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Original Article

Association of Triglyceride-Glucose (TyG) Index with Diabetic Nephropathy (DN) In Patients of Type II Diabetes Mellitus Presenting in Primary Clinics

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ABSTRACT

Objective: To determine the association of triglyceride-glucose (TyG) index with diabetic nephropathy (DN) in patients with type II diabetes mellitus presenting in primary clinics

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Family Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Oct 2023 to Jan 2024.

Methodology: Patients aged between 25 and 60 years, known cases of Type 2 DM, oral hypoglycemics, and reporting to family medicine clinic for their follow-up were included. Samples of 231 patients were collected for serum triglyceride, fasting plasma glucose, and urinary ACR. Patients were divided into DN and non-DN groups based on urinary ACR (cut off <30 mg/g). The TyG index was compared between the two groups. Correlation and association were determined between the TyG index and DN.

Results: DN was detected in 48(20.8%) patients while 183(79.2%) were non-DN. Patients with DN had a greater TyG index as compared to those without DN (8.13±0.46 vs 7.19±0.33), and the difference was statistically significant (p-value <0.001). Correlation studies revealed a positive linear correlation of urinary ACR levels with serum triglyceride (r =0.898, p-value <0.01) and an association study of TyG index with DN revealed OR 1.89 (95% CI 1.38 - 2.35) p<0.001.

Conclusion: TyG index is greater in patients with DN as compared to non-DN. TyG index, being a low-cost and routinely available test, has the potential to be used as a risk assessment and early detection tool for DN.

Keywords: Diabetic Nephropathy, Insulin Resistance, Triglyceride Glucose Index, Type II DM.

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INTRODUCTION

Diabetes Mellitus (DM) is a disorder of the endocrine system with excessively elevated blood glucose levels resulting from absolute or relative insulin deficiency, insulin resistance (IR), or both. It is a prevalent and rapidly expanding global ailment. It is estimated that by 2045, this condition will impact around 693 million people worldwide.[1] Type II DM is the commonest subtype of DM, representing 90-95% of all cases.[2] Poor glycemic control in diabetics may result in acute complications such as Diabetic ketoacidosis (DKA) and non-ketotic hyperosmolar state (NKHS). While chronic complications can be separated into microvascular (nephropathy, neuropathy, and retinopathy) and macrovascular complications (cerebrovascular, coronary artery, and peripheral vascular disease). Achieving specific target glucose levels is crucial to preventing complications in individuals with diabetes.[3] While the exact mechanisms underlying vascular damage induced by hyperglycemia remain intricate and not completely understood, it is hypothesized that elevated intracellular glucose levels stimulate the generation of reactive oxygen species, activating protein kinase C, the polyol pathway flux, and formation of the advanced glycation end-product.[4] Apart from it, elevated plasma triglyceride levels have been linked to metabolic disorders and cardiovascular illness as a result of their interaction with higher levels of glucose in skeletal muscle, adipose tissue, and pancreatic beta cells.[5]

Asian people with Type-II DM have a significantly high incidence of diabetic nephropathy (DN). Due to the substantial diabetic population in the Asia-Pacific area, the healthcare system is heavily burdened by the high number of patients with DN.[6] Scientific studies have confirmed that the formation and progression of DN are strongly linked to the

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regulation of blood sugar levels. DN is determined by the presence of albuminuria or reduced glomerular filtration rate. Elevated levels of albuminuria serve as a robust indicator for the progression of overt DN.[7] People with microalbuminuria often show a greater degree of IR, suggesting that IR may contribute to the rapid advancement of DN.[8] Investigating the relation between IR and DN will enhance our understanding of the development of DN, and may reveal novel opportunities for better outcomes in Type II DM.

Most IR assessment methods, including the hyperinsulinemic euglycemic glucose clamp (HEGC), are expensive and cumbersome procedures. On the other side, the homeostasis model assessment for insulin resistance (HOMA-IR) is commonly practiced in clinical settings to assess IR through measurements of plasma fasting insulin and glucose.[9] However, the plasma insulin levels are expensive and not frequently available in laboratories. Thus, new biomarkers that are more cost-effective and simpler to detect are required. In comparison to HOMA-IR and HEGC, the triglyceride glucose (TyG) index, which is calculated from fasting plasma glucose (FPG) and triglyceride (TG) levels, has been demonstrated as a cost-effective and novel marker in identifying IR.[10] Few studies, however, have examined the association of TyG index and DN. The objective of this study was to determine the association between DN and the TyG index among individuals who have Type II DM.

METHODOLOGY

A cross-sectional study was carried out at the Department of Family Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Oct 2023 to Jan 2024 after approval from the Institute Ethical Committee (A/28/ERC/11/24). The sample size was determined using the WHO sample size calculator, with 95% confidence interval and 5% margin of error, considering a prevalence of DM of 13.7% amongst the Pakistani population.[11]

Inclusion Criteria: Both male and female patients aged 25 to 60 years with a known case of Type 2 DM, defined by American Diabetes Association criteria, who were on oral hypoglycemics and reported to the family medicine clinic for follow-up were included in the study.

Exclusion Criteria: Patients diagnosed with Type II DM for < 1 year, Type I DM, who experienced acute complications of DM, malignancy, diagnosed with renal stones, UTI, primary renal disorder, on any pharmacological treatment such as steroids for last 3 months, and pregnant patients were excluded from our study.

A total of 231 patients were included in our study by nonprobability convenient sampling technique. After taking informed written consent and carrying out history and anthropometric measurements, fasting blood samples with at least 10 hours of overnight fast were collected in the morning for analysis of FPG and serum TG levels. A spot urine sample was collected at the same time for analysis of urinary albumin to creatinine ratio (ACR) from the spot urine sample. As soon as the blood and urine samples were collected, they were all analyzed. The levels of FPG, serum TG and urinary creatinine were assessed using a fully automated chemistry analyzer Cobas 501 (Roche Diagnostics). The immunoturbidimetric method was used for estimation of urinary albumin on the same instrument. DN was defined as urinary ACR> 30 mg/g in two of the three consecutive urine samples.[12] The TyG index was derived by using equation: TyG Index = ln (fasting triglycerides [mg/dL] x fasting glucose [mg/dL] / 2) where ln represents the natural logarithm function.[13]

IBM Statistical Package for the Social Sciences (SPSS) version 23 was used for statistical analyses. The Shapiro-Wilk test was applied to determine distribution of data, which revealed a parametric distribution. Percentages and frequencies were used for qualitative variables while Mean±SD were used for quantitative variables. Mean comparison of serum triglyceride, plasma fasting glucose and TyG index between DN and non-DN patients was done by independent sample t-test, *p*-value ≤0.05 was considered statistically significant and Pearson correlation was used to determine correlation between serum TG, FPG and TyG index with urinary ACR levels. The association of TyG index and DN was determined by Logistic regression analysis.

RESULTS

Our study included 231 diabetic patients, of whom 132(57.1%) were male and 99(42.9%) were female. The mean age of patients was 44.62±7.05 years. Mean values of biochemical parameters were serum TG (156.92±27.99 mg/dl), FPG (129.30±23.20 mg/dl), urinary ACR (51.89±44.10 mg/g), and TyG index (7.38±0.52). Of 231 patients, 183(79.2%) had urinary ACR <30 mg/g, considered the non–DN group (Group 1), while 48(20.8%) had urinary ACR >30 mg/g, considered the DN group (Group 2). Group 1 patients had a mean urinary ACR of 20.81±4.20 mg/g,

while patients in Group 2 had a mean urinary ACR of 170.3±85.33 mg/g. Mean values of serum triglyceride, FPG, and TyG index were compared between patients of Group 1 vs Group 2 using an independent sample t-test as depicted in Table-I.

Table-I: Mean comparison of Biochemical parameters between Group-1 & Group-2 (n=231)

Total Patients = 231			
Biochemical Parameters	**Group 1 – Non-DN (Urinary ACR <30 mg/g) n=183**	**Group 2 - DN (Urinary ACR >30 mg/g) n=48**	***p*-value**
	Mean ± SD	**Mean ± SD**	
Serum TG (mg/dl)	144.50±10.74	204.28±22.28	<0.001
FPG (mg/dl)	118.43±7.92	170.75±13.28	<0.001
TyG Index	7.19±0.33	8.13±0.46	<0.001

TG = Serum Thyroglobulin, FPG=Fasting Plasma Glucose, TyG= Triglyceride-Glucose Index

The results indicated that the TyG index was elevated in patients with DN as compared to patients without DN (8.13±0.46 vs 7.19±0.33). Other biochemical parameters, such as serum triglyceride & fasting plasma glucose were also higher in DN patients in comparison to those who didn't have DN. Statistically significant differences were observed in the mean values of all parameters between the two groups, with a *p*-value <0.05.

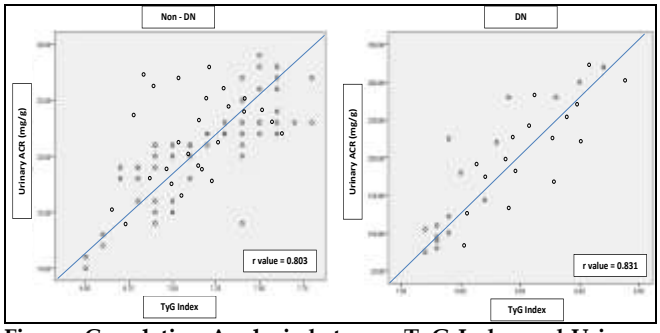

Figure: Correlation Analysis between TyG Index and Urinary ACR levels

The results additionally demonstrated that urinary ACR values increased in parallel with TyG Index values amongst the patients. Pearson's correlation applied to determine correlation revealed a positive linear correlation of urinary ACR levels with serum triglyceride (r=0.898, *p*-value <0.01), fasting plasma glucose (r=0.912, *p*-value <0.01), and TyG index (r=0.829, *p*-value <0.01) as depicted in Figure. Logistic regression analysis revealed a strong association of TyG index with DN, having an OR 1.89 (95% CI 1.38 - 2.35), *p*<0.001, as shown in Table-II.

Table-II: Logistic regression analyses of TyG index on Diabetic Nephropathy

	Univariate		**Multivariate**	
	OR	***p*-value**	**OR**	***p*-value**
Diabetic Nephropathy	1.89 (95% CI 1.38 - 2.35)	<0.001	1.48 (95% CI 1.26-1.73)	<0.001

OR = Odds Ratio

DISCUSSION

Our findings indicate a noteworthy positive correlation and association between DN and an elevated TyG index among type 2 DM patients. Insulin resistance (IR) is characterized as reduced tissue sensitivity to insulin; it increases risk of developing hyperglycemia, hypertension, and dyslipidemia. The clamp method, considered the most accurate way to measure insulin resistance, does not seem viable in clinical settings due to the complexity of procedure. As a result, numerous other surrogate techniques have been investigated for indirect measurement of IR.[14]

HOMA-IR is a common technique for assessing IR. HOMA-IR is derived by measuring fasting insulin and glucose levels. However, the level of serum insulin varies significantly between individuals and is not standardized for assessment, as concluded by Hansen *et al.*[15] Several other parameters have also been identified for measurement of IR. Elevated triglyceride levels are associated with impaired glucose metabolism in muscles, suggesting a connection between triglyceride increase and reduced insulin sensitivity, although the precise mechanism requires further exploration, as described by Ma *et al.*[16] Simoniene *et al.*, found that the triglycerides and glucose index (TyG) in plasma can be used to estimate insulin resistance.[17] Individual indicators, including BMI, waist circumference, FBS, triglycerides, insulin, Homa-IR, and TyG-index, were used to identify IR in healthy, overweight, and diabetic participants. The TyG index closely resembled the glucose clamp technique in IR measurement, with a 96.5% sensitivity and 85.0% specificity, hence having an edge over other indices in assessing insulin resistance.[16,17]

Studies similar to Pan *et al.*, conducted a study on 4721 Type II DM Chinese patients and found that a high TyG index was substantially associated with development of microalbuminuria (OR 1.39, 95% CI 1.22-1.5). In their study, patients were categorized into four quartiles according to the increasing order of TyG Index. Patients who were in the fourth quartile (TyG Index: 9.67 – 12.87) exhibited the greatest risk for development of microalbuminuria (OR = 1:73, 95% CI

1:28 − 2:35). Hence, it was determined that IR is related to micro and macrovascular complications of DM.[18] In our study, it was found that TyG Index, an indicator of insulin resistance, was elevated in patients who developed diabetic nephropathy, a microvascular consequence of DM, as compared to those diabetic patients who didn't develop DN (7.19±0.33 vs 8.13±0.46, *p*-value <0.005). There was a strong association of high levels of TyG Index with DN (OR 1.89, 95% CI 1.38 - 2.35).

In a similar study performed on 1413 diabetic patients, Liu *et al.*, concluded that TyG Index was greater in patients with DN in comparison to those who didn't have DN (7.6±0.6 vs 7.4±0.7, *p*-value <0.005), with a notable association of TyG index with DN (OR 1.70, 95% CI 1.36-2.11).20 TyG Index was greater in DN patients in comparison to non-DN patients (9.42 ± 0.74 vs 9.10 ± 0.38), findings that were similar to our study. They also concluded that for DN identification, TyG index with a cut-off value >9.66 had a greater AUC (0.67, *p*=0.002) as compared to AUC for HOMA-IR (0.61, *p*=0.029). Odds ratio for DN at TyG index cut off >9.66 was 2.99 (95% CI 1.61 – 5.06).

This study has contributed to the literature that the TyG index is associated with DN. The TyG index, being a convenient and easily assessable tool, can be used as an alternative to other parameters of IR. It can aid in the early prediction and monitoring of diabetic patients for the development of DN.

LIMITATIONS OF THE STUDY

The main limitation of the study was that it was a cross-sectional study conducted at a single center with a limited sample size. Secondly, only a single parameter for measurement of IR was used, and data were collected at a single point in time. As insulin sensitivity varies across ethnicities, we would recommend further prospective multicentric studies to determine population-based results for the TyG index using various biomarkers of IR simultaneously to determine the association with DN development and progression.

CONCLUSION

TyG index is higher in DN patients as compared to non-DN patients. Our findings indicate a noteworthy correlation and association between DN and an elevated TyG index among type 2 DM patients. IR is a critical and significant factor in the pathogenesis of DN; therefore, it could be a viable therapeutic and preventative target. TyG index, being a low-cost and routinely available test, has the potential to be used as a risk assessment and early detection tool for DN.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ST & SN: Data acquisition, data analysis, critical review, approval of the final version to be published.

AAK & AIP: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

NN & HT: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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