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Triglyceride Glucose Index in Predicting the Development of Diabetic Kidney disease

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ABSTRACT

Introduction: Chronic kidney disease (CKD) related to diabetes, known as diabetic kidney disease (DKD), affects 20–40% of adults living with diabetes. Although the exact causes are still being explored, factors like insulin resistance (IR), high blood sugar levels, and genetic predispositions seem to play significant roles. DKD is typically diagnosed by checking protein levels in urine and assessing kidney function, with microalbuminuria serving as an early warning sign. However, this can be influenced by other health issues. IR contributes to the progression of DKD by promoting inflammation and harming kidney cells. Researchers are currently investigating the triglyceride-glucose (TyG) index as a promising marker for IR, which could assist in the early detection and management of DKD.
Aims & objectives: The aim of this study is to explore how the TyG index can predict the development of diabetic kidney disease.
Materials & Methods: This cross-sectional, case-control study took place at a tertiary hospital in northern India and involved 160 patients. They were divided into three groups based on their levels of albuminuria: 79 patients in the normoalbuminuric DKD group (Group I), 37 in the microalbuminuria group (Group II), and 44 in the macroalbuminuria group (Group III).
Results: As albuminuria levels increased, we noticed significant changes in several factors: mean age, blood pressure, serum urea, serum creatinine, uric acid, and HbA1c all rose, while haemoglobin levels decreased. In the macroalbuminuria group, cholesterol, triglycerides, LDL, and VLDL levels increased, but HDL levels remained stable. The TyG Index also showed a significant increase across all groups, particularly when comparing those with normoalbuminuric to those with micro- and macroalbuminuria. We found positive correlations between the TyG Index and levels of urea, creatinine, HbA1c, and urine albumin-to-creatinine ratio, while eGFR showed an inverse correlation.
Conclusion: This study emphasizes a strong link between a higher TyG Index and an increased risk of microalbuminuria and declining kidney function. The TyG Index appears to be a reliable marker for insulin resistance, offering potential as an early tool for predicting DKD progression. Regular monitoring of the TyG Index may help detect kidney issues sooner and guide preventive measures

Keywords: Dyslipidaemia, Diabetic Nephropathy, Proteinuria, Cardiovascular risk

INTRODUCTION

Chronic kidney disease (CKD) resulting from diabetes, known as diabetic kidney disease (DKD), affects 20–40% of adults with diabetes. Despite extensive research, the precise etiology of DKD remains elusive, though contributing factors are thought to include insulin resistance (IR), genetic predisposition, hyperglycemia, and autoimmune mechanisms.[1]

DKD is clinically identified by a persistent elevation in the urinary albumin-to-creatinine ratio (UACR) (≥ 30 mg/g) and/or a progressive decline in eGFR (< 60 mL/min/1.73 m²). Microalbuminuria is an early indicator of increasing albumin excretion rates (AERs) that typically characterize DKD progression. The accuracy of microalbuminuria detection is contingent upon proper specimen collection. It may be influenced by concurrent conditions such as urinary tract infections or heart failure, often marking irreversible stages of DKD. However, nearly 50% of diabetic patients develop a reduced GFR (e.g., 60 mL/min/1.73 m²) while remaining normoalbuminuric. [1-2]

IR is pivotal in the onset and progression of diabetic nephropathy. Studies have shown that individuals with T2DM who develop diabetic nephropathy exhibit greater IR than those without kidney involvement. IR and hyperglycemia contribute to generating reactive oxygen species (ROS) and activate several pathogenic pathways, including protein kinase C, the polyol pathway, the hexosamine pathway, and the formation of advanced glycation end products (AGEs). These pathways drive a cascade of inflammatory responses, characterized by increased levels of cytokines and chemokines such as interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-beta (TGF-beta), and vascular endothelial growth factor (VEGF). This inflammatory milieu promotes fibrosis, increases vascular permeability, and induces podocyte injury, leading to albuminuria.[3-4]

The subsequent systemic and intraglomerular hypertension exacerbates proteinuria, which in turn triggers epithelial-mesenchymal transition (EMT), leading to the proliferation of fibroblasts and chronic tubular injury. Given the central role of IR in DKD, the triglyceride-glucose (TyG) index has been investigated as a surrogate marker for IR, with studies demonstrating its comparability to gold-standard methods such as the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). This study aims to elucidate the relationship between the TyG index and its predictive value in the onset and progression of DKD, offering it as a potential avenue for early intervention and management of this debilitating complication.[3-4]

MATERIALS & METHODS

This study was a cross-sectional, case-control study conducted at a tertiary hospital in northern India. The study population was divided into four groups based on the participants' level of albuminuria.

First group: Normoalbuminuric DKD group (Group I) (urine albumin creatinine ratio <30 mg/gm creatinine)

Second group: DKD group with microalbuminuria (Group II, urine albumin creatinine ratio from 30 to 300 mg/gm creatinine)

Third group: DKD group with macroalbuminuria (Group III, urine albumin creatinine ratio >300 mg/gm creatinine)

A sample size of 160 patients divided into 3 groups. Group 1 – 79 patients, Group 2-37 patients, and Group 3- 44 patients, enrolled using the software G Power analysis (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; http://www.gpower.hhu.de/) with a medium effect size of 0.30, 95% confidence interval, and 80% power of the study.

T2DM patients, per the American Diabetes Association (ADA) criteria of ages 18-65 years and who gave written informed consent, were included in the study. Staging of DKD was done based on the kidney disease: Improving Global

Outcomes (KDIGO) guidelines. Patients with acute or chronic kidney diseases, polycystic kidney, hepatic diseases, malignancy, inflammatory conditions, and sepsis were excluded.

The Institutional Ethics Committee approved the study. The procedure was based on the Declaration of Helsinki and the International Council for Harmonization-Good Clinical Practice (ICH-GCP).

The clinical and laboratory findings were compared between the four groups. Demographic and clinical data (e.g., comorbidities, duration of type 2 diabetes, and blood pressure) were recorded. Blood samples were collected for testing complete blood count, including sodium (Na+), potassium (K+), urea/creatinine (Cr), glycosylated hemoglobin (HbA1c), serum cholesterol (CHL), serum triglyceride (TG), serum low-density lipoprotein cholesterol (LDL), serum very low-density lipoprotein (VLDL), serum high-density lipoprotein (HDL), serum phosphate (PO4), serum uric acid (UA), and TyG Index. A urine examination was done for the albumin-creatinine ratio (UACR). UACR was reported as mg albumin/g creatinine. The plasma and serum were centrifuged and frozen at -70 °C until further laboratory analysis. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula (MDRD):

$eGFR = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ only if female}) \times (1.212 \text{ only if black})$

STATISTICAL ANALYSIS

Baseline characteristics were assessed using standard descriptive statistics. The normality of data was tested by the Kolmogorov-Smirnov test. If the data were not found to be continuous, then the non-parametric test was used. Continuous variables were presented as mean ± standard deviation. Categorical variables were presented in number and percentage (%). Quantitative variables were compared using an F-test between groups, while qualitative variables were compared using the Chi-Square test/Fisher's exact test where they are appropriate. Here, a p-value of < 0.05 was considered statistically significant. The one-way analysis of variance (ANOVA) was also used to determine whether there were statistically significant differences between the means of two or more independent (unrelated) groups. The Pearson correlation coefficient was applied to measure the strength of a linear association between two variables, where the value r = 1 means a perfect positive correlation, and the value r = -1 means a perfect negative correlation. The data were entered into a Microsoft Excel spreadsheet, and the analysis was done using Statistical Product and Service Solutions (SPSS) (IBM SPSS Statistics for Windows, Version 29.0, Armonk, NY).

RESULT

Association of different demographic, and clinical parameters of DKD with Normoalbuminuric, Microalbuminuria, and Macroalbuminuria (Urine ACR) as shown in Table 1

With increase in albuminuria there was significant increase in mean age, blood pressure, S. Urea, S . creatinine, uric acid & HbA1C while there was significant decrease in hemoglobin level. Cholesterol (CHL), Triglycerides (TG), Low-Density Lipoprotein (LDL), and very low-density lipoprotein (VLDL) significantly increased in the macroalbuminuria group. High-density lipoprotein (HDL) didn't differ significantly among the groups. TyG Index which is related to triglycerides and fasting blood glucose, increased significantly across the groups.

In Post-hoc Tukey test TyG index was compared across groups as shown in Table 2

TyG index mean difference between Normoalbuminuric vs. Microalbuminuria & Normoalbuminuric vs. Macroalbuminuria was significant while mean difference was

not statistically significant in Microalbuminuria vs. Macroalbuminuria.

As shown in Table 3

A significant positive correlation was observed between the TyG Index and urea (r=0.2), creatinine (r=0.5), HbA1c (r=0.8) and urine albumin-to-creatinine ratio (ACR) (r=0.3) while eGFR was significantly inversely corelated.

Table 1: Association of different demographic, and clinical parameters of DKD with Normoalbuminuric, Microalbuminuria, and Macroalbuminuria (Urine ACR)

	Normoalbuminuric (n=79)		Microalbuminuria (n=37)		Macroalbuminuria (n=44)		p-Value
	Mean	±SD	Mean	±SD	Mean	±SD	
Age	45.28	9.82	48.68	7.18	49.41	8.81	0.029
Gender							
Male	38	48.10%	22	59.46%	16	36.36%	0.115
Female	41	51.90%	15	40.54%	28	63.64%	
Systolic BP	122.43	13.78	132.81	10.82	135.80	10.44	0.000
Diastolic BP	74.38	10.05	79.89	9.37	80.91	7.84	0.000
PR	79.73	8.06	82.49	8.89	81.23	10.26	0.281
HB	11.37	1.33	10.88	1.61	9.52	1.31	<0.001
TLC	8215.97	2681.94	8071.62	2972.65	10076.86	3459.52	0.002
PLT	2.00	0.75	1.90	0.93	2.20	0.85	0.232
UREA	36.68	15.44	63.47	80.93	56.61	30.71	0.003
CREAT	1.11	0.38	1.72	0.57	2.49	1.25	<0.001
HBA1C	6.13	1.63	8.06	1.20	8.62	1.67	<0.001
eGFR	93.29	88.27	49.88	24.07	35.39	16.77	<0.001
CHL	162.44	35.37	183.73	52.03	201.18	41.82	<0.001
TG	152.58	53.33	249.11	77.09	257.61	78.34	<0.001
LDL	84.38	30.73	92.11	45.05	107.84	41.39	0.001
HDL	43.56	15.53	42.81	15.09	50.41	27.84	0.125
VLDL	31.09	11.49	38.82	16.05	43.62	14.19	<0.001
PO4	5.78	0.67	6.30	0.97	7.16	1.16	<0.001
URIC ACID	5.90	0.94	6.40	1.06	6.89	1.33	<0.001
Fasting BS	129.11	46.87	184.76	34.46	200.64	47.83	<0.001
TyG Index	9.09	0.41	9.98	0.37	10.08	0.38	<0.001

Table 2: Post-hoc Tukey test

	Normoalbuminuric vs Microalbuminuria		Normoalbuminuric vs Macroalbuminuria		Microalbuminuria vs Macroalbuminuria	
	Mean Diff.	p-Value	Mean Diff.	p-Value	Mean Diff.	p-Value
Age	-3.40	0.144	-4.13	0.042	-0.73	0.929
Systolic BP	-10.38	<0.001	-13.37	<0.001	-2.98	0.523
Diastolic BP	-5.51	0.010	-6.53	0.001	-1.02	0.877
PR	-2.75	0.270	-1.49	0.646	1.26	0.802
HB	0.49	0.189	1.84	<0.001	1.36	<0.001
TLC	144.35	0.968	-1860.89	0.003	-2005.24	0.008
PLT	0.10	0.805	-0.20	0.402	-0.30	0.228
UREA	-26.80	0.006	-19.94	0.041	6.86	0.758
ZA2GP	28.26	<0.001	46.62	<0.001	18.36	0.001
CREAT	-0.61	<0.001	-1.37	<0.001	-0.76	<0.001
HBA1C	-1.94	<0.001	-2.49	<0.001	-0.55	0.250
eGFR	43.42	0.002	57.91	<0.001	14.49	0.567
CHL	-21.29	0.029	-38.74	<0.001	-17.45	0.146
TG	-96.53	<0.001	-105.03	<0.001	-8.51	0.836

LDL	-7.73	0.556	-23.46	0.003	-15.73	0.147
HDL	0.75	0.980	-6.85	0.154	-7.60	0.194
VLDL	-7.73	0.012	-12.53	<0.001	-4.80	0.247
PO4	-0.52	0.041	-1.38	<0.001	-0.86	<0.001
URIC ACID	-0.50	0.112	-0.99	<0.001	-0.49	0.127
Fasting BS	-55.65	<0.001	-71.53	<0.001	-15.88	0.250
TyG Index	-0.89	<0.001	-0.99	<0.001	-0.10	0.471

Table 3: Pearson Correlation of TyG Index with UREA, ZA2GP, CREAT, HBA1C, URINE ACR, and eGFR

TyG Index	Pearson Correlation	Sig. (2-tailed)
UREA	0.2	0.045
ZA2GP	-0.6	<0.001
CREAT	0.5	<0.001
HBA1C	0.8	<0.001
URINE ACR	0.3	<0.001
eGFR	-0.3	<0.001

DISCUSSION

This study presents strong evidence that an elevated TyG Index is linked to a higher risk of developing microalbuminuria and a decline in eGFR. The TyG Index is often disrupted when insulin resistance (IR) occurs. Although the TyG Index correlates with IR measured by the hyperinsulinemic-euglycemic clamp or HOMA-IR, it has been shown to outperform both methods. Consequently, the TyG Index is considered a surrogate marker for IR. Research in non-diabetic individuals has demonstrated a strong positive linear relationship between the TyG Index and UACR.5 In a study by Zhao et al., 22.96% of participants had diabetes, and they observed that a higher TyG Index was associated with an increased risk of both microalbuminuria and DKD defined by an eGFR ≤60 mL/min/1.73 m². Additionally, a Japanese cohort study, where 22% of participants had diabetes, identified the TyG Index as a predictor of CKD prevalence. These findings highlight the TyG Index's value in forecasting CKD risk. In a cross-sectional analysis of 1432 DM patients, patients with a higher TyG Index had a higher risk of microalbuminuria (OR = 2.342, 95% CI = 1.744–3.144, p < 0.001), and eGFR <60 mL/min/1.73 m^2 (1.696, 95% CI =1.096–2.625, p = 0.018). Longitudinally, 94 of 424 participants developed DKD. After confounder adjustment, patients in the high tertile of the TyG Index at baseline had a greater risk of developing DKD than those in the low tertile (HR = 1.727, 95% CI = 1.042–2.863, p = 0.034).[5]

Additionally in our study, the TyG index mean difference between the Normoalbuminuric vs. Microalbuminuria group was significant which tells us that it can be used to predict the risk of developing DKD even before the appearance of microalbuminuria. In our study, the mean difference in the TyG index between the normoalbuminuric and macroalbuminuric groups was statistically significant, indicating its potential utility as a predictive marker for the development of diabetic kidney disease (DKD) before the onset of microalbuminuria.

Insulin resistance contributes to the early stages of diabetic kidney disease (DKD) by driving glomerular hypertension and hyperfiltration. It disrupts capillary Vaso regulation through increased nitric oxide (NO) and transforming growth factor β1 (TGF-β1), leading to vasodilation and elevated glomerular pressure. Activation of the renin-angiotensin system and heightened angiotensin II sensitivity further exacerbate this imbalance. Insulin resistance also increases salt sensitivity, promoting blood

pressure rise, albuminuria, and renal dysfunction. Additionally, altered adipokine levels, particularly low adiponectin, and high leptin, contribute to endothelial dysfunction, inflammation, and fibrosis, worsening DKD progression through complex metabolic pathways. TyG Index has been significantly correlated with IR which explains its relationship with DKD development.[5-6]

TyG index was also positively correlated with HbA1C & BP which are related to increased risk of development of DKD. The TyG index has been significantly correlated with HbA1c in previous studies, representing poor glycemic controls that trigger oxidative stress and kidney injury. A total of 140 patients with T2DM were included in this cross-sectional study and divided into two groups according to their HbA1c levels: participants with HbA1c 7.0% (n=65). TyG index was significantly correlated with HbA1c.[5,7]

Data for adults were extracted from the China Health and Nutrition Survey (CHNS) in 2009–2015 in this retrospective cohort study & the TyG index was calculated. After adjusting for covariates, it was found that compared with participants with a TyG index ≤ 8.41 (median value), those who had a higher TyG index seemed to have higher odds of hypertension [OR = 1.17, 95%CI: (1.01–1.37)].[8]

TyG index showed a positive correlation with UACR, S. Urea & S. Creatinine & was inversely related to eGFR. A cross-sectional study was done obtaining data from the 2015–2018 National Health and Nutrition Examination Survey. eGFR and UACR served as kidney function indicators. Participants with a higher TyG index showed a higher UACR level ($\beta = 25.10$, 95% CI: 6.76, 43.44, $P = 0.0074$) and higher levels of CKD (OR = 1.34, 95% CI: 1.13, 1.59, $P = 0.0006$).[9]

Cholesterol (CHL), Triglycerides (TG), Low-Density Lipoprotein (LDL), and very low-density lipoprotein (VLDL) significantly increased in the macroalbuminuria group and were associated with increased TyG Index. Previous studies have also shown that elevated TyG values (≥9.04) were positively associated with cardiometabolic risk factors (total cholesterol, LDL, VLDL, uric acid, alanine aminotransferase, aspartate aminotransferase, waist-hip ratio, systolic blood pressure, HOMA-IR, smoking, metabolic syndrome, diabetes, and hepatic steatosis).

CONCLUSION

This study highlights a crucial link between a higher TyG Index and an increased risk of developing microalbuminuria and declining kidney function. Essentially, the TyG Index acts as a reliable marker for insulin resistance, even more effective than traditional methods like HOMA-IR. Its strong connection with urinary albumin-to-creatinine ratio and other kidney health indicators suggests that it could be a valuable tool for predicting the progression of diabetic kidney disease, even before the first signs of microalbuminuria appear. This underscores the importance of monitoring the TyG Index in patients, as it may help catch potential issues earlier and guide preventive strategies.

Declaration by Authors

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