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Diabetology

ASSOCIATION OF TRIGLYCERIDE–GLUCOSE INDEX WITH HbA1C AND INSULIN RESISTANCE IN DIABETES MELLITUS.

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ABSTRACT **Background :** The aim of the study was to investigate the association of triglyceride–glucose (TyG) index with Glycated haemoglobin (HbA1c) and insulin resistance in diabetes mellitus (DM) and to further explore the association of TyG index and related parameters with diabetic retinopathy(DR). **Methodology:** In a single centre case-control study, 80 type 2 diabetes mellitus patients of more than 5 yrs duration were divided into two groups of with and without DR. DR group was classified, as per early treatment diabetic retinopathy study (ETDRS) scale. Detailed history was taken, examination was carried out and blood samples were taken for FBS, HbA1c and lipid profile. TyG and TyG-related paramteres were calculated. **Results:** Mean levels of HbA1c, TC,TG and LDL were significantly increased($p< 0.05$) in patients with DR in comparison to those without DR. Mean levels of TyG, TG/HDL, TyG-BMI and TyG-WC were increased significantly (<0.01) in diabetic subjects with DR as compared to diabetic subjects without DR. TyG index was significantly correlated with HbA1c, TG/HDL, TyG-BMI and TyG-WC. The receiver operating characteristic (ROC) analysis showed that TyG-BMI had a maximum area under the curve of 0.816 for identifying DR. **Conclusions:** TyG index can be used as a simple and inexpensive alternative to assess glycemic control and insulin resistance in diabetes mellitus in patients with diabetes.

KEYWORDS : Triglyceride–Glucose Index, insulin resistance, diabetic retinopathy

INTRODUCTION:

Diabetes Mellitus (DM) refers to a group of metabolic disorders characterised by hyperglycemia due to defects in insulin secretion, action or both. It is expected to become the seventh leading cause of mortality by the year 2030.[1] Prevalence of DM in India ranges from 5%-15%.[2]

Persistent hyperglycemia, dyslipidemia and insulin resistance plays a major role in development of micro- and macrovascular complications of diabetes mellitus. Insulin resistance may cause an imbalance in glucose metabolism which generates chronic hyperglycemia, that in turn triggers oxidative stress and leads to an inflammatory response and cell damage.[3,4] This aberrant insulin signaling induces endothelial dysfunction, contribute to various micro- and macrovascular complications of diabetes mellitus.

Diabetes retinopathy (DR) is one of the microvascular complication of diabetes that often results in blindness. The global prevalence of DR is 34.6%.[5] The pathological changes of DR like retinal vascular and neural damage are often concealed, leading to delay in medical intervention, and progression of disease, that results in irreversible vision loss. Therefore, early diagnosis and treatment of DR has significant clinical importance. The pathogenesis of DR is a multifaceted, and several factors that contribute to its progression and severity, such as insulin resistance, abnormal lipid metabolism, hypertension and inflammation and insulin are known.[6,7,8]

At present, the gold standard for assessment of insulin resistance is hyperinsulinemic normoglycemic clamp, that measures the sensitivity of peripheral tissues to insulin.[9] Alternatively, in clinical practice, the homeostasis model assessment of insulin resistance (HOMA-IR), that has a good correlation with HIEC is the most commonly used method for assessing insulin resistance.[10] However, fasting insulin levels are required to calculate HOMA-IR, that can be difficult to obtain and time consuming in some primary medical institutions. Therefore, a large number of surrogate indexes are being investigated to assess glycemic control which do not rely on fasting insulin levels.

Recently, various indexes such as Triglyceride–Glucose (TyG) index, Triglyceride/High Density Lipoprotein (TG/HDL) ratio, Body Mass Index (BMI), waist circumference (WC) and visceral adiposity index (VAI) showed promising results as surrogate markers for the assessment of insulin resistance. Several studies have evaluated that TyG-related parameters are more effective than the isolated TyG index, such as TyG combined with body mass index (TyG-BMI), TyG combined with waist circumference (TyG-WC) and TyG combined with waist-height ratio (TyG-WHtR).[11] However, the effect of applying the TyG index and TyG-related parameters in diabetic subjects with chronic complications like retinopathy is still unclear. Hence, the present study was conducted to investigate the association of TyG index with HbA1c and insulin resistance in DM and to further explore association of TyG index and TyG-related parameters with DR.

Methodology:

It was a case-control and single centric study conducted over a period of 2 years December 2020 to September 2021 in the department of Biochemistry, in collaboration with the department of Ophthalmology and General Medicine, Government Medical College and Hospital, Chandigarh. It was initiated after obtaining permission from the institutional research and ethics committee(IEC).

Study Population

The study was conducted among patients with type-2DM, of more than 5 years duration, attending the outpatient clinics of the departments of Medicine & Ophthalmology. The study group comprised of 80 patients of Type2 DM(diagnosed on the basis of WHO criteria for DM of more than 5 years duration, of which 40 patients had DR (group 1) and 40 patients were without DR (group 2).[12] DR was categorized according to early treatment diabetic retinopathy study (ETDRS) retinopathy severity scale.[13] Patients with a history of cardiac stroke, malignancies, end-stage renal disease, severe eye disease, or retinal detachment were excluded from the study.

Data Collection

A detailed history and clinical findings were recorded on a structured proforma at the time of enrolment after taking consent of the participants. Anthropometric measurements were recorded and body

mass index (BMI) was calculated and categorized based on NHLBI criteria.[14] The WC was measured to the nearest 0.1 cm midpoint between the iliac crest and costal margin at the end of expiration. TyG index, TyG-WC, TyG-BMI, VAI and TG/HDL indices were calculated using the following formula: [15,16,17]

VAI (women) = [WC/(36.58+1.89 x BMI)] x (TG/0.81) x (1.52/HDL)
VAI (men) = [WC/(39.68+1.88 x BMI)] x (TG/1.03) x (1.31/HDL)
(where TG and HDL-C concentrations are in mmol/L and WC in cm)
TyG index = ln [fasting TG (mg/dL) x fasting glucose (mg/dL)/2]
TyG-WC = TyG index x WC
TyG-BMI = TyG index x BMI
TG/HDL = TG (mg/dL)/HDL (mg/dL)

Enrolled patients were assessed by an experienced ophthalmologist with slit lamp biomicroscopy and finding were recorded and classified according to early treatment diabetic retinopathy study (ETDRS). Peripheral venous blood samples were collected at the time of recruitment for the estimation of biochemical parameters like fasting blood glucose (FBG), HbA1c and lipid profile.

Data Analysis:
Discrete categorical variables were reported as counts and percentages. Continuous data was presented in the form of its mean and standard deviation. Comparison between the groups was done using student's t-test. Pearson correlation analysis was done to assess the correlation between TyG and HbA1c, TG/HDL, TyG-BMI, TyG-WC and VAI. Receiver Operative Characteristic (ROC) Curve analysis was done to find the cut off value of all indexes. A p-value <0.05 was considered as significant. Statistical analysis was conducted using IBM SPSS statistics.

RESULTS:
The demographic and clinical characteristics of the diabetic subjects are shown in Table 1. Mean age of the study group was found to be (56.7±5.2 years). Mean duration of diabetes was (10.0±3.3 years).Mean BMI was found to be (24.0±2.4 kg/m^2) in the subjects of study group. Mean Fasting blood glucose and HbA1c levels were found to be (162.2±34.1 mg/dl and 9.7±0.4%) respectively.

The demographic and clinical characteristics of the age and gender matched subjects of the study groups are shown in Table 2. Mean duration of DM, BMI and waist circumference were found to be more in patients with DR as compared to patients without DR and the difference was found to be statistically significant (p< 0.01).

Table 1:Demographic and clinical characteristics of diabetic subjects.

Subject Characteristics	Mean±SD (n=80)
Age(years)	56.7±5.2
Duration of diabetes(years)	10.0±3.3
Male(%)	44(55%)
female(%)	36(45%)
Waist Circumference(cm)	94.4±1.4
Body Mass Index(BMI)(kg/m2)	24.0±2.4
Fasting blood glucose(mg/dl)	162.2±34.1
HbA1c(%)	9.7±0.4
TC(mg/dl)	211.7±52.1
TG(mg/dl)	183.4±63.0
LDL(mg/dl)	138.3±39.2
VLDL(mg/dl)	35.3±4.0
HDL(mg/dl)	44.1±10.2
TG/HDL	4.4±1.8
Visceral Adiposity Index(VAI)	6.3±2.7
TyG index	9.5±0.5
TyG-BMI	229.7±28.9
TyG-WC	898.8±51.8
Urea(mg/dl)	41.7±14.3
Creatnine (mg/dl)	1.2±0.7

SD=standard deviation, TC=Total Cholesterol, TG=Triglycerides, LDL=Low density lipoprotein, VLDL=very low density lipoprotein, HDL=High density lipoprotein, TG/HDL=Triacylglycerol/High density lipoprotein ratio, TyG=Triglyceride-Glucose index

Table 2:Demographic and clinical characteristics of subjects of study groups

Parameter	Diabetic subjects without DR (n=40)	Diabetics subjects with DR (n=40)	p value
Age(years)	56.1±4.3	57.3±5.9	0.31
Duration of diabetes(years)	8.2±1.8	11.8±3.4	<0.01
Male(%)	55%	60%	0.35
female(%)	45%	40%	
WC(cm)	93.3±0.9	95.4±1.0	<0.01
BMI(kg/m2)	22.8±1.8	25.2±2.4	<0.01

The difference in the mean levels of HbA1c, TC,TG and LDL were found to be significantly increased(p< 0.05) in patients with DR in comparison to those without DR as shown in Table 3.

The mean levels of fasting blood glucose is increased in patients in DR as compared to diabetic patients without DR. However, the difference is not statistically significant. Mean levels of TyG, TG/HDL, TyG-BMI, TyG-WC and VAI were also found to be increased significantly (<0.01) in diabetic subjects with DR as compared to diabetic subjects without DR.

Table 3: Biochemical parameters and indices of diabetic patients with and without retinopathy

Parameter	Diabetic subjects without DR (n=40)	Diabetics subjects with DR (n=40)	p value
FBS(mg/dl)	158.4±36.5	166.0±31.5	0.32
HbA1c(%)	9.1±1.7	10.3±2.3	0.01
TC(mg/dl)	199.7±49.7	223.4±52.3	0.04
TG(mg/dl)	158.8±60.1	207.4±56.7	<0.01
LDL(mg/dl)	128.0±36.6	148.3±39.5	0.01
VLDL(mg/dl)	33.2±4.2	37.3±4.6	0.16
HDL(mg/dl)	44.5±11.2	43.6±9.2	0.69
TG/HDL	3.8±1.9	4.9±1.6	<0.01
VAI	5.6±2.9	6.9±2.3	0.02
TyG	9.3±0.5	9.7±0.3	<0.01
TyG-BMI	213.8±23.0	245.1±25.7	<0.01
TyG-WC	870.8±51.1	926.2±35.6	<0.01

In Table 4, the TyG index was found to be positively correlated with HbA1c (r=0.304, p<0.01), TG/HDL (r=0.691, p<0.01), TyG-BMI (r=0.641, p<0.01), TyG-WC (r=0.966, p<0.01) and VAI (r=0.664, p<0.01).

Table 4: The correlation analysis of TYG with HbA1c, TG/hdl ratio, TYG-BMI,TYG-WC and VAI in type 2 diabetes mellitus

Parameter	Correlation coefficient(r)	P value
HbA1c	0.304	<0.01
TG/HDL	0.691	<0.01
TyG-BMI	0.641	<0.01
TyG-WC	0.966	<0.01
VAI	0.664	<0.01

Figure 1 shows the receiver operating characteristic (ROC) curve analysis for TyG, TG/HDL, TyG-BMI, TyG-WC and VAI to evaluate the area under curve values for discrimination between diabetic subjects with and without retinopathy. The ROC analysis showed that TyG-BMI (AUC=0.816,p<0.01 and cut off value = 217.6) was the best marker for discriminating diabetic subjects with DR with sensitivity of 85% and specificity of 58% when compared with the other indexes.

Areas under the curve for TG/HDL (AUC=0.699, p<0.01), TyG (0.704, p<0.01), TyG-WC (AUC=0.801,p<0.01) and VAI(AUC=0.684, p<0.01) are shown in Table 5.

Table 5: Area under the curve of different parameters in diabetic subjects with and without retinopathy

Parameters	Area	Asymptotic 95% confidence interval		P value
		Lower bound	Upper bound	
TyG	0.704	0.591	0.817	<0.01
TG/HDL	0.699	0.585	0.814	<0.01
TyG-BMI	0.816	0.725	0.908	<0.01
TyG-WC	0.801	0.707	0.894	<0.01
VAI	0.684	0.567	0.801	<0.01

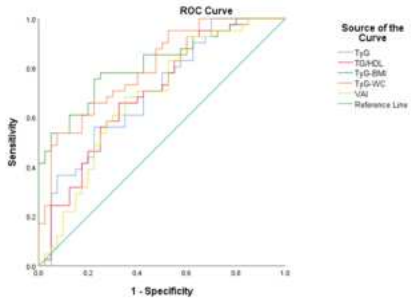

Figure 1. ROC plot for Area Under the Curve for different parameters in diabetic subjects with and without retinopathy

DISCUSSION:

Diabetes mellitus is a serious public health concern and has significant impact on health expenditure globally. Hyperglycemia damages the retinal microvascular system, resulting in diabetic macular edema (DME), neovascularization, vitreous hemorrhage, tractive retinal detachment, and ultimately blindness.[18] Apart from hyperglycemia, abnormal lipid metabolism exacerbates the condition.

Insulin resistance is associated with chronic complications of diabetes mellitus involving different organs, especially eyes, kidneys and the heart.[19] Obesity, characterized by abnormal or excessive fat accumulation, is one of the established risk factors for diabetes mellitus. It is observed that chronic low-level inflammation due to obesity promotes the development of diabetic complications by aggravating insulin resistance.[20] Previous studies showed that hypertrophy or hyperplasia of adipose cells results in the enhanced or weakened expression of adipokines, that further exacerbates the presence of insulin resistance.[21,22] Therefore, lipid abnormalities and oxidative stress aggravates the damage caused by diabetes to the retina.

The TyG index has been reported to be surrogate biochemical index that reflects the combined effect of glucose and lipids.[23] Multiple studies have demonstrated that combining the TyG index with obesity related indicators, such as waist circumference, BMI, and WHtR, enhances the ability to predict insulin resistance.

In our study, BMI and WC was found to be significantly increased ($p<0.01$) in diabetic subjects with DR as compared to diabetic subjects without DR, thus underpinning the role of insulin resistance in the development of diabetic retinopathy. Dyslipidemic changes in diabetic subjects with DR were also found as illustrated by elevated levels of TC, TG, LDL($p<0.05$) and reduced levels of TG/HDL and HDL levels. The results are in accordance with Montgomery et al. that observed a severe decrease in b/a wave ratio and retinal function which is considered to be caused by dyslipidemia and increased oxidative stress.[24]

In the present study, TyG, TyG-BMI, TyG-WC and VAI were found to be significantly increased ($p<0.01$) in diabetic subjects with DR as compared to diabetic subjects without DR. in accordance, Selvi NMK et al showed elevated levels of TyG, TyG-BMI, TyG-WC and VAI in diabetic subjects with poor glycemic control as compared to good glycemic control.[25]

In the present study, pearson correlation analysis showed positive correlation between TyG index and HbA1c($r=0.304, p<0.01$), TG/HDL($r=0.691, p<0.01$), TyG-BMI($r=0.641, p<0.01$), TyG-WC($r=0.966, p<0.01$) and VAI($r=0.664, p<0.01$). Hameed et al showed that increased VAI adversely affects glycemic control in women with T2DM.[26] A five-year prospective study conducted in Chinese T2DM adults demonstrated that Chinese VAI is a better predictor of T2DM and prediabetes than BMI, WC and waist-to-hip ratio.[27]

A large-scale cross-sectional study concluded that TyG-BMI had the best discriminative power for assessing insulin resistance in clinical settings.[28] In the present study, ROC curve analysis showed the TyG-BMI had the best discriminative power to discriminate diabetic subjects with and without DR(AUC=0.816, $p<0.01$) as compared to TG/HDL (AUC=0.699, $p<0.01$), TyG (0.704, $p<0.01$), TyG-WC (AUC=0.801,$p<0.01$) and VAI(AUC=0.684, $p<0.01$). Taiwo et al. concluded that TyG-WHtR is a superior predictor of metabolic syndrome risk in Nigerians compared to the TyG index and other TyG-related parameters.[29]

CONCLUSIONS:

TyG index could potentially serve as a straightforward, reliable and practical measure in the treatment and management of DR. It has reflected the glycemic control and also predicted the insulin resistance. TyG index derived from fasting blood glucose and triglyceride levels is routinely measured in small laboratories and readily available. Thus, it acts as a simple and inexpensive marker, which identifies both glycemic control and insulin resistance in diabetes mellitus.

Nonetheless, the presence of numerous combined risk factors in diabetic patients with vasculopathy may weaken the correlation of the TyG index. Future studies should thus aim to determine the safety threshold of the TyG index to guide medication and treatment in diabetic individuals, thereby delaying the onset and progression of diabetic retinopathy.

Limitations

In our study we used a small sample size. A large scale multicentric cohort study can be done in the future to confirm the reported findings in various ethnic population and external validity.

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