Original Article

To study the role of triglyceride glucose index (TyG Index) as a novel biomarker in patients of type 2 diabetes mellitus (T2DM) developing acute coronary syndrome (ACS)

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Abstract

Objectives: To study the role of the triglyceride glucose (TyG) index as a novel biomarker in patients with type 2 diabetes mellitus (T2DM) developing acute coronary syndrome (ACS). **Methods:** This was a cross-sectional, case–control study conducted over 1 year with a sample size of 175 T2DM subjects divided into cases and controls at a ratio of 2:5 (50 cases: T2DM with ACS, 125 controls: T2DM without ACS). The TyG index was calculated using the formula Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg (dL)/2]. **Result:** In this study, nearly half of the patients had ST-elevation myocardial infarction with a male preponderance. The TyG index was significantly higher in the ACS group. Body mass index, fasting blood sugar, serum cholesterol, and serum urea levels were significantly higher in the cases. The TyG index showed a strong correlation with ACS, and linear regression analysis identified it as the strongest risk factor for ACS in these patients, with a cutoff value of 8.9, providing 99% sensitivity and specificity. Interestingly, high-sensitivity CRP levels were not significantly different between the two groups. **Conclusion:** The TyG index, derived from fasting triglycerides and blood glucose, is a simple and cost-effective marker for insulin resistance (IR) and cardiovascular risks. It is comparable to other markers in predicting conditions such as coronary artery disease (CAD) and atherosclerosis and can be incorporated into the routine clinical evaluation of T2DM patients to predict the risk of ACS, which remains a leading cause of cardiovascular morbidity and mortality in T2DM.

Keywords: Hs-CRP, insulin resistance, lipid profile, myocardial infarction

Introduction

T2DM is a chronic metabolic disease closely linked to coronary artery disease (CAD) and other cardiovascular diseases (CVD). It significantly increases the risk of heart failure and mortality, particularly in patients with ACS. The risk of ACS in T2DM

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patients without a history of CAD is equal to that in patients with nondiabetic CAD.[1]

IR, a key factor in type 2 diabetes, is linked to coronary and carotid atherosclerosis and increase risk of poor outcomes.[2] The TyG index, derived from fasting triglycerides (TG) and fasting blood glucose (FBG), serves as a surrogate biomarker for IR, correlating strongly with the hyperinsulinemic-euglycemic clamp, the gold standard for assessing IR.[3] The TyG index outperforms other methods in determining IR and cardiovascular risks, including CAD, carotid atherosclerosis, metabolic syndrome, arterial stiffness, and coronary artery calcification. The TyG index also predicts cardiovascular disease (CVD) incidence and prognosis in people with CAD. Furthermore, many recent studies have reported the predictive value of TyG index in CAD.[4] The TYG index is easy to calculate, as the variables required for calculation (FBG and TyG) are easily available in all health care settings, inexpensive, and routinely performed in patients with diabetes which will be beneficial for primary care physician. To provide more evidence for clinical practice as T2DM is an important risk factor for developing ACS and the TyG index is a reliable and cost-effective marker, this study evaluated the role of the TyG index as a novel biomarker in patients with T2DM developing ACS.

Materials and Methods

The study was conducted at a tertiary care hospital in northern India. Ethically approved by Institutional Ethical Committee on 22nd August 2023.

Study design

Cross-sectional, case–control study.

Study duration

One year.

Sample size

175 cases

The sample size for the study was estimated using G Power 3.1.9.7.

For 90% power to detect a significant difference of 0.35 in triglyceride glucose index at a 5% level of significance, the study required a total of 175 individuals with an allocation ratio of 2:5, that is, 50 cases and 125 controls.[5]

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

Study groups: 2 groups

1. T2DM without any features suggestive of acute coronary syndrome (control).
2. T2DM with recent acute coronary syndrome (case).

Inclusion criteria

Patients giving written informed consent.

Age group 40–65 years.

T2DM patients as per American Diabetic Association.

Exclusion criteria

Patients not giving consent.

Age <40 and > 65 years.

Hepatic failure.

Autoimmune diseases.

Inflammatory conditions and sepsis.

BMI > 45 (body mass index).

Familial hypertriglyceridemia.

Thyroid disorders.

Malignancy.

Renal failure.

All subjects were subjected to an assessment of medical history and thorough clinical examination according to the patient case record form. Routine investigations, including complete blood count, fasting and random blood glucose levels, HbA1c, serum creatinine (S. Cr), urea, lipid profile, and high-sensitivity CRP (hs-CRP) TyG index, were calculated using the formula Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg (dL)/2].

Statistical analysis

The baseline characteristics were assessed using standard descriptive statistics. Normality of the data was tested using the Kolmogorov–Smirnov test. If the data were not continuous, the nonparametric test was used. Continuous variables are presented as mean ± standard deviation. Categorical variables were presented as numbers and percentages (%). Quantitative variables were compared between groups using an F-test, while qualitative variables were compared using the Chi-square or Fisher's exact test, where appropriate. The Pearson correlation coefficient was applied to measure the strength of a linear association between two variables, where a value of r = 1 indicated a perfect positive correlation and r = -1 indicated a perfect negative correlation. The data were entered into a Microsoft Excel spreadsheet, and analysis was done using Statistical Product and Service Solutions (SPSS) (IBM SPSS Statistics for Windows, Version 29.0, Armonk, NY).

Results

Of the 50 patients, 27 (54%) had STEMI and 14 (28%) had NSTEMI, followed by 2 (4%) unstable angina. Heart failure with preserved ejection fraction was most common (90%). The details of the various variables between the case and control groups are shown in Table 1. The mean age in the case group (54.92 ± 8.49 years) and in the control group (53.12 ± 12.28 years) was comparable. In the case group, there was a male preponderance of 74.0% (37) and 58.4% (73) of patients in the control group ($P = 0.03$). The mean BMI, FBS, and S. urea were significantly higher in these cases. Among the various lipid profile parameters, only S. CHL was significantly higher in cases than in controls, and the TyG index was significantly increased, suggesting that triglycerides and fasting blood sugar play an important role. Although HS-CRP is considered a cardiovascular risk predictor, the mean HS-CRP in both controls and cases was not significant.

Among all subjects, the Pearson correlation [Table 2] of TyG INDEX showed a significant correlation with ACS, S. CHL, HDL, and BMI (r- 0.7 $P < 0.001$, r-0.4 $P < 0.001$, r-0.3 $P < 0.003$, r-0.28 $P < 0.005$). The risk of developing ACS in T2DM was significantly associated with TYG index ($P < 0.001$), age (P value-0.008), BMI ($P < 0.001$), S. TG ($P < 0.001$), S. urea (P – 0.02), and FBS ($P < 0.001$). Furthermore, linear regression [Table 3] analysis to assess potential risk factors in T2DM patients for developing ACS showed that the TYG index was the strongest risk factor ($P < 0.001$) along with age (p-0.02) and S. urea (p-0.02). AUC curve analysis predicted the TyG Index's cutoff value as 8.9 with 99% sensitivity and 99% specificity to predict T2DM patients at risk for developing ACS.

Discussion

The mean TyG index was significantly higher in diabetic patients with ACS and was significantly associated with the risk of developing ACS in T2DM on linear regression analysis. A retrospective study was conducted with 5,593,134 individuals over 40 years of age, categorizing the participants into TyG index quartiles. Stroke, MI, and combined outcomes were analyzed using Cox proportional hazards regression. The highest TyG index quartile was linked to the greatest likelihood of developing incident stroke, MI, or both, with these probabilities progressively decreasing in the lower quartiles (all log-rank $p < 0.001$).[6] A 10-year follow-up study, which included 5014 patients, demonstrated that a higher TyG index was significantly linked to an increased risk of developing CVD. The TyG index offers additional predictive value for CVD's Framingham risk score (FRS). A cross-sectional study of 264 individuals at cardiometabolic risk was conducted. The FRS assesses the 10-year CVD risk. The ROC curve was used to define the cutoff point for the TyG index. Elevated TyG levels (≥9.04) were positively associated with CVD.[7,8] The TyG index cutoff value in our ROC curve study was 8.9. The precise mechanism linking the TyG index to CVD remains unclear. The TyG index,

Table 1: Comparison of various biochemical and clinical parameters between 2 groups

	Case (n=50)		Control (n=125)		t	P
	Mean	±SD	Mean	±SD		
Age (years)	54.92	8.5	53.12	12.3	0.96	0.338
BMI (kg/m^2)	28.13	2.4	24.59	5.1	4.04	<0.001*
S.TG	158.47	86	139.21	59	1.7	0.092
S. CHL	155.98	59	138.81	46.3	2.04	0.043*
LDL	69.49	35.5	66.77	32.8	0.48	0.631
HDL	48.11	18.3	43.65	24.08	1.18	0.239
VLDL	25.84	8.1	26.66	9.23	-0.44	0.661
FBS	167.76	65.92	139.56	46.85	3.18	0.002*
HbA1C	7.34	0.89	7.14	1.15	1.07	0.285
Hb	12.10	3.80	10.77	2.08	2.96	0.004*
TLC	9652.06	5168.86	9505.18	5195.74	0.07	0.948
S. Urea	49.10	24.28	38.49	15.83	3.27	0.001*
S. Creatinine	1.23	0.47	1.09	0.36	1.71	0.089
TyG Index	9.33	0.53	9.06	0.45	3.40	0.001*
hs-CRP	5.02	2.01	4.5	1.57	2.44	0.06

*Significant P value

Table 2: Pearson correlation of TYG INDEX with baseline and clinical parameters with in type 2 diabetes mellitus

	Pearson correlation (r)	P
ACS	0.74	<0.001*
Gender	-0.18	0.05
Age	0.14	0.10
S. TG	0.80	0.001*
S. Chol	0.43	0.001*
LDL	0.05	0.52
HDL	0.27	0.002*
VLDL	0.02	0.80
FBS	0.74	<0.001*
Hb	0.17	0.05
TLC	0.06	0.47
S. urea	0.14	0.09
S. creatinine	0.03	0.71
hs-CRP	0.02	0.80

*Significant P value

Table 3: Linear regression analysis to assess the potential risk factor association with case

	Beta	95% CI		Sig.
		Lower bound	Upper bound	
Age	0.06	0.00	0.00	0.84
Gender	0.05	-0.08	0.09	0.94
S.TG	0.012	0.01	0.01	0.11
S.CHL	0.00	0.00	0.00	0.89
LDL	0.04	0.00	0.00	0.59
HDL	-0.06	0.00	0.00	0.45
VLDL	-0.008	-0.04	-0.02	0.01
FBS	0.008	0.00	0.00	0.30
Hb	0.02	-0.01	0.02	0.31
TLC	-0.01	0.00	0.00	0.92
S. Urea	0.003	0.00	0.00	0.63
S. Creatinine	-0.01	-0.01	0.01	0.93
TYG Index	0.424	0.21	0.64	<0.001*
HBA1C	-0.03	0.00	0.00	0.52

*Significant P value

which combines lipid and glucose-related factors, indicates IR in the body, both of which are risk factors for CVD. IR causes imbalances in glucose metabolism, leading to hyperglycemia, inflammation, and oxidative stress. IR is associated with systemic lipid disturbances that contribute to atherosclerosis. In ischemic myocardium, reduced insulin activity shifts metabolism to fatty acids, increasing oxygen consumption, and reducing the compensatory capacity of noninfarcted myocardium, worsening CAD. IR leads to increased production of glycosylated products and free radicals, inactivating nitric oxide (NO) and damaging vascular endothelium, causing impaired endothelial function and vasodilation. IR activates the mitochondrial electron-transport chain, overproducing ROS, further impairing endothelial function, and extending damage to the coronary microcirculation and myocardial energy metabolism.[9]

Male patients with diabetes have a higher prevalence of ACS. The mean age of males was 54+/- 8.5 years while that of females was 52+/-12.3 years. Male sex is a known risk factor for CVD. Women's well-known biological defense against CAD before menopause can cause more than 10 years of delay in presenting with CAD symptoms.[10] Estrogen reduces the risk of CVD by downregulating inflammatory markers that help combat atherosclerosis. In addition, it stabilizes atherosclerotic plaques by lowering the expression of matrix metalloproteinases and production of plasminogen activator inhibitor-1 (PAI-1). Furthermore, high estrogen levels promote vasodilation by generating prostacyclin, inhibiting endothelin synthesis, and blocking calcium channels.[11,12] Similar to our study, no significant sex-wise correlation between CAD and TyG index was found in patients with diabetes.[13]

The ACS and TyG also showed a significant positive correlation with BMI. It is well known that obesity, when accompanied by conditions such as hypertension, dyslipidemia, and glucose intolerance, raises the risk of CVD.[14] TyG Index was positively correlated with BMI (*P* value <0.001).[6,14] Adipocytokines play a significant role in the incidence of cardiovascular disease. Hormones and other molecules secreted by adipose tissue likely act as proatherogenic markers.[15]

The risk of ACS and TyG showed a significant positive correlation with S. urea levels. In another study, compared to the control group, ACS patients had significantly higher mean levels of Cr (1.53 mg/dl vs 0.90 mg/dl, $P < 0.001$) and BUN (33.47 mg/dl vs 12.06 mg/dl, $P < 0.001$). Although Cr is the gold standard test for GFR, it is not as accurate for normal or mildly reduced kidney function, such as serum blood urea nitrogen (BUN). In such cases, BUN may rise independently of changes in GFR under the influence of the sympathetic, arginine–vasopressin, and renin–angiotensin–aldosterone systems, which are activated in ACS and increase the renal tubular reabsorption of urea. The TyG index has also been linked to higher S. urea levels.[16,17]

Of the various lipid profile parameters, difference in S.CHL levels was significantly associated with ACS in patients with T2DM. High TyG index values have been associated with CVD risk factors such as S.CHL, LDL, and VLDL in previous studies.[5,18] In our study, the TyG index was significantly correlated with S. HDL and S. CHOL. This finding underlines the importance of cholesterol in the development of ACS in patients with T2DM. S.TG values were calculated using the Friedewald equation: LDL = S. CHL - HDL - 0.2 × S. TG, suggesting that various parameters of the lipid profile are interrelated. TG levels did not differ significantly between the two groups. FBS levels were significantly higher in these cases. However, the TyG index showed better predictability for ACS, highlighting its importance over the individual parameters.

Linear regression analysis also indicated that increased age was a risk factor for ACS. Studies show that advanced age is a strong risk factor for CAD and an independent predictor of poor outcomes following ACS. A higher TyG index quartile was positively associated with age (Q4 – 9.0 vs Q1-7.76, *P* value <0.001).[6,10] Each 10-year increase in age resulted in a 75% increase in in-hospital mortality in patients with ACS. In older adults, there are more extensive calcifications of coronary atherosclerosis with more multivessel and left main diseases.[11]

Patients with ACS had significantly higher FBS levels. The lowest CVD risk in both sexes corresponded to serum glucose levels ranging from 70 to 109 mg/dL, with increased risk at higher and lower concentrations. During MI, elevated levels of hormones, such as glucagon and cortisol, along with cytokines, enhance gluconeogenesis and glycogenolysis. Concurrently, the failure of pancreatic β-cells to secrete adequate insulin fails to counteract the hyperglycemic effect, leading to stress-induced hyperglycemia. This is exacerbated by the activation of the sympathetic nervous system. Stress hyperglycemia can initiate inflammation, elevate oxidative stress levels, worsen endothelial dysfunction, stimulate a prothrombotic state, and cause impaired coronary flow. HbA1c did not differ significantly between the two groups, implying that both groups had similar glycemic profiles.[19,20]

Higher hs-CRP levels in patients with ACS suggested a positive correlation with CVD. The hs-CRP level is a predictor of mortality and adverse outcomes in patients with ACS. It affects CAD progression through various pathways such as activation of the complement system and platelets, suppression of fibrinolysis, promotion of smooth muscle cell proliferation, macrophage polarization, and lipid deposition. However, it was not significantly correlated with TyG index.[21] A longitudinal analysis was conducted to evaluate the joint and individual associations of the TyG index and hs-CRP with CVD. Individuals with elevated hs-CRP (>1 mg/dl), elevated TyG (>8.6), and both elevated hsCRP and TyG had an independently increased risk of incident CVD compared to those with low hs-CRP and TyG index.[22]

Conclusions

Our study emphasizes the need for the early identification of high-risk T2DM patients who could benefit from intensive

cardiovascular risk treatment**.** The TyG index was significantly associated with ACS on linear regression (r = 0.4, $P < 0.001$) with a cutoff value of 8.9 (AUC 0.974, 90% sensitivity and 99% specificity). It is derived from regular lipid and glucose testing, is simple and inexpensive, and could be used to identify T2DM patients with a high risk of developing acute coronary syndrome. Incorporating TyG scores into routine clinical examinations could improve risk prediction and help prevent cardiovascular morbidity and mortality in T2DM patients. Hence, primary care physician can timely refer these high-risk patients for further detailed investigations and management to tertiary healthcare centers. Our results must be confirmed by prospective studies to determine the association between the increase in the TyG index and ACS risk in T2DM patients.

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Conflicts of interest

There are no conflicts of interest.

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