Review Article

Triglyceride-Glucose Index As A Biomarker Of Insulin Resistance, Diabetes Mellitus, Metabolic Syndrome, And Cardiovascular Disease: A Review

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Keywords
Cardiovascular, diabetes, insulin resistance, TyG index

Abstract

The triglyceride-glucose (TyG) index is one of the parameters that have been used in assessing insulin resistance. Triglycerides and fasting blood glucose are two low-cost, common laboratory indicators that are used to compute the TyG index. This article reviews the link between the TyG index and several aspects concerning insulin resistance-related disorders and cardiovascular disease, as well as the use of various TyG index cutoffs in the above conditions with sensitivity and specificity, respectively, in various populations in the world.

Introduction

The triglyceride and glucose index or TyG index is a parameter that has been widely used recently in various reports and research in the field of medical laboratories concerning insulin resistance-related disorders and cardiovascular disease [1,2]. The calculation of TyG index is easy and inexpensive to do because it only requires the results of fasting blood triglycerides and glucose, which are routinely examined both in hospitals and clinical laboratories [3].

The lipoproteins that have the highest triglyceride content include chylomicron and very low-density lipoprotein (VLDL). Hyperglycemic conditions and insulin resistance trigger increased VLDL production and the release of chylomicron, which cause serum triglyceride levels to rise in these subjects [4]. Insulin resistance in the liver causes liver metabolism disruptions in regulating blood glucose levels. In insulin resistance and diabetes mellitus, hepatic glycogenesis decreases, while increased hepatic glyconeogenesis leads to increased hepatic glucose production, so blood glucose levels increase [5]. The association of the increased of triglycerides and glucose levels in insulin resistance is the basis for the use of both (indicated in the TyG index) to assess various abnormalities related to insulin sensitivity disorders. The TyG index is measured using the formula: TyG index = Ln (fasting triglycerides [mg/dL] x fasting glucose [mg/dL])/2 or TyG index = Ln (fasting triglycerides [mmol/L] x 88.57 x fasting glucose [mmol/L] x 18)/2) [6].

The role of TyG index in assessing insulin resistance

Insulin resistance is one condition that precedes the occurrence of diabetes. Among patients with insulin resistance, blood insulin production in normal amounts cannot optimally trigger the transfer of glucose from within the blood to peripheral tissues, including muscle and fat tissues, so blood glucose levels tend to rise. To maintain normal blood glucose levels, more insulin production is needed due to insulin resistance [7,8]. When it comes to diagnosing insulin resistance, the hyperinsulinemic-euglycemic clamp (HEC) method is regarded as the best, but this technique is rather complicated, less practical, and quite expensive. Some easier-to-do tests have been used as alternative tests to diagnose insulin resistance condition including the homeostatic model assessment for insulin resistance or HOMA-IR, the Matsuda index, and other tests [7]. The TyG index is a fairly easy and affordable test to be conducted. Various studies have shown its usefulness in assessing insulin resistance [1]. Guerrero-Romero et al. reported that TyG Index showed an excellent association with HEC gold standard method in diagnosing insulin resistance (area under the curve (AUC) = 0.858), with TyG index cutoff 4.68 having a sensitivity of 96.5% and a specificity of 85% in estimating insulin resistance in the adult population [6]. Several investigations have been carried out to evaluate the TyG index's ability to measure insulin resistance based on HOMA-IR because the HEC method is quite difficult to do. Aman et al. showed that the TyG index was associated with HOMA-IR (r = 0.436) and could be used to predict insulin resistance using a cutoff of 4.66 (sensitivity 86.2%, specificity 44.1%) in an adult male population of non-diabetic mellitus in Indonesia [9]. A study conducted in the adult population of Venezuela showed that TyG index with 4.49 cutoff had specificity of 0.821 and sensitivity of 0.826 in determining insulin resistance (this study used a cutoff HOMA-IR >2 to diagnose insulin resistance) [10]. A study in the 2170 population of Xinjiang Kazakh in China demonstrated that TyG and the body mass index (BMI) had the closest relationship with the incidence of insulin resistance (HOMA-IR > 3.45 (75 percentile)) [11]. The TyG index may also predict the occurrence of insulin resistance in children. A study conducted on 915 school-age children in Argentina showed that the TyG index correlates with HOMA-IR (r = 0.34), but its ability to predict insulin resistance is generally lower than that reported in adults (AUC = 0.65, cutoff TyG Index = 8.00, sensitivity 0.62, specificity 0.62) [12]. A study among teenagers aged 10-19 in South Korea showed the 8.26-cutoff TyG index could predict the occurrence of insulin resistance (HOMA-IR >95th percentile) with an AUC value of 0.723 (sensitivity 66.45% and specificity 65.56%) [13]. In the population of women with polycystic ovarian syndrome (PCOS), HOMA-IR and TyG index were also shown to be significantly correlated (r = 0.515). By using HOMA-IR cutoff > 2.5 as having insulin resistance, the occurrence of insulin resistance in PCOS subjects can be predicted by TyG index (AUC = 0.781, the cutoff TyG Index = 8.51, with specificity of 87% and sensitivity of 63.2%) [14]. Table 1 provides an overview of the TyG index's role in predicting the occurrence of insulin resistance.

The role of TyG index in assessing diabetes mellitus

TyG index has also been extensively studied concerning diabetes mellitus. One of the risk factors for type 2 diabetes is insulin resistance. Hyperglycemia due to abnormalities in insulin secretion or insulin resistance in peripheral tissues is a hallmark of diabetes mellitus [15]. Various reports describe the association between TyG index and various aspects of diabetes mellitus. A study of 2,900 subjects undergoing medical check-ups in Korea showed that the TyG index might be used as a marker in assessing risk of developing diabetes. Those with TyG index >8.97 (quartile 4) had a hazard ratio of having diabetes 5.65 times higher than those with a TyG index <8.21 (quartile 1) [16)]. A study conducted on 140 type 2 diabetes subjects in India showed that TyG index with a cutoff of > 15.50 could be used to predict poor glycemic control (HbA1c >7%) with an AUC = 0.802 [17]. Another study performed in 914 subjects, including normoglycemic, prediabetic, and diabetic patients, in China showed that TyG Index can be applied for assessing the function of pancreatic β cells. The TyG index value had negative correlation with pancreatic β cells function in the three groups above. The cutoff value of TyG index 9.08 can be used to determine the occurrence of early β phase cell dysfunction, whereas the cutoff value of 9.20 can be utilized to evaluate advanced β-phase cell dysfunction [18]. TyG index is reported having a stronger predictor value than HOMA-IR in diagnosing type 2 diabetes among adolescents and children subjects in Korea (AUC 0.839 versus 0.645) [19]. Interestingly, the TyG Index can also be used for assessing macrovascular complications in type 2 diabetes subjects using the 9.31 cutoff (AUC = 0.702, sensitivity 59%, specificity 74%) [20]. A report of 157 type 2 diabetes subjects conducted in Harbin, China, revealed that the TyG index had association with incidence of mild cognitive impairment in people suffering from type 2 diabetes. The TyG index 9.45 cutoff (AUC = 0.79) can be used to diagnose slight cognitive impairment in those subjects, with 69% sensitivity and 80% specificity [21]. Table 2 provides an overview of the TyG index's role in relation to diabetes mellitus.

The role of the TyG index in assessing metabolic syndrome

Metabolic syndrome, formerly known as syndrome X, is a disorder marked by insulin resistance, impaired glucose and lipid metabolism, and elevated blood pressure linked to a higher risk of cardiovascular disease [22,23]. There are several criteria for establishing metabolic syndrome diagnosis, including those proposed by the American Heart Association (AHA), International Diabetes Federation (IDF), Adult Treatment Panel III (ATP III), European Group for Study of Insulin Resistance (EGIR), and World Health Organization (WHO), which generally involve measuring fasting glucose, triglycerides, high-density lipoprotein (HDL) levels, blood pressure, and waist circumference [22]. The prevalence of metabolic syndrome is increasing worldwide, along with the increasing incidence of overweight and obesity [23].

A study involving a large population (298,652 subjects) in Wuhu, China, reported the greater the TyG index quartile, the greater the percentage of population suffering from metabolic syndrome. The TyG index has a higher AUC (AUC = 0.89) than triglycerides (AUC = 0.77) and fasting glucose (AUC = 0.81) in diagnosing metabolic syndrome. The best TyG index cutoff value in determining metabolic syndrome is 8.85, with 81% sensitivity and 91% specificity [24]. Another report from China that conducted a study of 30,291 subjects found that TyG index has a better AUC value than metabolic score for IR (METS-IR) and ratio of triglyceride/HDL in diagnosing metabolic syndrome. In male subjects, the 8.81 TyG index cutoff (AUC = 0.863) had 77.47% sensitivity and 83.55% specificity in determining metabolic syndrome, while in women, a cutoff of 8.73 (AUC = 0.867) had 71.49% sensitivity and 88.57% specificity in determining metabolic syndrome [25]. Similar findings were reported in the Argentina population, which found the TyG index had a higher AUC value than triglyceride/HDL ratio to determine the occurrence of metabolic syndrome (AUC = 0.88 vs. 0.85) with a TyG index cutoff value similar to the population in China of 8.80 in males (sensitivity 84%, specificity 82%) and 8.70 in females (sensitivity 72%, specificity 91%) [26]. A meta-analysis and systematic review was conducted to assess accuracy of TyG index in determining metabolic syndrome in adults, which analyzed 13 reports with a total of 49,325 subjects, reported that the summary receiver operating characteristic (ROC) curve in male had AUC of 0.90 (79% specificity, 82% sensitivity) and in female had AUC of 0.87 (85% specificity, 81% sensitivity), so that TyG index showed the capability to determine the occurrence of metabolic syndrome with high accuracy, although the determination of TyG index cutoff value for each population needs further investigation [3]. Table 3 provides an overview of the TyG index's role in identifying the presence of metabolic syndrome.

The role of TyG index in cardiovascular disorders

Globally, cardiovascular disease is the primary cause of mortality. The incidence of cardiovascular disease increased by almost 100% from 1990 (estimated at 271 million cases) to 2019 (estimated at 523 million cases). Deaths from cardiovascular disease increased by nearly 50% (18.6 million) in 2019 compared to 1990 (12.1 million). Ischemic heart disease is the primary mortality cause from cardiovascular disease, which accounts for nearly 50% of deaths [27]. The number of deaths from ischemic heart disease worldwide in 2021 is estimated at 9,440,00 deaths [28]. Countries with the largest number of deaths from cardiovascular disease include China, India, Russia, the United States, and Indonesia [27]. The TyG index also plays a role in assessing incidence of cardiovascular disorders. Yoon et al. who conducted a study on more than 9000 Korean children and adolescents, reported the TyG index is linked with various cardiometabolic variables including systole and diastole blood pressure, glucose, triglycerides, and waist circumference while it is negatively associated with HDL [19]. Fiorentino et al. conducted a study on 631 normoglycemic, prediabetes, and diabetes subjects, finding that subclinical vascular damage characterized by vascular atherosclerosis and vascular stiffness deals with various markers of insulin sensitivity, including the TyG index. TyG index with cutoff 9.19 can be used to assess the presence of vascular atherosclerosis (AUC = 0.739, sensitivity 82.5%, specificity 59.2%), and cutoff 8.99 can be used to assess vascular stiffness (AUC = 0.579, sensitivity 74.4%, specificity 41.7%) [29]. The TyG index had association with mortality, both during treatment and during follow-up, in patients with cardiovascular disease. Zhai et al. in China conducted a study on 4839 hospitalized heart disease subjects with critical condition. The higher the TyG index quartile, the higher the mortality rate during treatment (12.1% in quartile 4 with a TyG index >9.37 vs. 5.3% in quartile 1 with a TyG index <8.51), and the longer the intensive care unit stay period [30]. Jin et al. performed an investigation on 3,745 subjects with stable coronary artery disease in China and followed them up for 36 months. They found that TyG index had positive association with cardiovascular events (mortality and myocardial infarction) during the monitoring period. Patients in highest quartile (TyG index >9.17) experienced higher risk of cardiovascular events than subjects in quartiles 3, 2, and 1 (20.3% vs. 17.5% vs. 12.8% vs. 16.1%) [31]. In healthy adults, the TyG index may also be used to predict the occurrence of cardiovascular disease. Cho et al. conducted a study using data from more than 6 million healthy young Korean adults, conducted 7.4 years of median time of monitoring, and found that the higher the TyG index, the greater the hazard of stroke, myocardial infarction, and mortality. Subjects in quartile 4 had a 25.8% myocardial infarction risk and 15.1% mortality, higher than quartile 1 [32]. TyG index had association with mortality in subjects with acute decompensated heart failure. Huang et al. conducted a study on 932 acutely decompensated heart failure patients hospitalized in China. During the 478-day (median) follow-up, subjects with the top tertile (TyG index >9.32) got a 2.31 times higher cardiovascular-related death risk compared to subjects with the bottom tertile (TyG index <8.83) [33]. Table 4 provides an overview of the TyG index's role in relation to cardiovascular disease.

Conclusions

The TyG index is a low-cost insulin resistance parameter and widely studied in several populations around the world concerning insulin resistance-related disorders and cardiovascular disease. The TyG index correlates well with the HEC method of assessing insulin resistance. The TyG index may be used in predicting the occurrence of insulin resistance, both in pediatric and adult populations. The TyG index could also be used in predicting the occurrence of diabetes mellitus, assess poor glycemic control in diabetes, assess diabetes complications, and assess the function of pancreatic β cells. The TyG index can also be applied to assess the presence of metabolic syndrome in various populations around the world. The TyG index also had significant association with cardiometabolic risk factors, vascular disorders, cardiovascular events, and mortality and can be used as a cardiovascular disorder predictor. In the studies above, various TyG cutoff values were found that vary depending on population and conditions, so further study is needed to determine the TyG cutoff index that can be used universally in these conditions. The limitation of this review is that most of the data obtained comes from Asian populations and data from the Caucasian race is still limited . In general, high TyG index value is linked to the occurrence of insulin resistance, diabetes mellitus, metabolic syndrome, and cardiovascular disease risk, as well as the occurrence of various complications related to the above conditions.

ACKNOWLEDGEMENTS

None.

AUTHOR CONTRIBUTIONS

The author is responsible for the entire content of this manuscript and approves its submission.

CONFLICTS OF INTEREST

None declared.

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Table 1: The association between TyG index and insulin resistance

Reference	Year	Place, Country	Population	Age (years)	Methods	AUC	TyG index cutoff	Sensitivity	Specificity
6	2010	Guadalajara, Mexico	32 type 2 diabetes and 67 healthy subjects	39.9±9.30	Comparation between TyG index with euglycemic-hyperinsulinemic clamp as the gold standard	0.858	4.68	0.965	0.85
9	2021	Makassar, Indonesia	88 subjects without diabetes	51.15±6.83	Comparation between TyG index with HOMA-IR. HOMA-IR cutoff >2.24 (tertile 3) used to define insulin resistance	0.701	4.66	0.862	0.441
10	2018	Maracaibo, Venezuela	2004 subjects >18 years consist of 1050 female and 954 male	39.6±15.3	TyG index was compared with HOMA2IR. HOMA2IR >2 was used to define insulin resistance	0.889 (all subjects) 0.903 (male) 0.871 (female)	4.49 4.51 4.45	0.826 0.872 0.803	0.821 0.831 0.806
12	2022	Argentina	915 school-age children	9.24±2.17	Comparation between TyG index with HOMA-IR. HOMA-IR >3rd quartile (cutoff not mentioned) was used to define insulin resistance	0.65	8.00	0.62	0.62
13	2021	South Korea	3728 young subjects	14.56±0.06	Comparation between TyG index with HOMA-IR. HOMA-IR >95 percentile was used to define insulin resistance	0.723 (all subjects) 0.756 (male) 0.680 (female)	8.26 8.17 8.26	0.664 0.766 0.644	0.655 0.604 0.635

14	2022	Shantou, China	175 female subjects consist of 114 PCOS and 61 control subjects	29 (mean)	Comparation between TyG index with HOMA-IR. HOMA-IR>2.5 was used to define insulin resistance	0.781	8.51	0.632	0.87

Table 2: The role of TyG index concerning diabetes mellitus condition

Reference	Year	Place, Country	Population, Method	Age (years)	TyG index cutoff	Important Finding
16	2016	Seoul, Korea	2900 nondiabetic adults enrolled in the study and followed for 4 years. The baseline of the TyG index was documented, its association with the occurrence of diabetes after 4 years was assessed	44.3±6.5	8.97	Those with an initial TyG index >8.97 (quartile 4) had a 5.65 times hazard ratio having diabetes within 4 years compared to subjects with TyG index <8.21 (quartile 1)
17	2021	Puducherry, India	140 type 2 diabetes mellitus subjects were recruited, the link between TG index and poor glycemic control (HbA1c >7%) was measured	51.2±9.2	15.50	TyG index >15.5 (AUC 0.806) could be used to predict poor glycemic control among type 2 diabetes mellitus patients
18	2022	Changsha, China	914 participants undergoing medical check-ups consisting of 315 diabetes mellitus patients, 276 normoglycemic, and 323 impaired glucose tolerance (IGT) subjects were recruited and the association between TyG index with β cell dysfunction was measured	44.68±9.30 (NGT), 48.46±9.14 (IGT), 50.92±9.47 (DM)	9.08 and 9.20	TyG index >9.08 (AUC 0.68, sensitivity 0.76, specificity 0.53) could be used to predict early-phase β cell dysfunction while TyG index >9.2 (AUC 0.74, sensitivity 0.76, specificity 0.62) could be used to predict late-phase-β cell dysfunction
19	2022	South Korea	170 adolescents and children with overweight and obesity were recruited. TyG index and HOMA-IR ability to predict the occurrence of type 2 diabetes mellitus was compared	11.34±3.24	(-)	TyG index had a better capability compared to HOMA-IR in predicting the occurrence of type 2 diabetes mellitus (AUC = 0.839 vs 0.645)
20	2022	Zhejiang, China	858 type 2 diabetes mellitus subjects were recruited in the retrospective research	67.13±11.07	9.31	TyG index >9.31 could be used to predict macrovascular complications among type 2 diabetes mellitus subjects (AUC 0.702, sensitivity 0.59, specificity 0.74)
21	2022	Harbin, China	517 type 2 diabetes patients were recruited. TyG index was used to predict mild cognitive impairment among the subjects	58 (median)	9.45	TyG index >9.45 (AUC 0.79) had 0.69 sensitivity and 0.80 specificity in predicting mild cognitive impairment in type 2 diabetes patients

Table 3: The association between TyG index and metabolic syndrome

Reference	Year	Place, Country	Population	Age (years)	AUC	TyG Index Cutoff To Define Metabolic Syndrome	Sensitivity	Specificity
24	2022	Wuhu, Anhui, China	298,652 subjects who came for medical check-ups	47.08±12.94	0.89	8.85	0.81	0.91
25	2019	China	30,291 adult subjects. Metabolic syndrome was defined according to harmonized IDF criteria	43.26±13.66	0.863 (male),	8.81	0.774	0.835
					0.867 (female)	8.73	0.714	0.885
26	2014	Bahia Blanca, Buenos Aires, Argentina	525 participants with metabolic syndrome (89 subjects) and without metabolic syndrome (436 subjects)	45 (median, metabolic syndrome), 33 (median, without metabolic syndrome)	0.88	8.80 (male)	0.84	0.82
						8.70 (female)	0.72	0.91
3	2022	(-)	A systematic review of 13 researches involving 49,325 subjects	(-)	0.90 (male)	(-)	0.82	0.79
					0.87 (female)	(-)	0.81	0.85

Table 4: The association between TvG index concerning cardiovascular disorders

Reference	Year	Place, Country	Population	Age (years)	TyG Index	Important Finding
29	2019	Rome and Cantazaro, Italia	631 adults consisting of normoglycemic, prediabetes, and diabetes subjects were recruited in the research. The TyG index was used in determining subclinical vascular damage	39.6±10.7	9.19	TyG Index >9.192 (AUC 0.739) could be used to predict vascular atherosclerosis with 82.5% sensitivity and 59.9% specificity.
					8.99	TyG Index >8.987 (AUC 0.579) could be used to predict increased vascular stiffness with a sensitivity of 74.4% and specificity of 41.7%.
30	2022	China	4,839 heart disease subjects with critical conditions were studied. The relationship of TyG index with mortality while hospitalized was assessed	65.2±13.8	9.37	Patients in highest quartile (TyG index >9.37) had a higher mortality rate than patients in quartile 1 (TyG index <8.51) with mortality 12.1% vs. 5.3% (OR 1.83, 95% CI = 1.27-2.64)
31	2018	China	3,745 subjects with stable coronary artery disease were recruited in the study and were followed up for 3 years. Initial TyG index and cardiovascular events were analyzed	59.5 (mean)	9.17	Subjects in quartile 4 (TyG index >9.17) experienced the highest mortality rate compared to those in quartile 3, 2 and 1 (20.3% vs. 17.5% vs. 12.8% vs. 16.1%)
32	2022	South Korea	6,675,424 healthy subjects joined the national health program and a mean of 7.4 years follow up period performed. The initial TyG index was used in predicting cardiovascular disease and mortality	20-39 (range)	9.42 (quartile 4, male), 8.71 (quartile 4, female)	Subjects in quartile 4 had a 25.8% higher risk of having myocardial infarction and a 15.1% higher risk of mortality compared to those in quartile 1
33	2022	Nanjing, Jiangsu, China	932 subjects with acute decompensated heart failure were followed up (median 478 days)	70 (median)	9.32	Subjects in tertile 3 (TyG index >9.32) had 2.31 times higher cardiovascular-related death risk compared to subjects compared to subjects in tertile 1 (TyG index <8.83)

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