severe insulin resistance in patients with DN, as shown by the TyG index and HOMA2-IR ($P = 0.000$ and $P = 0.011$, respectively); however, there was no difference in the fasting insulin levels between groups. In addition, patients in the DN group were more likely to use insulin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, β-blockers and diuretics, and less likely to use biguanides, sulfonylureas and α-glucosidase inhibitors than patients in the non-DN group ($P < 0.05$ for each).

ROC analysis for identification of patients with risk of DN

ROC analysis was carried out to evaluate the performance of the TyG index for identifying patients with the risk of DN. The AUC value of the TyG index was 0.67 (95% confidence interval [CI] 0.57–0.78, $P = 0.002$), which was higher than that of HOMA2-IR (AUC 0.61, 95% CI 0.55–0.77, $P = 0.029$). When the Youden Index reached the maximum, the optimal cut-off point of the TyG index was defined as >9.66. The corresponding sensitivity and specificity were 61.7% and 76.0%, respectively.

Association of TyG with metabolic indicators

Then, patients were separated into two groups as a low-TyG group (TyG ≤9.66) and a high-TyG group (TyG >9.66), according to the cut-off value determined in the ROC analysis. Compared with the low-TyG group, patients with a high level of TyG index had higher levels of risk factors of metabolic syndrome and higher proportion of DN, as indicated by older age, fatty liver disease, smoking, and a higher bodyweight, HbA_{1C}, triglycerides, total cholesterol, serum uric acid, fasting glucose, HOMA2-IR and 24h-AER ($P < 0.05$ for each; Table 2). Accordingly, the TyG index positively correlated with the levels of these metabolic indicators (bodyweight, HbA_{1C}, triglycerides, total cholesterol, serum uric acid, fasting glucose and HOMA2-IR) and negatively correlated with high-density lipoprotein cholesterol ($P < 0.05$ for each; Table S1).

Correlation of TyG index with albuminuria and eGFR

We also investigated the relationship between the TyG index and albuminuria and eGFR. In the correlation analysis, the TyG index positively correlated with lnAER ($r = 0.190$, $P = 0.003$). After adjustment for age, sex, disease duration, bodyweight, presence of hypertension, HbA_{1C} and serum uric acid, the positive relationship between TyG index and lnAER remained significant ($r = 0.173$, $P = 0.006$). Consistently, the TyG index was higher in patients with macro- and microalbuminuria than those with normoalbuminuria ($P < 0.05$; Figure 1). The difference remained significant even after adjusting for the aforementioned confounding factors ($P < 0.05$). However, there was no significant correlation between the TyG index and lneGFR with ($r = -0.095$, $P = 0.138$) or without ($r = -0.016$, $P = 0.805$) adjustment for confounding factors. There was also no difference in the TyG index among DN patients with eGFR <30, 30–59, 60–89 and ≥90 mL/min/1.73 m^2 ($P = 0.786$).

Association of TyG index with diabetic nephropathy on multivariate analysis

On multivariate logistic stepwise regression analysis (Table 3), the TyG index was independently associated with DN in adult patients with type 2 diabetes after adjustment for age, sex, disease duration, bodyweight, presence of hypertension, HbA_{1C} and serum uric acid. It is noteworthy that the odds ratio (OR) of TyG index (OR 1.91, $P = 0.001$) was higher than that of HbA_{1C} (OR 1.35, $P = 0.000$).

We further assessed the effect of the TyG index in the subgroups of patients (Table 4). An increased TyG index remained significantly associated with DN in the subgroups of age ≥60 years (OR 2.24, $P = 0.032$), age <60 years (OR 2.14, $P = 0.004$), HbA_{1C} ≥7% (OR 2.28, $P = 0.002$) and eGFR ≥90 mL/min/1.73 m^2 (OR 2.60, $P = 0.001$), and patients with or without hypertension (OR 2.04, $P = 0.018$; OR 1.89,

Table 1 | Characteristics of type 2 diabetes patients with and without diabetic nephropathy

Variable	Non-DN (n = 450)	DN (n = 232)	P-value
Age (years)	57.4 ± 0.6	59.0 ± 0.7	0.094
Women (%)	46.0	43.1	0.471
Disease duration (years)	6 (3–10)	10 (5–13)	0.000
Hypertension (%)	38.2	65.5	0.000
Fatty liver disease (%)	4.7	9.1	0.024
Retinopathy (%)	20.7	41.8	0.000
Macrovascular complications (%)	17.6	22.4	0.127
Peripheral neuropathy (%)	47.8	58.2	0.010
Smoking (%)	31.3	34.9	0.344
Drinking (%)	23.8	26.7	0.398
Bodyweight (kg)	63.6 ± 0.5	66.8 ± 6.6	0.001
SBP (mmHg)	133.4 ± 1.0	146.4 ± 1.8	0.000
DBP (mmHg)	79.5 ± 0.6	84.0 ± 1.0	0.000
HbA_{1C} (%)	7.5 (6.6–9.0)	8.1 (6.6–10.35)	0.002
Triglycerides (mmol/L)	1.40 ± 0.04	2.05 ± 0.15	0.000
Total cholesterol (mmol/L)	4.42 ± 0.05	4.94 ± 0.11	0.000
HDL-C (mmol/L)	1.29 ± 0.15	1.14 ± 0.03	0.448
LDL-C (mmol/L)	3.45 ± 0.83	2.96 ± 0.19	0.663
Serum uric acid (μmol/L)	318.8 ± 5.7	361.7 ± 9.2	0.000
Serum creatinine (μmol/L)	58.7 (48.5–71.3)	82.0 (61.5–159.4)	0.000
eGFR (mL/min/1.73 m^2)	128.9 (100.7–157.7)	76.1 (38.0–121.8)	0.000
AER (mg/24 h)	15 (6–25)	245 (55–829)	0.000
Fasting glucose (mmol/L)	6.8 ± 0.1	7.3 ± 0.3	0.203
Fasting insulin (mU/L)	5.1 (3.5–8.8)	6.1 (3.0–11.2)	0.365
Fasting C-peptide (μg/L)	1.9 (1.5–2.6)	2.2 (1.7–3.3)	0.012
HOMA2-B	72.4 (48.3–112.0)	70.9 (47.4–123.0)	0.829
HOMA2-IR	1.53 (1.14–2.09)	1.79 (1.28–2.69)	0.011
TyG index	9.10 ± 0.38	9.42 ± 0.74	0.000
Medication			
Insulin (%)	65.8	83.2	0.000
Biguanides (%)	34.7	23.3	0.000
Sulfonylureas (%)	8.4	2.6	0.003
Meglitinides (%)	12.9	10.8	0.424
α-Glucosidase inhibitors (%)	32.2	22.4	0.007
Thiazolidinediones (%)	10.7	11.2	0.830
ACEI/ARB (%)	20.7	44.0	0.000
CCB (%)	19.1	41.8	0.000
β-Blockers (%)	4.2	10.3	0.002
Diuretics (%)	3.8	15.9	0.000
Lipid lowering (%)	31.9	38.4	0.093

Data are presented as the mean ± standard error or median (interquartile range) for continuous variables, and the percentage for categorical variables. Missing data: 237 participants without triglyceride–glucose (TyG) index data. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AER, albumin excretion rate; CCB, calcium channel blockers; DBP, diastolic blood pressure; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; HbA_{1C}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA2-B, homoeostasis model assessment 2 estimates of β-cell function; HOMA2-IR, homoeostasis model assessment 2 estimates of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

P = 0.034) after multivariable adjustment. However, this association was not significant in patients with HbA_{1C} <7% and eGFR <90 mL/min/1.73 m^2.

DISCUSSION

In the present study, patients with type 2 diabetes and DN manifested a greater burden of clinical parameters associated with metabolic syndrome, including greater bodyweight, blood pressure, HbA_{1C}, triglycerides, total cholesterol, serum uric acid and 24h-AER. Importantly, patients with type 2 diabetes and DN showed more severe insulin resistance, as indicated by a higher TyG index and HOMA2-IR scores compared with patients without DN ($P < 0.05$ for each). The TyG index showed a greater ROC AUC score (AUC 0.67, P = 0.002) for

Table 2 | Clinical and metabolic characteristics in patients with different levels of the triglyceride–glucose index

Variables	TyG index ≤9.66 (n = 310)	TyG index >9.66 (n = 108)	P-value
DN (%)	25	50	0.000
Age (years)	54.7 ± 1.7	58.7 ± 0.7	0.003
Women (%)	44.2	37.0	0.195
Disease duration (years)	7 (3–11)	7 (3–10)	0.420
Hypertension (%)	43.9	51.9	0.152
Fatty liver disease (%)	3.9	13.0	0.001
Smoking (%)	31.0	41.7	0.043
Bodyweight (kg)	63.1 ± 0.6	70.1 ± 1.3	0.000
SBP (mmHg)	136 ± 1	139 ± 2	0.152
DBP (mmHg)	80 ± 1	83 ± 1	0.063
HbA_{1C} (%)	7.4 (6.4–8.9)	8.5 (7.3–10.5)	0.000
Triglycerides (mmol/L)	1.21 ± 0.03	2.73 ± 0.21	0.000
Total cholesterol (mmol/L)	4.51 ± 0.06	5.00 ± 0.14	0.000
HDL-C (mmol/L)	1.20 ± 0.03	1.00 ± 0.02	0.000
LDL-C (mmol/L)	2.67 ± 0.05	2.85 ± 0.12	0.113
Serum uric acid (μmol/L)	315.5 ± 5.8	355.0 ± 11.5	0.001
Serum creatinine (μmol/L)	61.7 (49.6–76.1)	65.1 (53.3–91.1)	0.038
eGFR (mL/min/1.73 m^2)	122.9 (94.5–153.3)	110.9 (70.3–152.2)	0.163
AER (mg/24 h)	40 (15–74)	55 (30–240)	0.002
Fasting glucose (mmol/L)	6.9 ± 1.3	10.0 ± 0.4	0.000
Fasting insulin (mU/L)	5.3 (3.4–9.0)	7.5 (3.8–14.1)	0.050
HOMA2-IR	1.55 (1.19–2.13)	1.98 (1.38–2.65)	0.006
TyG index	8.88 ± 0.03	10.11 ± 0.04	0.000

Data are presented as the mean ± standard error or median (interquartile range) for continuous variables, and the percentage for categorical variables. AER, albumin excretion rate; DBP, diastolic blood pressure; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; HbA_{1C}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA2-IR, homoeostasis model assessment 2 estimates of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TyG, triglyceride–glucose.

identification of DN in type 2 diabetes patients in comparison with HOMA2-IR (AUC 0.61, P = 0.029), and the optimal cut-off point for the TyG index was defined as >9.66, with a corresponding sensitivity and specificity of 61.7% and 76.0%, respectively. The TyG index was positively correlated with the levels of metabolic indicators (bodyweight, HbA_{1C}, triglycerides, total cholesterol, serum uric acid, fasting glucose and HOMA2-IR) and lnAER ($P < 0.05$ for each), but not lneGFR. Multiple regression analysis showed that an increased TyG index, as a surrogate marker of insulin resistance, was independently associated with DN in patients with type 2 diabetes (OR 1.91, P = 0.001).

The TyG index has been proposed as a simple and reliable surrogate marker for metabolic syndrome and insulin resistance[32–34]. Accumulating evidence has also confirmed the important role of TyG index in predicting macrovascular disease[35–37]. However, data on the association between TyG index and DN in patients with type 2 diabetes are limited. In the present study, we observed a significant positive correlation between the TyG index and DN in type 2 diabetes patients. Indeed, several studies have shown that insulin resistance is implicated in the development of DN. Although the mechanism underlying the relationship has not been fully elucidated, insulin resistance is associated with an elevation in the glomerular hydrostatic pressure, leading to increased renal vascular permeability and ultimately glomerular hyperfiltration[9]. Other possible mechanistic pathways linking insulin resistance to DN are inflammation[38], oxidative stress[39], metabolic acidosis[40] and increased lipotoxicity[41], leading to the development of microangiopathy. Several reports have suggested that dyslipidemia has an important role in the progression of renal disease in both type 2 diabetes[42] and type 1 diabetes[43].

Previous studies have reported the association of DN with HOMA-IR, another surrogate marker of insulin resistance. De Cosmo *et al.*[44] showed that adult male patients with type 2 diabetes in the highest quartile of HOMA-IR were more likely to have albuminuria than those in the lowest quartile. Others have shown a longitudinal relationship between insulin resistance, as assessed by baseline HOMA-IR, and development of microalbuminuria in a 5-year prospective cohort study[12]. HOMA2-IR is an improvement over its predecessor, as it integrates the estimation of peripheral resistance with the fasting C-peptide level, and some authorities consider it a better metric for Asian populations[45]. The present results coincide with these previously reported findings that patients with DN typically have a higher HOMA2-IR. Importantly, we indeed found that, compared

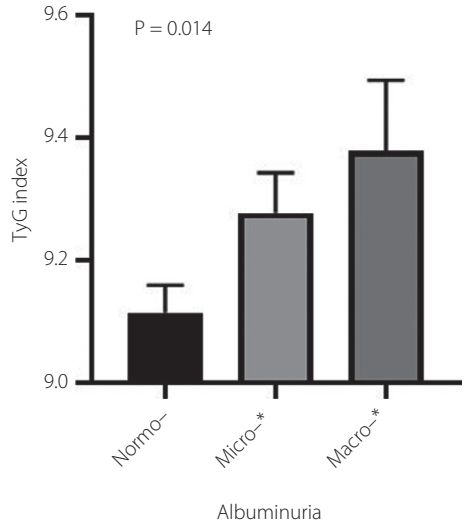

Figure 1 | Levels of the triglyceride–glucose (TyG) index in patients with type 2 diabetes stratified by normoalbuminuria, microalbuminuria and macroalbuminuria. The difference remained significant even after adjusting for age, sex, disease duration, bodyweight, presence of hypertension, glycated hemoglobin and serum uric acid ($P = 0.04$). *$P < 0.05$ compared with normoalbuminuria.

Table 3 | Odds ratio of diabetic nephropathy in patients with type 2 diabetes

Variable	Odds ratio	95% CI	*P*-value
TyG index (per 1 unit increase)	1.91	1.29–2.85	0.001
≤9.66	1.00	–	–
>9.66	2.99	1.61–5.06	0.000
Hypertension	2.46	1.40–4.30	0.002
HbA_{1C}	1.35	1.19–1.53	0.000
Disease duration	1.07	1.02–1.12	0.009

The triglyceride–glucose (TyG) index was adjusted for age, sex, disease duration, bodyweight, presence of hypertension, glycated hemoglobin (HbA_{1C}) and serum uric acid. CI, confidence interval.

with HOMA2-IR, the TyG index showed a stronger association with DN in type 2 diabetes patients and a greater ROC AUC, indicating that TyG is a better marker for identification of DN in type 2 diabetes patients compared with HOMA2-IR. In addition, the TyG index incorporates indicators of both glucose and lipid metabolisms, demonstrating the importance of serum triglycerides and glucose in the pathophysiology of insulin resistance in DN.

Additionally, the subgroup analysis revealed that patients with more frequent episodes of insufficient glycemic control (HbA_{1C} ≥7%) showed greater OR values for DN, findings that were not seen in patients with HbA_{1C} <7%. One explanation is that insulin resistance might be involved in the early phase of DN in type 2 diabetes patients, but not the late phase. Interestingly, patients in the subgroup of DN with HbA_{1C} <7% showed higher blood pressure, worse renal function and a greater degree of albuminuria (Table S2), indicating that some patients with HbA_{1C} <7% had progressed to a more serious stage of renal disease. Furthermore, the present results showed a significant association between TyG index and DN in patients with eGFR ≥90 mL/min/1.73 m^2, but an insignificant association in patients with eGFR <90 mL/min/1.73 m^2. The TyG index was associated with the development of albuminuria, but not grade of albuminuria. In addition, previous evidence also shows that reduced insulin sensitivity is independently associated with microalbuminuria in type 2 diabetes patients, but is not significantly associated with macroalbuminuria. Therefore, we speculate that the role of insulin resistance might be more obvious in the early phase of DN than in the late phase. In contrast, hypertension might also play a central role in this stage, as seen in Table S3, which shows that these patients were more likely to be treated with one or more antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers, all of which have been reported to improve insulin sensitivity. Hsu *et al.*[12] previously also reported that in the subgroup of type 2 diabetes patients with HbA_{1C} <8% or blood pressure >130/80 mmHg, the role of insulin resistance in the incidence of DN was reduced. To summarize, the role of insulin resistance in the development of DN in these patients remains unclear, especially in the late phase, and requires further studies.

Several limitations to this study should be acknowledged. First, this was a cross-sectional observational study. A causal relationship cannot be established directly based on the results of this study. Second, we continuously collected all participants at a particular location over a period of time; thus, our participants are well representative of hospitalized patients with type 2 diabetes, but not the general population with type 2 diabetes. Indeed, prospective cohort studies are required to evaluate the predictive potential of the TyG index for development of DN in patients with type 2 diabetes, especially in the general population. Third, we did not use the HEGC for measuring insulin resistance, as HEGC is time-consuming and costly, and thus not suitable for the present large sample study. This limitation was compensated by the use of the TyG index, which is easy to detect and has been proposed as a reliable surrogate of insulin resistance with high sensitivity, when compared with HEGC[23].

In conclusion, we showed a significant association between an increased TyG index and DN in patients with type 2 diabetes. We found that the TyG index was a better marker than HOMA2-IR for the identification of DN in type 2 diabetes patients. Insulin resistance is an important and crucial player in the pathophysiology of DN, and might be an important target for its treatment and prevention. Future studies are required for a detailed understanding of the link between the insulin resistance parameters, especially the TyG index, and renal dysfunction in type 2 diabetes patients at different stages of DN.

Table 4 | Subgroups analysis of odds ratios of the triglyceride–glucose index with diabetic nephropathy in patients with type 2 diabetes

Subgroups	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age						
≥60 years	1.74 (1.05–2.89)	0.031	2.30 (1.21–4.37)	0.011	2.24 (1.07–4.68)	0.032
<60 years	2.32 (1.53–3.53)	0.000	2.25 (1.40–3.61)	0.001	2.14 (1.27–3.62)	0.004
HbA_{1C}						
≥7.0%	2.47 (162–3.77)	0.000	2.50 (1.55–4.02)	0.000	2.28 (1.37–3.80)	0.002
<7.0%	1.40 (0.75–2.60)	0.295	1.39 (0.67–2.88)	0.373	1.52 (0.72–3.23)	0.275
eGFR						
<90 mL/min/1.73 m^2	0.85 (0.50–1.47)	0.565	1.01 (0.50–2.01)	0.983	1.34 (0.57–3.15)	0.509
≥90 mL/min/1.73 m^2	2.99 (1.89–4.73)	0.000	3.00 (1.81–4.97)	0.000	2.60 (1.49–4.54)	0.001
Hypertension						
Yes	1.53 (0.98–2.39)	0.063	1.64 (0.98–2.72)	0.058	2.04 (1.13–3.67)	0.018
No	2.23 (1.41–3.52)	0.001	2.42 (1.43–4.09)	0.001	1.89 (1.05–3.40)	0.034

Model 1: adjusted for age and sex; model 2: model 1 + bodyweight, disease duration, presence of hypertension and serum uric acid; model 3: model 2 + glycated hemoglobin (HbA_{1C}). CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (81770817 to GY and 81700727 to LL) and China Diabetes Young Scientific Talent Research Project of China International Medical Foundation (2018-N-01 to LL). We also thank all the doctors, nurses, technicians and participating patients for their dedication to this study. The study was funded by National Natural Science Foundation of China (81770817 to GY and 81700727 to LL) and China Diabetes Young Scientific Talent Research Project of China International Medical Foundation (2018-N-01 to LL).

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Correlation analysis of the triglyceride–glucose index with metabolic indicators.

Table S2 | Characteristics of type 2 diabetes patients with and without diabetic nephropathy according to glycated hemoglobin.

Table S3 | Medication of patients with diabetic nephropathy in the subgroups of glycated hemoglobin.