MAEDICA – a Journal of Clinical Medicine
2021; 16(3): 375-381
https://doi.org/10.26574/maedica.2021.16.3.375

MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

Association of Triglyceride–Glucose Index (TyG index) with HbA_{1c} and Insulin Resistance in Type 2 Diabetes Mellitus

Nachimuthu MAITHILI KARPAGA SELVI[a], Sivakumar NANDHINI[a], Varatharajan SAKTHIVADIVEL[c], Shanmugam LOKESH[b], Abu Raghavan SRINIVASAN[a], Saravanan SUMATHI[a]

[a]Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute, SBV, Puducherry, India

[b]Department of Medicine, Mahatma Gandhi Medical College and Research Institute, SBV, Puducherry, India

[c]Department of Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

ABSTRACT

Background: *The aim of this study was to assess the association of triglyceride–glucose (TyG) index with glycated haemoglobin (HbA_{1c}) and insulin resistance in type 2 diabetes mellitus (T2DM).*

Methods: *A total of 140 patients with T2DM were included in this cross-sectional study and divided into two groups according to their HbA_{1c} levels: participants with HbA_{1c} <7.0% (n=75) and those with HbA_{1c} >7.0% (n=65) were defined as having a good glycemic control (group I) and a poor glycaemic control (group II) in T2DM. Anthropometric and biochemical parameters were measured, while the values of triglyceride (TG) to high density lipoprotein cholesterol (HDL-C) (TG/HDL-C) ratio and TyG index were calculated using formula.*

Results: *Body mass index (BMI), fasting blood glucose (FBS), HbA_{1c} and homeostatic model assessment for insulin resistance (HOMA-IR) were significantly higher in diabetic patients with poor glycemic control. TyG index was significantly correlated with HbA_{1c}, HOMA-IR, TyG-BMI and TyG-WC. The receiver operating characteristic (ROC) analysis showed that TyG had a maximum area under the curve of 0.806, with a cut off value of 15.5 for identifying glycemic control in diabetic patients.*

Conclusion: *TyG index is a useful tool for assessing glycemic control in T2DM patients and positively correlated with HbA_{1c} and HOMA-IR. Hence, TyG can be used as a simple and inexpensive alternative to assess glycemic control in patients with diabetes.*

Keywords: type 2 diabetic subjects, glycemic control, insulin resistance, TyG index and TG/HDL-C ratio.

Address for correspondence:
Dr. Maithili Karpaga Selvi N
Department of Biochemistry, AIIMS, Jodhpur, Rajasthan- 342005, India
Email: maithilibiochem@gmail.com

Article received on the 24th of April 2021 and accepted for publication on the 3rd of September 2021

INTRODUCTION

Diabetes mellitus has become a global health menace and has been alarmingly increasing, with T2DM being the most common form which accounts for about 90% of all cases of diabetes due to a decreased sensitivity of target tissues to insulin (1). As *per* the International Diabetes Federation, in 2019 the global prevalence of diabetes was 9.3%, and it was estimated that almost 463 million people were suffering from diabetes (2). In India, more than 62 million individuals were found to have diabetes. Patients with T2DM have two to four times and 1.5 to 3.6 fold increases in risks of cardiovascular disease and mortality, respectively (3). Persistent hyperglycaemia and insulin resistance are associated with long term damage to organs, especially eyes, kidney, nerves and the heart (4).

Patients with T2DM often display an atherogenic dyslipidemia and obesity, which greatly increases their risk for coronary artery disease. Studies have shown that elevated triacylglycerol, low density lipoprotein cholesterol (LDL-C) and TG/HDL, a marker of small dense LDL particle, augmented the development of cardiovascular disease in diabetes (5). The higher prevalence of lipid abnormalities in diabetes mellitus has been attributed to insulin resistance and its associated complications (6). Effective glycemic control and enhancing insulin sensitivity are essential in order to reduce the risk of developing diabetes complications. Glycated haemoglobin and HOMA-IR are commonly employed to assess long term blood glucose concentration and insulin resistance, respectively (7, 8), also being found to predict microvascular and macrovascular complications of T2DM (9). Although they are used to assess glycemic control and insulin sensitivity, they are expensive, time consuming, and not readily available in many laboratories. Thus, a simple and inexpensive marker, which identifies both glycemic control and insulin resistance, is essential. Therefore, a large number of surrogate indicators are being investigated to assess glycemic control in diabetic patients for effective management. Recently, various indexes such as TyG index, TG/HDL ratio, BMI, waist circumference (WC) and visceral adiposity index (VAI) showed promising results as surrogate markers for the assessment of insulin resistance (10, 11). Visceral adiposity index is an indicator of visceral adipose function and insulin sensitivity, which is calculated by BMI, WC, TG and HDL (10), being also strongly associated with cardiometabolic risk in healthy subjects. Mounting evidence indicate that TyG index, which is derived from triglycerides (TGs), and fasting glucose levels correlate with the HOMA-IR and hyperinsulinemic-euglycemic clamp test (12). The TyG index is used to assess the progression of coronary artery calcification (CAC) in adults (13) and it also predicts cardiovascular mortality among patients on peritoneal dialysis (14). Since an increased TG level is an important risk factor for cardiovascular disease (15) and metabolic syndrome, measuring the product of TG and glucose as TyG index represents the glycemic control and cardiovascular status of an individual simultaneously. Hence, the present study was designed to investigate the association of TyG index with HbA_{1c} and insulin resistance in T2DM. ❑

MATERIALS AND METHODS

The present study was conducted in the Departments of Biochemistry, in collaboration with the Department of General Medicine at Mahatma Gandhi Medical College and Research Institute (MGMCRI), Puducherry, India. It was initiated after obtaining permission from the Institute Human Ethics Committee (IHEC) and informed consent from study subjects.

This cross-sectional study included 140 patients with T2DM from a tertiary healthcare unit in MGMCRI, Puducherry, India. Subjects were divided into two groups, according to their HbA_{1c} levels. Thus, HbA_{1c} <7.0% (n=75) and HbA_{1c} >7.0% (n=65) were defined as good control (group I) and poor glycemic control (group II), respectively. Diabetes mellitus was defined as *per* the American Diabetes Association (ADA) criteria (16). The National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guidelines were used for the reference level of serum lipid profile (17). Patients with type 1 diabetes mellitus, pregnancy, previous history of hyperthyroidism, hypothyroidism, autoimmune disorders, cardiovascular diseases, liver and muscle diseases were excluded from this study. Demographic data, anthropometrics,

clinical details, family history of diabetes and duration of diabetes were recorded.

Anthropometric measurements

The BMI was calculated by dividing an individual's weight in kilograms by the square of height in meters. The WC was measured to the nearest 0.1 cm midpoint between the iliac crest and costal margin at the end of expiration. TyG and TG/HDL indices were calculated according to previous study or formula (11, 12), and VAI for male and female subjects were calculated using the following formula (18):

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)

Estimation of biochemical parameters

Venous blood sample was collected following an overnight fasting. Fasting plasma glucose, HbA_{1c}, plasma insulin, HOMA-IR and lipid profile were measured in blood samples. Fasting blood glucose and lipid profile were analysed by clinical chemistry analyser. Fasting plasma glucose was determined by the glucose oxidase and peroxidase method. HbA_{1c} was estimated by an HPLC method using reagent kits from Biorad. Total cholesterol, triacylglycerol (TAG) and high density lipoprotein (HDL) were assessed by glycerol kinase, enzymatic method and polyanion precipitation respectively. Friedwald equation (19) was used to calculate low density lipoprotein cholesterol (LDL-C): LDL cholesterol = total cholesterol – (HDL-cholesterol + VLDL). Very low density lipoprotein cholesterol (VLDL-C) was calculated using the following formula: VLDL = TAG/5. Atherogenic index of plasma (AIP) was calculated using the formula: Log_{10}[TG (mmol/L)/HDL (mmol/L)], fasting plasma insulin was determined by direct chemiluminescent technology, and HOMA-IR was calculated using the fasting glucose level (mmol/L) multiplied by fasting insulin level (IU/mL) and then divided by 22.5 (7).

Statistical analysis

Results are expressed as mean±SD. Categorical data were presented as number and percentage. Difference in means between the groups was evaluated by independent t test. Spearman correlation analysis was done to assess the correlation between TyG index, HbA_{1c} and HOMA-IR. Receiver operating characteristic (ROC) curve analyses were done to find the cut off value of all indexes with maximum sensitivity and specificity to assess the glycemic control. A p-value of less than 0.05 (two-sided) was considered statistically significant.

RESULTS

Table 1 depicts the baseline, clinical and anthropometric characteristics of subjects with

TABLE 1. Baseline anthropometric and biochemical characteristics of subjects with diabetes

Variables	Mean ± SD (n=140)
Age (years)	51.2 ± 9.2
Duration of diabetes	2.4 ± 1.4
No. of males (%)	75 (54%)
No. of females (%)	65 (46%)
WC (cm)	95.1 ± 9.9
Body mass index (BMI)	27.5 ± 5.1
SBP (mm Hg)	122 ± 7.8
DBP (mm Hg)	82.3 ± 6.9
Fasting blood glucose (mg/dL)	170.1 ± 46
Fasting plasma insulin (mIU/L)	19.7 ± 6.0
HOMA-IR	8.1 ± 3.0
HbA_{1c} (%)	8.5 ± 4.6
TC (mg/dL)	188 ± 42.6
TAG (mg/dL)	176.7 ± 22.6
LDL (mg/dL)	108.4 ± 42.3
VLDL (mg/dL)	35.3 ± 4.5
HDL (mg/dL)	44.2 ± 10.8
Non-HDL	143.7 ± 42.1
TAG/HDL ratio	4.20 ± 1.1
VAI	3.0 ± 1.0
TYG index	4.16 ± 0.1
TYG-BMI	114.2 ± 21.6
TYG-WC	395.6 ± 43.5
AIP	0.6 ± 0.11
Urea (mg/dL)	23.1 ± 6.2
Creatinine (mg/dL)	0.9 ± 0.2
Uric acid (mg/dL)	4.4 ± 1.4
Calcium (mg/dL)	10 ± 7.9

SD=standard deviation, BMI=body mass index, WC=waist circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure, HOMA-IR=homeostatic model assessment insulin resistance, TC=total cholesterol, TAG=triacylglycerols, VLDL=very low density lipoprotein, LDL-C=low density lipoprotein-cholesterol, HDL-C=high density lipoprotein-cholesterol, VAI=visceral adiposity index, TYG=triglyceride glucose index, AIP=atherogenic index of plasma.

TABLE 2. Baseline, clinical and anthropometric characteristics among good glycemic and poor glycemic control of subjects with diabetes

Variables	Good glycemic control (n=75)	Poor glycemic control (n=65)	P value
Age (years)	51.9 ± 9.8	50.5 ± 8.3	0.388
Duration of diabetes	2.5 ± 1.4	2.3 ± 1.2	0.447
No. of males (%)	38 (51%)	37 (57%)	
No. of females (%)	37 (49%)	28 (43%)	
WC (cm)	94.1 ± 8.6	96.4 ± 11.1	0.167
Body mass index (BMI)	26.3 ± 4.1	28.8 ± 5.7*	0.002
SBP (mm Hg)	121.4 ± 6.3	123.1 ± 9.5	0.192
DBP (mm Hg)	81.4 ± 4.1	83.3 ± 9.1	0.135

Data were represented as mean ± SD.

*Statistically significant compared to good glycemic control group, p value <0.01
BMI=body mass index, WC=waist circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure.

TABLE 3. Comparison between biochemical parameters and indices of diabetic patients with good and poor glycemic control

Variables	Good glycemic control (n=75)	Poor glycemic control (n=65)	P value
Fasting blood glucose (mg/dL)	147.6 ± 41.0	161.7 ± 49.1**	0.001
Fasting plasma insulin (mIU/L)	19.3 ± 6.3	20.1 ± 6.0	0.458
HOMA-IR	6.9 ± 2.7	7.8 ± 2.6**	0.001
HbA_{1c} (%)	6.5 ± 0.7	10.7 ± 6.1**	0.001
TC (mg/dL)	184.6 ± 42.7	191.9 ± 42.4	0.313
TAG (mg/dL)	175.5 ± 21.3	178.2 ± 24.2	0.483
LDL (mg/dL)	103.5 ± 42.4	114.1 ± 41.8	0.138
VLDL (mg/dL)	35.1 ± 4.3	35.6 ± 4.8	0.483
HDL (mg/dL)	46 ± 11.7	42.1 ± 9.3*	0.032
Non-HDL	138.5 ± 42.2	149.7 ± 41.4	0.117
TG/HDL ratio	3.97 ± 1.0	4.4 ± 1.2*	0.014
VAI	2.9 ± 0.9	3.1 ± 1.1	0.312
TyG index	4.1 ± 0.1	4.3 ± 0.2**	0.001
TyG-BMI	107.4 ± 16.8	121.9 ± 23.9**	0.001
TYG-WC	385.1 ± 36.6	407.8 ± 47.7**	0.002
AIP	0.58 ± 0.1	0.65 ± 0.1*	0.016

Data were represented as mean ± SD.
*Statistically significant compared to poor glycemic control, p value <0.05,
**Statistically significant compared to poor glycemic control, p value <0.01.
HOMA-IR=homeostatic model assessment of insulin resistance, TC=total cholesterol, TAG=triacylglycerol, VLDL=very low density lipoprotein, LDL-C=low density lipoprotein-cholesterol, HDL-C=high density lipoprotein-cholesterol, VAI=visceral adiposity index, TYG=triglyceride glucose index, AIP=atherogenic index of plasma.

good and poor glycemic control. The duration of diabetes was less than 2.5 years in both groups. The number of males and females was 38 (51%) and 37 (49%), respectively, in group I, and 37 (57%) and 28 (43%), respectively, in group II. The BMI was significantly higher in group II (P <0.05). There was no significant difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the two groups (Table 2).

TABLE 4. The correlation analysis of TYG with HbA1c, HOMA-IR, TYG-BMI and TYG-WC in type 2 diabetes mellitus

Variables	Correlation coeffient (r value)	P value
HbA_{1c}	0.541	0.000
HOMA-IR	0.474	0.000
TYG-BMI	0.285	0.001
TYG-WC	0.325	0.000

TYG-BMI=triglyceride–glucose index-body mass index, TYG-WC-triglyceride–glucose index-waist circumference, HOMA-IR=homeostatic model assessment of insulin resistance.

Table 3 shows the comparison between biochemical parameters and metabolic indexes of diabetic patients with good and poor glycemic control. Fasting blood glucose (167.7±49.1, p <0.001), HOMA-IR (7.8±2.6, p <0.001), HbA_{1c} (10.7±6.1, p <0.001) and TG/HDL (4.4±1.2, p <0.05) ratio were significantly higher in group II. High density lipoprotein cholesterol (42.1±9.3) was significantly lower in group II. TyG indices such as TyG index (4.3±1.2, p <0.001), TyG-BMI (121.9±23.9, p <0.001) and TYG-WC (407.8±47.7, p <0.001 were significantly higher in T2DM subjects with poor glycemic control.

In Table 4, the TyG index positively correlated with HbA_{1c} (r=0.541, p <0.000) and HOMA-IR (r=0.464, p <0.000), TyG-BMI (r=0.285, p <0.001) and TyG-WC (r=0.325, p <0.000).

Receiver operating characteristic curve was plotted based on the sensitivity and specificity for HOMA-IR and TyG indexes were shown in Figure 1. The ROC analysis showed that TyG (AUC 0.806, cut off value 15.5) was the best marker for identifying glycemic control when compared with the other indexes. Areas under the curve for TG/HDL (0.620), HOMA-IR (0.780), TyG-BMI (0.691) and TyG-WC (0.657) are shown in Table 5. ❑

DISCUSSION

Type 2 diabetes mellitus is a major global health problem and maintaining good glycemic control in T2DM remains a challenge. Dyslipidemia and

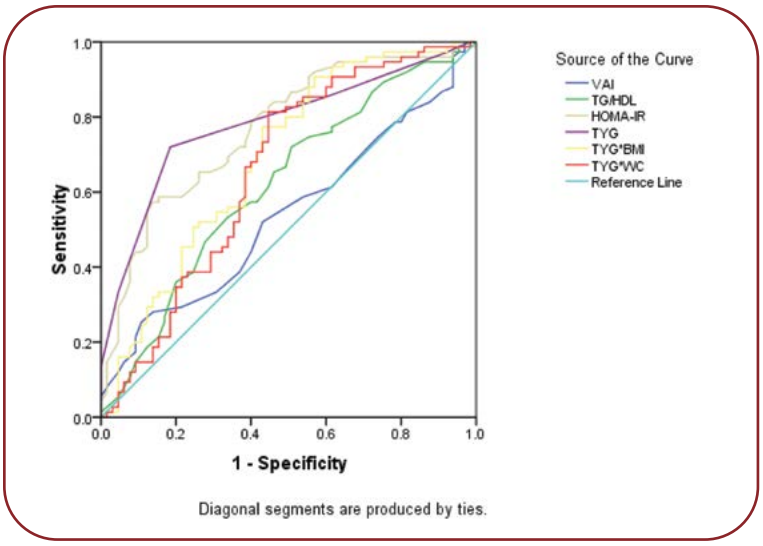

FIGURE 1. Receiver operating characteristic curve (ROC)

TABLE 5. Area under the curve of different parameters in predicting poor glycemic control

Variable	Area	Asymptotic 95% confidence interval		P value
		Lower bound	Upper bound	
VAI	0.537	0.442	0.633	0.444
TG/HDL	0.620	0.527	0.713	0.015
HOMA-IR	0.780	0.703	0.857	0.000
TYG	0.802	0.73	0.875	0.000
TYG-BMI	0.691	0.602	0.78	0.000
TYG-WC	0.657	0.564	0.751	0.001

insulin resistance plays a major role in development of micro- and macrovascular complications. We sought to attain a modest, sensitive and economically feasible biochemical predictors of glycemic control in diabetic patients. In the present study, we assessed the association between HbA_{1c} and metabolic indices in T2DM.

The diabetes complications and control trial (DCCT) represent HbA_{1c} as the good marker for glycemic control (20). Maintaining $HbA_{1c} < 7.0\%$ reduces the risk of developing microvascular and macrovascular complications. Hence, diabetic patients were divided into two groups based on their HbA_{1c} levels. In our study, we found dyslipidemic changes in subjects with poor glycemic control as illustrated by elevated TG/HDL ratio and reduced levels of HDL-C. In association with this, we also observed increased values of BMI, fasting blood glucose (FBG) and HOMA-IR in subjects with $HbA_{1c} > 7\%$ (group II). Hyperglycaemia and decreased insulin sensitivity in T2DM are accompanied by low HDL-C and hypertriglyceridemia. Increased plasma cholesteryl ester transfer protein (CETP) is frequently seen in diabetes due to increased VLDL-C, which facilitates the transfer of cholesterol ester and TAG between lipoproteins (HDL and LDL particles) (21, 22). This led to increased small dense LDL, which is considered to be one of the hallmarks of diabetic dyslipidemia and also associated with cardiovascular risk. Moreover, estimation of small dense LDL particle is cumbersome and not feasible, thus the measurement of TG/HDL ratio indirectly reflects the size of LDL that could be comparable with the actual assessment of small dense LDL. ROC analysis of TG/HDL ratio yielded an AUC of 0.620 with a cut off value of 4.4 and a sensitivity of 73% to assess the magnitude of glycemic control in diabetic patients. Babic *et al* showed that TG/HDL-C ratio was found to be a useful marker in the prediction of glycemic control in T2DM (11). The TG/HDL-C ratio and BMI were independently associated with HbA_{1c} after adjusting for age and gender (23). The average cut off value of TG/HDL-C ratio was 3.40 mg/dL and 5.82 mg/dL in good and poor glycemic control groups, respectively, suggesting the presence of insulin resistance in T2DM (23). Other authors have also stated the TG/HDL-C ratio with a cut off value of 3.0 mg/dL was a better marker for detecting insulin resistance (24).

The VAI is gender specific as well as a surrogate marker of visceral adiposity. Excess visceral adiposity has been linked to a greater risk of T2DM and cardiometabolic risk. Obesity and increased visceral fat accumulation induces metabolic derangement like increased free fatty acid and pro-inflammatory cytokines ultimately culminate in insulin resistance and poor glycemic control (25). In association with this, we found a significant positive correlation between VAI and HbA_{1c}. In accordance with this, Hameed *et al* showed that increased VAI adversely affects glycemic control in women with T2DM. Also, VAI was significantly associated with adipocytokines and cardio-metabolic risk serum markers (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).

Marco *et al* reported that VAI was significantly associated with cardiometabolic risk in Caucasian Sicilian subjects (28).

In the current study, TyG index, TyG-BMI and TyG-WC were significantly elevated in group II, while TyG index, TyG-BMI and TyG-WC were significantly correlated with HbA_{1c} and HOMA-IR. Therefore, we performed ROC analysis for TyG indices, which showed a maximum AUC of 0.806 for TyG index, followed by TyG-BMI and TyG-WC. Among these indexes, TyG index was found to be a good predictor of glycemic control when compared to others. Similarly, Hameed *et al* illustrated that TyG index had the largest AUC of 0.836 in ROC analysis, followed by TyG-WC and TyG-BMI and correlated with HbA_{1c} and HOMA-IR (12). Also, TyG index is useful in assessing the magnitude of insulin resistance in T2DM (11). Lee *et al* concluded that TyG index could be used as diagnostic criteria for identification of metabolically obese but normal weight individuals (29). Elevated triacylglycerol in patients with diabetes causes poor glycemic control by affecting glucose metabolism (30). Studies have shown that TyG index not only reflected the glycemic control but it was also good predictor of insulin resistance. Fernando *et al* reported that TyG index was significantly correlated with HOMA-IR and euglycemic-hyperinsulinemic clamp test for identifying insulin resistance (31). In agreement with previous studies, our study found that TyG index was an effective screening tool in predicting the glycemic control and insulin resistance in T2DM.

Measurement of HbA_{1c} and insulin is expensive, requires automated procedures, and may not be feasible in primary health care settings. TyG index derived from fasting blood glucose and triglyceride levels is routinely measured in small laboratories and readily available. The diagnostic accuracy of TyG index in identifying glycemic control and insulin resistance in diabetic patients has been documented in few studies. Hence, TyG index could be used as a simple cost-effective surrogate marker of glycemic control and insulin resistance in T2DM.

Study 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. ❑

CONCLUSION

The TyG index can be used as a simple surrogate marker of glycemic control and insulin resistance in patients with T2DM. Owing to its cost effectiveness and easy quantifiability, it can be measured in small laboratories. ❑

Conflicts of interest: none declared.
Financial support: none declared.
Acknowledgments: We thank Mahatma Gandhi Medical College and Research Institute (MGMCRI), SBV for providing the infrastructure required for the study.

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