RESEARCH ARTICLE

Triglyceride-glucose index: A surrogate marker of homeostasis model assessment of insulin resistance to predict diabetic nephropathy

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Abstract

Objective: To determine the association of triglyceride-glucose index with homeostasis model assessment of insulin resistance in type 2 diabetes mellitus patients, and to determine the association of triglyceride-glucose index with urinary albumin-to-creatinine ratio for predicting diabetic nephropathy.

Method: The observational, cross-sectional study was conducted from September 2021 to September 2022 at the Department of Chemical Pathology, Pakistan Railway Hospital, Rawalpindi, Pakistan and comprised recently-diagnosed type 2 diabetes mellitus patients. Recorded data included age, gender, vitals, diabetes duration, body mass index and other pertinent demographic and clinical information. Measurements included spot urine albumin-to-creatinine ratio, triglyceride-glucose index, homeostasis model assesment of insulin resistance as well as fasting serum insulin, fasting plasma glucose, glycosylated haemoglobin, triglycerides, total cholesterol and serum creatinine. On the basis of triglyceride-glucose index scores, the participants were divided into 4 quartiles; Q1=4.5-5, Q2=5.1-5.5, Q3=5.6-6, and Q4=>6. Data was analysed using SPSS 26.

Results: Of the 218 patients, 141(64.7%) were females and 77(35.3%) were males. The overall mean age was 49.22±11.46 years. There were 102(46.8%) overweight patients, 33(15.1%) obese and 82(37.2%) had normal weight. There were 58(26.6%) patients in Q1, 86(39.4%) in Q2, 46(21.1%) in Q3 and 28(12.8%) in Q4. Those in Q4 showed elevated fasting plasma glucose, glycated haemoglobin, triglycerides, total cholesterol, low-density lipoprotein cholesterol, homeostasis model assessment of insulin resistance and urine albumin-to-creatinine ratio (p<0.05), as well as low values for high-density lipoprotein cholesterol and estimated glomerular filtration rate(p<0.05). Fasting serum insulin was negatively linked to glycated haemoglobin (r=-0.12, p=0.07). Triglyceride-glucose index (r=0.76, p<0.001), homeostasis model assessment of insulin resistance (r=0.48, p<0.001), and urine albumin-to-creatinine ratio (r=0.10,p=0.05) positively correlated with glycated haemoglobin. Fasting serum insulin (r=-0.13, p=0.05), negatively correlated with triglyceride-glucose index, while homeostasis model assessment of insulin resistance (r= 0.32, p<0.001) and urine albumin-to-creatinine ratio (r=0.28, p=0.05) had a positive correlation. The estimated glomerular filtration rate was significantly positively linked with fasting serum insulin (r=0.05, p=0.05), and correlated significantly negatively with triglyceride-glucose index (r=-0.35, p=0.01), homeostasis model assessment of insulin resistance (r=-0.01, p=0.86) and urine albumin-to-creatinine ratio (r=-0.02, p=0.8).

Conclusions: The triglyceride-glucose index showed a strong association with homeostasis model assessment of insulin resistance, and surpassed it in terms of predicting diabetic nephropathy in type 2 diabetes mellitus patients.

Keywords: Diabetic nephropathy, Triglyceride-glucose index, Homeostasis model assessment of insulin resistance.

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Introduction

Diabetes mellitus (DM) is a collection of metabolic illnesses characterised by hyperglycaemia, irregularities in carbohydrate, lipid and protein metabolism, and progressive damages, malfunctions and failures of different essential organs, like eyes, kidneys, nerves, heart and blood vessels.[1,2] The expected worldwide prevalence of diabetes in 2021 was 10.5%, or more than 537 million people. This was projected to grow to 643% by 2030 and 783% by 2045.[3] The incidence of diabetes in adults in Pakistan has increased to 26.7%, according to the latest data from the International Diabetes Federation (2022) making the total number of cases approximately 33,000,000.[4,5] The World Health Organization (WHO) reports that diabetes claimed almost 1.5 million lives in 2019 and was the leading cause of mortality.[6] Pakistan is one of the most vulnerable countries to diabetes-related deaths, as the prevalence is higher in low and middle-income countries. The main risk factors for developing diabetes in adults, are genetics and adopting an unhealthy lifestyle. These include eating more processed food with added sugar, leading a sedentary lifestyle, which leads to obesity.[4] Pakistan's overall weighted prevalence of generalized obesity was 57.9% (42% in males and 58% in females), and central obesity was 73.1% (37.3% in males and 62.7% in females), as determined by the WHO Asia-Pacific cutoffs.[7] Diabetic

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nephropathy (DN) is the most common underlying cause of end-stage renal disease (ESRD) in people with diabetes. Around 40% of people on Earth have DN.[8] Chronic renal impairment, as shown by albuminuria or a decrease in glomerular filtration rate (GFR), accounts for 31% of all DN cases in Pakistan.[9,10]

Since type 2 DM (T2DM) progresses slowly, patients must be tested for DN upon diagnosis and annually. Screening must assess estimated GFR (eGFR) after estimating spot urine albumin-to-creatinine ratio (UACR) from serum creatinine, urinary creatinine and albumin in a spot urine specimen.[11] Micro-albuminuria and macro-albuminuria are characterised by ACRs of 30-300mg/g and >300mg/g, respectively. Normal ACR is <30mg/g.[12] Albuminuria is a common symptom of diabetic kidney disease and a well-recognised indication of kidney impairment.[13]

Insulin-resistant kidneys experience hyper-filtration due to increased glomerular hydrostatic pressure. Glomerular hyper-filtration in DN relates to disease progression, and more chances of developing advanced disease.[14] Micro-albuminuria is linked to endothelial dysfunction and impaired vasodilation, potentially reversible with early intervention.[15]

The triglyceride-glucose (TyG) index is a recommended, cost-effective method to measure insulin resistance. It correlates with DN prediction, potentially replacing homeostasis model assesment of insulin resistance (HOMA-IR). A study in Taiwan established TyG's link to T2DM angiopathies, and a significant association between TyG score and T2DM micro-angiopathies and macro-angiopathies.[12] Chinese and Indian researchers also explored TyG association with IR.[16,17] A study in Pakistan linked TyG score to metabolic syndrome (MS).[18]

Relevant data has remained scarce in Pakistani. There is a need for new, accessible, affordable and reliable marker to predict early-stage DN in Pakistani population. The current study was planned to determine the association of TyG index with HOMA-IR in T2DM patients, and to determine the association of TyG index with UACR for predicting DN.

Patients and Methods

The observational, cross-sectional study was conducted from September 2021 to September 2022 at the Department of Chemical Pathology in collaboration with the Diabetic Clinic at Pakistan Railways Hospital, Islamic International Medical College Trust (IIMCT), Rawalpindi, Pakistan. After getting approval from the institutional ethics review committee, the sample size was determined using the formula: Z2(pq)/e2, with Z=1.96, p=prevalence of T2DM in Pakistan 17.1%, q=1-p, and margin of error e=5%.[19]

The sample was raised using non-probability consecutive sampling technique from among those attending the Diabetic Clinic. Those included were known T2DM patients with fasting plasma glucose (FPG) ≥126mg/dl, diagnosed for 1-5 years. Patients with type 1 DM (T1DM), chronic/systemic illnesses, pregnancy, smoking and those on dialysis were excluded.

Data was collected after taking informed consent from the patients and ensuring anonymity. Demographic and clinical data included age, gender, diabetes duration, waist circumference (WC), height, weight, blood pressure (BP) and body mass index (BMI). After an overnight fast of 10-12 hours, venous blood samples (5ml) were collected, using specific tubes for various parameters, and stored at -20°C. FPG and insulin concentrations were measured for HOMA-IR assessment. A spot urine sample was taken for ACR determination. UACR is measured by dividing the albumin content (in mg) by the creatinine concentration (in g) in a spot urine sample for albuminuria.[20]

On the basis of TyG index scores, the participants were divided into 4 quartiles; Q1=4.5-5, Q2=5.1-5.5, Q3=5.6-6, and Q4=>6.

Data was analysed using SPSS 26. Pearson correlation was used to analyse the relationship among TyG index, HOMA-IR, UACR, eGFR, anthropometric indices, and biochemical parameters. Linear regression analysis was used to assess the predictive capacity of HOMA-IR and TyG index for UACR and eGFR determination. P<0.05 was considered significant.

Results

Of the 218 patients, 141(64.7%) were females and 77(35.3%) were males. The overall mean age was 49.22±11.46 years. There were 102(46.8%) overweight patients, 33(15.1%) obese and 82(37.2%) had normal

Table-1: Demographic characteristics according to triglyceride-glucose (TyG) index quartiles.

Demographic Characteristics	Quartile 1 (4.5-5) n=58	Quartile 2 (5.1-5.5) n=86	Quartile 3 (5.6-6) n=46	Quartile 4 (>6) n=28
Age (years)	51.55±11.84	46.66±11.67	49.50±10.04	51.75±11.46[b]
Body Mass Index (BMI)	26.31±3.21	26.18±3.87	26.28±3.53	26.66±4.12
Waist circumference (inches)	30.98±3.03	30.73±3.62	30.00±2.62	30.93±2.23
Systolic blood pressure (SBP) (mmHg)	129.14±11.28	125.35±12.90	126.74±16.47	125.00±11.38
Diastolic blood pressure (DBP) (mmHg)	86.72±8.45	85.23±10.03	84.13±10.66	90.00±9.43[bc]
Duration of type 2 diabetes mellitus (T2DM) (years)	3.91±1.22	3.50±1.53	3.80±1.14	4.07±1.09[b]

[a]$p<0.05$ vs quartile 1, [b]$p<0.05$ vs quartile 2, [c]$p<0.05$ vs quartile 3.

Table-2: Biochemical parameters according to triglyceride-glucose (TyG) index quartiles.

Biochemical Parameters	Quartile 1 (4.5-5) n=58	Quartile 2 (5.1-5.5) n=86	Quartile 3 (5.6-6) n=46	Quartile 4 (>6) n=28
Fasting plasma glucose (mg/dl)	156.52±32.81	215.50±57.56[a]	255.41±76.23[ab]	373.29±62.15[abc]
Fasting serum insulin (µIU/mL)	3.72±1.53[b]	3.59±1.62[c]	3.00±0.96	3.31±1.51
Glycated Haemoglobin (%)	5.12±1.43	6.64±2.03[a]	7.27±1.96[a]	8.81±1.90[abc]
Serum creatinine (mg/dL)	0.90±0.50	1.03±0.47	0.98±0.37	1.00±0.53
Serum cholesterol (mg/dL)	171.03±45.00	185.38±45.27	195.78±51.94[a]	239.96±69.60[abc]
Serum triglyceride (mg/dL)	127.74±33.87	207.27±54.41[a]	332.24±84.29[ab]	558.96±252.65[abc]
HDL-C (mg/dL)	43.57±6.74	37.15±8.71[a]	36.73±7.51[ab]	33.21±8.65[abc]
LDL-C (mg/dL)	125.59±36.25	135.5±36.44	140.06±40.37	177.18±56.35[abc]
HOMA-IR	1.44±0.70	1.84±0.85[a]	1.83±0.83[ab]	2.34±0.95[abc]
TyG Index	4.92±0.13	5.32±0.14[a]	5.66±0.11[ab]	6.10±0.09[abc]
Urinary albumin (mg/dL)	4.85±3.31	6.26±4.60[a]	5.38±3.88	7.25±5.04[a]
Urinary creatinine (mg/dL)	90.91±15.91	89.70±12.21	94.70±15.14[b]	90.86±11.75
UACR (mg/g)	59.08±47.14	73.09±58.06	56.44±41.52	78.18 ±53.09
eGFR	125.28±106.93	119.52±122.86 [a]	85.52±63.14[ab]	83.41±66.05[abc]

HbA1c: Glycated haemoglobin, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insulin resistance, UACR: Spot urine albumin-to-creatinine ratio, eGFR: Estimated glomerular filtration rate. [a]$p<0.05$ vs quartile 1, [b]$p<0.05$ vs quartile 2, [c]$p<0.05$ vs quartile 3.

Table-3: Correlation of biochemical parameters with TyG index, HOMA-IR and UACR.

Parameters	Fasting serum insulin		TyG index		HOMA-IR		UACR	
	r-value	*p*-value	*r*-value	*p*-value	*r*-value	*p*-value	*r*-value	*p*-value
Fasting plasma glucose	-0.14*	0.05	0.76**	<0.001	0.48**	<0.001	0.10*	0.05
Glycated Haemoglobin	-0.12*	0.07	0.35**	<0.001	0.05*	0.38	0.15*	0.05
Total Cholesterol	-0.01*	0.05	0.39**	<0.001	0.11*	0.05	0.08*	0.05
LDL-C	-0.01*	0.93	0.55**	<0.001	0.34**	<0.001	0.16*	0.05
HDL-C	0.13	0.01	-0.35**	0.01	-0.22**	0.11	0.11	0.10
TyG Index	-0.13*	0.05	1	-	0.32**	<0.001	0.28*	0.05
eGFR	0.05*	0.05	-0.35**	0.01	-0.01	0.86	-0.02	0.8

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TyG: Triglyceride-glucose index HOMA-IR: Homeostasis model assessment of insulin resistance, UACR: Spot urine albumin-to-creatinine ratio, eGFR: Estimated glomerular filtration rate, *significant at <0.05, **significant at <0.01.

Table-4: Association of Triglyceride-glucose (TyG) index quartiles with albuminuria.

Albuminuria Categories	TyG Index Quartiles				*p*-value
	I	II	III	IV	
	4.5-5	5.1-5.5	5.6-6	>6	
Normal (n=46) (<30 mg/g)	18 (31%)	17 (19.7%)	8 (17.3%)	3 (11%)	0.05
Microalbuminuria (n=172) (30–300 mg/g)	40 (68%)	69 (80.7%)	38 (82.6%)	25 (89%)	

Table-5: Regression analysis of HOMA-IR and TyG index predicting UACR.

Parameters	Beta Value	Std. Error	*p*-value	CI 95%
HOMA-IR	1.82	4.23	0.01	[4.479-21.17]
TyG index	12.85	9.32	0.001	[16.512-20.21]

HOMA-IR=Homeostasis Model Assessment of insulin resistance, TyG index=Triglyceride Glucose Index, CI = Confidence Interval.

Table-6: Regression analysis of HOMA-IR and TyG index predicting eGFR.

Parameters	Beta Value	Std. Error	*p*-value	CI 95%
HOMA-IR	-1.90	7.57	0.05	[13.019-16.83]
TyG index	-4.43	16.66	0.02	[28.42-37.265]

HOMA-IR=Homeostasis Model Assessment of Insulin Resistance, TyG Index=Triglyceride Glucose Index, eGFR=estimated Glomerular Filtration Rate, CI = Confidence Interval.

weight. Overall, mean fasting serum insulin, glycated haemoglobin (HbA1c), HOMA-IR and TyG index levels were 3.46±1.48, 6.65±2.17, 1.79±0.86 and 5.39±0.39 respectively. The mean urinary albumin, urinary creatinine, UACR and eGFR levels were 5.83±4.25mg/dl, 91.23±13.89mg/dl, 66.50±51.8mg/g, and 99.23±48.44, respectively.

There were 58(26.6%) patients in Q1, 86(39.4%) in Q2, 46(21.1%) in Q3 and 28(12.8%) in Q4. The TyG index mean values in the four groups were 4.92±0.13, 5.32±0.14, 5.66±0.11 and 6.10±0.09. There was a significant difference in age, diastolic BP (DBP) and duration of T2DM in Q4 compared to the rest of the quartiles ($p<0.05$) (Table 1).

FPG, HbA1c, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, HOMA-IR and UACR were significantly raised in Q4 compared to the other quartiles ($p<0.05$). High-density lipoprotein (HDL) cholesterol and eGFR were significantly low in Q4 compared to the other 3 quartiles ($p<0.05$) (Table 2).

Fasting serum insulin was inversely related to FPG (r=-0.14, p=0.05) and HbA1c (r=-0.12, p=0.07), whereas TyG index (r=0.76, $p<0.001$), HOMA-IR (r=0.48, $p<0.001$) and UACR (r=0.10, p=0.05) were positively related to FPG and HbA1c. A negative association was found between TyG index and fasting serum insulin (r=-0.13, p=0.05), but TyG index had a positive correlation with HOMA-IR (r= 0.32, $p<0.001$) and UACR (r=0.28, p=0.05).

A positive correlation was found between eGFR and fasting serum insulin (r=0.05, p=0.05), while a negative correlation was found of eGFR with TyG index (r=-0.35, p=0.01), HOMA-IR (r=-0.01, p=0.86) and UACR (r=-0.02, p=0.8) (Table 3).

Overall, 172(78.9%) patients were identified with micro-

Table-7: ROC analysis for predicting HOMA-IR & TyG index AUC against albuminuria.

Test Result Variable(s)	Area Under the Curve				
	Area	Std. Error	Asymptotic Sig	Asymptotic 95% CI LL	UL
HOMAIR	0.37	0.05	0.01	0.27	0.46
TyG index	0.51	0.05	0.01	0.28	0.47

LL: Lower Limit, UL: Upper Limit.

albuminuria and 46(21.1%) had normal UACR. None of the participants had macro-albuminuria. In terms of TyG quartiles, maximum number of the patients with micro-albuminuria 25(89.3%) were in Q4 (Table 4).

Linear regression analysis results demonstrated that both TyG index (OR: 12.85, 95% CI: 16.512-20.21, *p*=0.001) and HOMA-IR (OR: 1.82, 95% CI: 4.479-21.17, *p*=0.01) significantly predict UACR (Table 5) and linear regression analysis predicting eGFR by HOMA-IR and TyG index (OR: -4.43, 95% CI: 28.42-37.265, *p*=0.02) reveal that both TyG index and HOMA-IR (OR: -1.90, 95% CI: 13.019-16.83, *p*=0.05) significantly predicts eGFR (Table 6).

Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic efficiency by measuring area under curve AUC for the TyG index and HOMA-IR. The outcomes depict that highest AUC for TyG as (0.51, 95% CI: 0.28–0.47, *p*<0.01) followed by HOMA-IR (0.37, 95% CI: 0.27–0.46, *p*<0.01). This indicates that the TyG index is a highly effective marker against albuminuria and in predicting diabetic nephropathy in comparison to HOMA-IR. The TyG index is covering 0.51 area under the curve whereas HOMA-IR is covering 0.37 area under the curve. (Table 7).

Discussion

The current study investigated the association between the TyG index and HOMA-IR among T2DM patients. Additionally, it assessed the link between TyG index and UACR as a means of predicting DN.

The TyG index has been widely studied as an indicator for diabetes, metabolic problems and heart conditions. However, it has not received as much attention as other techniques for evaluating IR.[19,20]

Lipid levels have been investigated as a significant parameter to estimate the insulin action to judge IR, which is defined as reduced sensitivity to insulin in tissues which increases the risk of hyperglycaemia, hypertension and dyslipidaemia. Increased IR and lipoprotein metabolic abnormalities, including elevated levels of triglyceride-rich lipoprotein remnants, remnant-like particle cholesterol, and apolipoprotein B, are more common in overweight and obese people with higher triglyceride levels.[21] Lower insulin sensitivity has been linked to higher triglyceride levels, and vice versa. Muscles with high triglyceride levels have been shown to have impaired glucose metabolism.[17,22,23] FPG and triglycerides were found to be independently associated with DN in the current study.

A 2018 study in Pakistan explored the correlation of TyG index with IR and DN. TyG index had a stronger linear relationship with BMI, atherogenic dyslipidaemia, HbA1c and IR than the other indicators, such as fasting triglycerides, HOMA-IR and HDL-C. The study concluded that the TyG index was a more reliable indicator of MSm and reported no evidence establishing a connection between the TyG index and DN.[23]

The current study found a significant negative correlation of eGFR with TyG index, HOMA-IR and UACR. In contrast, a study in Chinese population showed no significant association between the TyG index and eGFR (*p*=0.786). However, consistent with the current findings, it found a strong link between an elevated TyG index and type 2 DN (*r*=0.173, *p*=0.006), and a positive correlation of TyG index with 24-hour albumin excretion rate.[16]

Previous research has also linked DN with HOMA-IR. The current findings confirmed the earlier studies in reporting that DN patients frequently had elevated HOMA-IR values. Specifically, the current study found that the TyG index had a higher area under the curve (AUC) (0.51, 95% confidence interval [CI]: 0.28-0.47, *p*<0.01) with sensitivity 67%, specificity 85% and a better association with DN than HOMA-IR (AUC 0.37, 95% CI: 0.27-0.46, *p*<0.01) with sensitivity 59% and specificity 65%. TyG index was evidently a more accurate diagnostic tool for predicting albuminuria and type 2 DN compared to HOMA-IR.

Similar to the current study, a 2020 study in India explored TyG index in association with DN, diabetic neuropathy and diabetic retinopathy, and concluded that FPG and triglycerides were independently associated with DN, while albuminuria was correlated with higher level of TyG index, but it did not include eGFR.[17] However, the difference between the studies is that the current study incorporated spot urine ACR instead of 24-hour albumin excretion rate.

Type 2 diabetics with and without nephropathy had more severe IR with higher TyG index and HOMA-IR scores. The current study identified a strong association between high TyG index and micro-albuminuria, which suggested diabetic micro-angiopathy, which is the major cause of renal failure.[17] Micro-albuminuria is the first sign of DN. Increased glomerular hydrostatic pressure, renal vascular permeability, and glomerular hyper-filtration result from IR.[14] According to several studies, dyslipidaemia is assumed to be the significant part in the development of renal impairment in T2DM.[25] Earlier studies have linked IR to a greater risk of progressive DN.[26] In the current study, 78.9% participants were identified with micro-albuminuria compared to 21.1% with normal UACR, while none of the participants were in the macro-albuminuria category. Maximum number of the patients with microalbuminuria (89%) were in QIV compared to QI (68%), Q2 (80.7%) and Q3 (82.6%).

Linear regression analysis demonstrated that TyG index (odds ratio [OR]: 12.85, 95% CI: 16.512-20.21, *p*=0.001) and HOMA-IR (OR: 1.82, 95% CI: 4.479-21.17, *p*=0.01) significantly predicted UACR. (Table 5) Similarly, regression analysis verified that TyG index (OR: -4.43, 95% CI: 28.42-37.265, *p*=0.02) and HOMA-IR (OR: -1.90, 95% CI: 13.019-16.83, *p*=0.05) significantly predicted eGFR, meaning that one-unit increase in the TyG index predicted 4.43-unit decrease in eGFR compared to one-unit increase in HOMA-IR predicting 1.90-unit decrease in eGFR. (Table 6)

The current study found that micro-albuminuria (n=172) was independently correlated with a higher TyG index, as the patients were recruited with 1-5 years of T2DM duration with the aim of predicting DN at an early stage. T2DM was linked with micro-angiopathies and macro-angiopathies in a 2020 study in China. A high TyG index was related with micro-albuminuria, although the research group was exclusively Chinese, therefore the findings may not apply to other populations.[12]

The current study found that the TyG index was the most sensitive and specific marker for early diabetic nephropathy diagnosis, with sensitivity 67% and specificity 85%. A 2021 study reported 61.7% sensitivity and 76% specificity for DN in T2DM patients with a high TyG index.[16]

The current study has certain limitations. Firstly, it was an observational, cross-sectional study that has inherent design constraints. It is essential to conduct prospective studies to investigate the association of TyG index score with the onset and progression of DN in T2DM patients. Secondly, it was a single-centre study. Multicentre epidemiological studies are recommended.

Conclusion

TyG index showed a strong association with HOMA-IR, and surpassed it in predicting DN in T2DM patients. It effectively predicted micro-albuminuria risk and DN in T2DM patients at an early stage.

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