Lipids in Health and Disease

REVIEW

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The role of the triglyceride-glucose index as a biomarker of cardio-metabolic syndromes

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Abstract

Background The Triglyceride-glucose (TyG) index represents a simple, cost-effective, and valid proxy for insulin resistance. This surrogate marker has also been proposed as a predictor of metabolic and cardiovascular disease (CVD). In this descriptive review, we aimed to assess the utility of the TyG index as a predictive biomarker of cardiometabolic diseases.

Methods A search was conducted in PubMed, and Web of Science to identify cross-sectional and more importantly prospective studies examining the use of the TyG index as a predictive biomarker. The following terms were utilized in addition to the TyG index: "insulin resistance", "metabolic syndrome", "diabetes"; "cardiovascular diseases".

Results This descriptive review included thirty prospective studies in addition to cross-sectional studies. Following adjustment for confounding variables, an elevated TyG index was associated with a significantly increased risk for the development of Metabolic Syndrome (MetS), Type 2 Diabetes, hypertension, and CVD. Also in limited studies, the TyG index was associated with endothelial dysfunction, increased oxidative stress and a pro-inflammatory phenotype.

Conclusion Overall, our findings support the use of the TyG index as a valid biomarker to assess the risk of developing MetS, T2DM, as well as atherosclerotic cardiovascular disease.

Keywords Triglyceride-glucose index, Cardiovascular disease, Metabolic syndrome, Insulin resistance, Diabetes

Introduction

Insulin resistance is a crucial pathogenic mechanism in the genesis of Metabolic Syndrome (MetS), Type-2 Diabetes (T2DM), and premature atherosclerotic cardiovascular diseases (ASCVD) [1, 2]. While the hyperinsulinemic-euglycemic clamp (HIEC) remains the gold standard for measuring insulin resistance, it is costly, labor-intensive, and not widely accessible. Thus, more practical methods such as the homeostasis model assessment of insulin resistance (HOMA-IR) and the triglyceride-glucose (TyG) index have been explored and validated as reliable proxies of insulin resistance when compared to HIEC [3, 4].

The TyG index is a cost-effective and reliable measure of insulin resistance that has been validated against the HIEC technique and in epidemiological and clinical studies [4–8]. In the initial report by Simental-Mendia et al. in 2008, they reported on a cross-sectional study comparing the TyG index with HOMA-IR [6]. In this study of 748 individuals with varying degrees of glucose tolerance, they calculated the TyG index by the following formula:

$$\mathrm{Ln}[\mathrm{fastingtriglycerides(mg/dl)}\ \mathrm{xfastingplasmaglucose(mg/dl)/2}]$$

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Where Ln is the natural logarithm.

They concluded based on their results that the TyG index had higher sensitivity (84%) but a low specificity of 45% compared to HOMA-IR and was a useful surrogate to identify insulin resistance. In a second more definitive report in 2010, Guerrero-Romero et al. compared the TyG index with the gold standard HIEC technique in 99 patients including males and females with varying degrees of glucose tolerance and body weight [4]. Insulin sensitivity was calculated as the total glucose metabolism rate (M). The TyG index correlated significantly with the M value, $r=0.68$. The Receiver Operating Characteristic (ROC) Area under the curve (AUC) of 0.86 was excellent and the optimum cut point on the ROC-AUC showed a high sensitivity and specificity of 96.5% and 85% respectively. Thus, these investigators validated their TyG index as a proxy for insulin resistance.

In 2011, a group from Brazil with a sample size of 82 persons (84% female) with varying degrees of glucose tolerance and body weight, showed using the hyperglycemic clamp technique that the TyG index correlated significantly with the mean glucose infusion rate (GIR), r=-0.64 [5]. This appeared to be better than the correlation between GIR and HOMA-IR of r= -0.51 which was also significant. The ROC-AUC for the TyG index was also very good at 0.79. This study further validates the TyG index as a reliable and cost-effective measure of insulin resistance. In a subsequent report, Guerrero-Romero et al. showed a very significant correlation between the TyG index and M value($r=0.88$) in young adults (60% female) with an average age of 19.2 yrs. They did not report on the ROC-AUC [7].

In this review, we examine the TyG index as a biomarker to predict MetS, T2DM, and ASCVD since these are most relevant to the cardio-metabolic space. The focus of the review is to present data primarily from prospective studies supporting the utility of the TyG-Index as a biomarker for the above-mentioned conditions. Prospective studies have advantages over cross-sectional studies at better implying causality, characterizing risk factors before disease onset and are subject to less bias from confounders. There have been several previous reviews examining the association of the TyG index with a wide spectrum of disorders. This review intended to focus specifically on the relationship of the TyG index with the three commonest cardio-metabolic conditions. To the authors' knowledge, this is the only review on this topic focusing on prospective studies in this population. In addition, we have included plausible pathogenic mechanisms related to the TyG index specifically and the above syndromes and recommendations on the correct formula to use. This review also critically appraises the different formulae utilized to derive the TyG index that is handicapping the development of cut points used in research and clinical settings.

We used PubMed and Web of Science as the database and adopted the following search terms and inclusion criteria:

- Triglyceride-glucose index and insulin resistance,
- Triglyceride-glucose index and metabolic syndrome,
- Triglyceride-glucose index and diabetes,
- Triglyceride-glucose index and cardiovascular diseases.

We also repeated the above searches by adding the term prospective studies to our searches. The search was performed over 6 weeks (in September-October 2024) and the period of the search was from 2016 to the present (2024). Further criteria for inclusion were studies with >500 participants and a median follow-up of at least 3 years. Publications reviewed were limited to English language journals. Prospective studies that did not meet these criteria were excluded.

TyG index and metabolic syndrome

MetS comprises a constellation of cardio-metabolic features, and insulin resistance has been advanced as a pivotal pathophysiological mechanism for this disorder. MetS confers a 2-fold increased risk for ASCVD and a 5-fold increased risk for T2DM [9, 10]. Whilst it is an advancing global problem, there is no optimum treatment to date.

The five MetS risk factors include higher waist circumference (≥102 cm or 40 inches for men and ≥88 cm or 35 inches for women), elevated triglycerides (≥1.7 mmol/L or 150 mg/dL), low high-density lipoprotein (HDL)-cholesterol levels (<1.0 mmol/l or 40 mg/dL for men and <1.2 mmol/l or 50 mg/dL for women), high blood pressure (systolic blood pressure≥130 mmHg or diastolic blood pressure≥85 mm Hg) and high glucose level (≥5.6 mmol/L or 100 mg/dL). Individuals are diagnosed as having MetS if they have at least three of these cardio-metabolic features of MetS [9, 10]. It is important to emphasize that there is now a harmonized definition of MetS, thanks to the tremendous, combined efforts of numerous international organizations [10].

Our recent report was prompted by the fact that the majority of studies, validating the TyG index emanate from Asian and Latin American populations [4–8, 11, 12]. Surprisingly, investigators from the US have not embraced the TyG index. In our recent report on a general US population using the National Health and Nutrition Examination Study (NHANES) we showed in 5380 individuals aged 20–80 years that the TyG index was superior to HOMA-IR in predicting MetS. In this cross-sectional study, representative of the US adult

population, the authors demonstrated an excellent ROC-AUC of 0.87 [95% Confidence Intervals (CI) of 0.85–0.88] [13]. The area under the curve is a commonly used metric that provides information regarding the diagnostic performance of a test. In terms of the clinical usability of the test, an AUC of around 0.7 is considered to show acceptable performance [13]. In addition, ROC-AUC between two tests, such as the TyG index and HOMA-IR, can be compared to determine significant differences. However, there are no firm criteria set for clinical research studies.

The most comprehensive report concerning the role of the TyG index in predicting MetS is a recent review and meta-analysis by Nabipoorashrafi et al. in 2022 [14]. This analysis included 13 cross-sectional studies with a total sample size of 49,325 participants. The pooled mean differences (MD) of the TyG index between groups was 0.83 units (CI of 0.74–0.92), $p<0.0001$. The bivariate diagnostic test accuracy meta-analysis showed the TyG index had a pooled sensitivity of 80% (CI of 75–84%, $p<0.001$) and specificity of 81% (CI of 77–84%, $p<0.001$) for screening for MetS. These analyses showed high heterogeneity between studies with no publication bias. The summary ROC-AUC was 0.87(CI of 0.84–0.90). Based on their findings, the authors concluded that the TyG index is a sensitive and specific measure for MetS.

It is important to emphasize that these are cross-sectional studies and cannot imply causality like prospective studies. Table 1 summarizes the limited data on prospective studies that reaffirm the role of the TyG index in predicting incident MetS. The largest ($n=6091$) longitudinal study with a duration of 12 years was by Son et al. and they showed that the TyG index was superior to HOMA-IR in predicting incident MetS using ROC-AUC in a Korean population [15]. In addition, the hazard ratio (HR) adjusting for age, BMI, smoking, diabetes, hypertension, etc. at baseline was 1.79(CI of 1.61-2.00, $p<0.001$). Kang et al. also reported on a large Korean group for a longer duration of 14 years and showed again that the TyG index was significantly superior to HOMA-IR in predicting MetS and displayed greater sensitivity and specificity [16]. In the smaller study by D'Elia et al. that only reported on Italian males, they showed that the TyG index was similar to HOMA-IR in predicting MetS [17]. They acknowledged their smaller sample size, gender differences, and rate of MetS compared to Son et al. [15].

Thus, it is reasonable to conclude based on cross-sectional and prospective data the totality of evidence collectively supports the TyG index as the superior discriminant of MetS.

TyG index and diabetes

According to the 2021 IDF Diabetes Atlas, the global adult population with diabetes reached 537 million, accounting for 10.5% of the total adult population. Type 2 Diabetes Mellitus (T2DM) accounts for around 90% of diabetes globally and both insulin resistance and beta cell dysfunction appear crucial in its pathogenesis. T2DM leads to an increased risk for both microvascular and macrovascular complications with increasing duration [18]. The TyG index, a valid measure of insulin resistance, appears to be a promising tool for assessing T2DM risk. Its simplicity and predictive capability make it a valuable addition to routine health evaluation.

Cross-sectional studies

An association between the TyG index and the development of T2DM has been demonstrated in previous cross-sectional studies [12, 19–21]. This association has been shown regardless of obesity or age. Fu et al., in a study

Table 1 Prospective studies showing that TyG index predicts incident metabolic syndrome

	Son et al.	Kang et al.	D'Elia et al.
Year	2022	2023	2024
Country	Korea	Korea	Italy
Participants	$N=6091$	$N=3580$	$N=440$
	(40–69 yrs)	(40–70 yrs)	50.3 yrs
	50% Male	47% Male	Male only
Follow up	12 yrs	14 yrs	8 yrs
New MetS diagnosis	38.5%	35.4%	21.6%
TyG Index: ROC-AUC	**0.65** (0.64–0.66)	**0.85** (0.84–0.87)	**0.69** (0.63–0.75)
Other Comments	ROC-AUC for TyG index was significantly higher than HOMA-IR ,**0.56**	ROC-AUC for TyG index was significantly higher than HOMA-IR ,**0.70** 5 SNPs were not additive to TyG index ROC-AUC	ROC-AUC for TyG index was not significantly different from HOMA-IR,**0.62**

Confidence Intervals in parenthesis ( )

SNP-single-nucleotide polymorphisms

of 2571 Chinese individuals aged over 75 years, in whom 231 new-onset T2DM cases were recorded, showed that following adjustment of confounding factors, elevated TyG index independently indicated a higher risk of T2DM (HR = 1.89; 95% CI, 1.47–2.44; $p < 0.01$). Higher TyG index quintile groups (Q3 to Q5) also presented with a higher risk of T2DM (hazard ratio (HR) = 1.36, 1.44, and 2.12, respectively) as compared with the lowest quintile group (Q1) [19]. Another study by Lee et al. in a retrospective analysis of 2,900 subjects in Korea showed that those with a TyG index in quartile 4 had a hazard ratio of having diabetes 5.65 times higher than those with a TyG index in quartile 1 [22].

Deng et al. showed in a cross-sectional study from the Guangzhou Heart Study ($n = 5321$ hypertensive patients), in which 20% had T2DM, that those in the highest quartile of TyG index had a significant (5.35-fold) risk of T2DM (95% CI 4.33–6.64) after adjusting for confounders when comparing with subjects within the lowest quartile. Every 1-unit increment of TyG was associated with an 81% increased risk of T2DM [23]. In one of the largest meta-analyses of 13 cohort studies of 70,380 subjects Da Silva et al. demonstrated that the TyG index had a positive association with diabetes risk in both adults and elderly people. They conclusively showed that, despite the heterogeneity observed in relative risk, the TyG index was significantly associated with T2DM risk (overall HR: 2.44, 95% CI: 2.17–2.76) and could become an adjunctive tool [24].

Table 2 Prospective studies showing that TyG index predicts incident T2DM

	Park et al.	Rong et al.	Li et al.	Lopez Jaramillo et al.	Wang et al.
Year	2022	2023	2020	2023	2021
Country	Korea	China	China	22 countries	China
Participants	*N* = 4285 lean adults	*N* = 862 elderly	*N* = 201,298	*N* = 141,243	N-684
	(40–69 yrs)	> 60 yrs (67–80 yrs.)	> 20 yrs	35–70 yrs	44–53 yrs
	48% Male	47% Male	32% Male	41% Male	58%
Follow up	12 yrs	20 yrs	3.12 yrs	13.2 yrs	15 yrs
Incident T2DM diagnosis	14.7%	63.1%	15.6%	5.5%	10.8%
TyG Index: HR Quartiles/ Tertiles	1.00, 1.63 (95%CI, 1.18–2.24), 2.30 (95%CI, 1.68–3.14), and 3.67 (95%CI, 2.71–4.98)	Tertiles 1.00, 1.457 (95%CI 1.17–1.80) and 1.70 (95%CI 1.37–2.11).	1.00, 1.83 (1.49–2.26), 3.29 (2.70–4.01) and 6.26 (5.15–7.60)	Tertiles 1.00, 1.54 (1.01–1.67); 1.99 (1.82–2.16)	Quartile 1.00, 0.77 (0.28–2.13), 0.611 (0.65–3.66), 3.36 (1.52–7.39)

Tertile or Quartile 1 was assigned a referent value of 1.0

Confidence Intervals in parenthesis ()

Prospective studies

Table 2 summarizes the largest prospective studies. In a 12-year longitudinal study of the Korean Genome and Epidemiology Study cohort, Park et al. showed in this large prospective study that a higher TyG index was positively and independently associated with incident T2DM. The HRs of incident type 2 diabetes in each TyG index quartile were 1.00, 1.63 (95%CI, 1.18–2.24), 2.30 (95%CI, 1.68–3.14), and 3.67 (95%CI, 2.71–4.98), respectively, after adjusting for age, sex, BMI, waist circumference, smoking status, alcohol intake, and physical activity. A higher TyG index precedes and significantly predicts T2DM among community-dwelling middle-aged and elderly lean Koreans [25].

In another 20-year follow-up study of 862 elderly males in China, of which there were 544 cases of incident T2DM, Rong et al. reported an increased TyG index with multivariable HR of 1.53 (1.29–1.80) which independently correlated with T2DM [26]. Li et al. conducted a 3.12 follow-up study of 201,298 individuals > 20 yrs who were enrolled in a health-screening program in China, out of which 3389 developed T2DM. After adjusting for potential confounders, elevated TyG indexes were independently correlated with a greater risk of incident diabetes (hazard ratio (HR), 3.34 (95% CI, 3.11–3.60). Compared with the lowest quartile (Q1), increasing TyG index (Q2, Q3, and Q4) was related to increased HR estimates of incident diabetes [HR (95% CI), 1.83 (1.49–2.26); 3.29 (2.70–4.01), and 6.26 (5.15–7.60), respectively] [27].

In a prospective cohort study across 5 continents, in 141 243 individuals aged 35–70 years from 22 countries, referred to as the Prospective Urban Rural Epidemiology (PURE) study during a median follow-up of 13·2 years (IQR 11·9–14·6), Lopez-Jaramillo et al. recorded 5191 incident cases of type 2 diabetes. After adjusting for all other variables, compared with the lowest tertile of the TyG index, the highest tertile (tertile 3) was associated with a greater incidence and incident type 2 diabetes (1·99; 1·82–2·16). Interestingly the correlation of Tyg Index and incident T2DM was significant in low-, middle- and high-income countries [28].

Wang Z et al. in a 15-year prospective cohort study of 687 participants showed that 74 participants developed T2DM and the risk of T2DM increased with the TyG index. The adjusted hazard ratio (HR) was 3.36 (95% CI:

1.52–7.39, $P<0.001$) comparing the top TyG quartile to the bottom quartile. The lack of association in other quartiles can perhaps be explained by the low number of participants in this study. Nevertheless, it is a prospective study showing a strong relationship between Tyg index and incident Type 2 diabetes [29].

The TyG index may also serve as a predictor of mortality in patients with diabetes. In a study involving 3,376 patients with type 2 diabetes (T2DM) from the US who were monitored for a median duration of 8.9 years, a higher TyG index correlated with an increased risk of both all-cause and non-cardiovascular mortality in T2DM patients under the age of 65. Notably, each one-unit rise in the TyG index was linked to a 1.33-fold increase in the hazard ratio (HR) after adjustment for possible confounding factors [30].

TyG index and gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is defined as glucose intolerance resulting in hyperglycemia that begins or is first diagnosed during pregnancy and is associated with adverse pregnancy outcomes such as cesarean section, birth injury, neonatal adiposity, and large size for gestational age of infants, etc [31]. The TyG index is also one of the emerging biomarkers for insulin resistance identification and GDM prediction, which is cost-effective and convenient in clinical practice, and could predict GDM earlier than oral glucose tolerance test (OGTT) diagnoses (usually 24–28 weeks). Thus, early action could be taken to prevent GDM and to mitigate the serious risk of complications due to GDM. In 661 pregnant women who participated in NHANES from 1999 to 2020, Zeng et al., using logistic regression models in this cross-sectional, retrospective cohort study, revealed a positive association between the TyG index and GDM, remaining significant even after adjusting for all confounding variables (OR = 3.43, 95% CI: 1.20–9.85, $p=0.022$) [32]. In another prospective study of pregnant women, Guo et al. also reported a 2.10-fold increase in the GDM risk for every 1-unit increase in the TyG index, after adjusting for covariates. The highest GDM risk was observed in the group with the highest TyG index compared with the lowest quintile group (odds ratios: 3.25; 95% CI: 2.23–4.75) [33]. Liu et al. reported a four-fold increase in TyG index in GDM patients compared with controls, especially in the second trimester [34].

TyG index and vascular complications of diabetes mellitus

Interestingly, the TyG Index can also be used for assessing macrovascular complications in type 2 diabetes subjects using the optimum cut point with an AUC = 0.702, sensitivity 59%, specificity 74%) [35]. Diabetic retinopathy (DR) is a common and serious chronic microvascular complication of diabetes mellitus (DM) and one of the leading causes of vision loss worldwide, therefore early diagnosis would be important for the prevention of such diabetic complications. In a recent meta-analysis, Zhou et al. incorporated ten observational studies of 13,716 individuals from four different countries including Iran, Singapore, China, and India, and showed that the highest TyG index group had a significantly increased risk of DR compared with the lowest TyG index group [36].

Diabetic Nephropathy (DN) is another common microvascular complication of diabetes. Studies have demonstrated that T2DM patients with a high TyG index have a higher rate of albuminuria and an eGFR < 60 mL/(min·1.73m^2), and an increased risk of developing DN [37]. Furthermore, in T2DM patients with chronic kidney disease elevated TyG index is significantly positively correlated with the risk of end-stage renal disease (ESRD), with each unit increase in TyG index increasing the risk of ESRD by 1.5 times [38]. In addition, the TyG index may serve as an important marker for the early identification of patients at high risk for diabetic neuropathy. In a cross-sectional study of 500 T2DM patients from Egypt, Kassab et al. showed that the TyG index was significantly higher in patients with diabetic retinopathy, diabetic nephropathy, and diabetic peripheral neuropathy compared to those without complications ($p<0.001$) [39].

A recent NHANES study reported a U-shaped association between TyG index and mortality in 1075 cardiovascular disease (CVD) patients with diabetes or pre-diabetes. Specifically, baseline TyG index lower than defined threshold values were negatively associated with mortality while baseline TyG index higher than the threshold values were positively associated with mortality [40].

Thus, in summary, based on the totality of the evidence, the TyG Index is an excellent biomarker of incident T2DM and appears to be significantly associated with increased micro and macrovascular complications and mortality in patients with T2DM.

The TyG index and cardiovascular disorders

Cardiovascular disease remains the leading cause of mortality worldwide. ASCVD accounts for the vast majority of cardiovascular deaths, approximately one-third of which are premature [41]. Current guidelines recommend the use of standardized risk calculators for the determination of risk in individuals without known ASCVD to facilitate primary prevention measures and improved management of ASCVD risk factors. Various risk calculator models have been developed to estimate future CVD risk. These include the Framingham risk score, QRISK score, HeartScore, and others [42]. The models are quite complex, using several variables, and have been found not to be universally applicable to all population groups [43]. Both MetS and T2DM have long been recognized as

major risk factors for ASCVD. Prediabetic states represent an intermediate state between normoglycaemia and overt diabetes mellitus and encompass both impairment of insulin secretion and insulin resistance. Various recent observational studies have demonstrated the association between prediabetes and risk for ASCVD. The recent Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapid in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial reported fasting hyperinsulinemia as an independent risk factor for CVD and CVD-related mortality [44]. This causal relationship has been demonstrated and reported in several studies over the last two decades.

The state of insulin resistance triggers a cascade of metabolic disruptions contributing to the development of various chronic diseases including ASCVD [45, 46]. The TyG index is an arithmetic expression of insulin resistance that is a more practical and reliable indicator of IR than previous conventionally utilized methods as described earlier in the introduction. Various studies have demonstrated the utility of the TyG index as a predictor of ASCVD, as well as related health outcomes such as cardiac failure. TyG index has also been demonstrated to be a predictor of other risk factors associated with ASCVD such as diabetes (discussed above in Sect. 3) and hypertension.

TyG index and hypertension

Hypertension is a very common modifiable risk factor for ASCVD. IR has been implicated in the pathogenesis of hypertension and as a predictor of hypertension. In a prospective study, participants without hypertension from the China National Health survey were followed up for 6 years. Of the 4866 participants, 1256 developed hypertension over the period of the study. Logistic regression analyses after adjusting for confounders were associated with a higher risk of hypertension OR 1.19 (1.05–1.34, p-value=0.006). ROC analysis showed a moderate AUC of 0.583 (0.569–0.597) for the TyG index identifying hypertension [47]. In a study of 15,056 adults whose TyG index were reviewed over 11 years, an elevated baseline TyG index was associated with an increased risk of hypertension. The study reported HRs of 1.38 (1.23–1.54) and 1.69 (1.4–2.02) respectively, for moderate and high stable TyG index over time [48]. An earlier Chinese population longitudinal study followed over 4000 participants for a 9-year period. 43.7% of the participants developed hypertension over the period of review. TyG index at baseline was found to be predictive of the development of hypertension with a higher risk with increasing TyG index values [49]. Similar findings were also reported in a younger cohort of participants. Elevated levels of baseline TyG index were independently associated with the development of arterial stiffness with the highest TyG index quartile demonstrating a fully adjusted odds ratio (OR) of 2.76 (95%CI 1.40–7.54) [50].

Zhou et al. reviewed data from over 8000 patients with hypertension over a median 82-month follow-up period. These individuals were part of NHANES. Patients with the highest TyG index had more significant comorbidities such as obesity with higher blood pressure, increased risk of CVD and 56% increased all-cause mortality (ACM). Using Kaplan- Meier survival curves the authors reported a higher risk of ACM and cardiovascular mortality in patients with the highest TyG index ($p<0.05$) [51]. Another longitudinal study using a different NHANES cohort reported similar findings with an L-shaped relationship between TyG index and hypertension for all-cause mortality among middle-aged and elderly participants with hypertension with HR of 1.28 (1.01–1.53 $p=0.006$) for the highest TyG index quartile [52].

TyG index and atherosclerotic cardiovascular disease

A large 16-year prospective community-dwelling study in Korea reported by Moon et al. demonstrated a 36% increased risk of CVD in participants in the highest TyG index quantile in comparison to those in the lowest quantile. This was following adjustment for confounding variables such as age, sex, BMI, hypertension, diabetes mellitus, and total cholesterol. The relative risk of CVD in males with the TyG index in the highest quartile was 1.53 (1.2–1.96) and 2.42 (1.87–3.14) in females. Carotid ultrasound to determine carotid plaque and intima-media thickness was carried out in a subset of the cohort. Carotid plaque was more frequently identified in those individuals in the higher quartiles of the TyG Index. The predictive power of the TyG index for CVD was further evaluated by ROC analysis. The TyG index AUC was reported as 0.578, and the addition of the risk factors of diabetes and hypertension moderately improved the AUC to 0.604. The authors reported no association between the TyG Index and all-cause mortality risk [53].

Park et al. examined the prediction value of the TyG index for ischemic heart disease (IHD) which is equivalent to ASCVD. This prospective study with a median follow-up of 50 months was also performed in a Korean community-dwelling cohort ($n=16455$) and utilized data obtained from the country's National Health Insurance Service. IHD was defined as angina pectoris or acute myocardial infarction and identified by means of ICD-10 codes utilized in the individual health records. The review period was relatively short, at 50 months. However, findings did show increased HRs for IHD for those individuals in the highest quartile of TyG index: 2.28 (95% CI 1.48–3.51) after adjusting for several confounders including age, BMI, sex, hypertension, smoking status, physical activity, alcohol intake and presence

of chronic kidney disease [54]. Interestingly for both the above studies, the greatest proportions of smokers and alcohol drinkers were found in the highest TyG index quartile group.

A prospective cohort study utilizing the Kailuan cohort in China examined the association between risk of myocardial infarction and the TyG index over a median 11-year period. A total of 98,849 participants were enrolled in the study at baseline and subsequent TyG index were calculated on three follow-up visits during the study period. Baseline TyG index quartiles were significantly associated with increased risk of MI over time with a HR of 2.08 (95% CI 1.77–2.45) for quartile 4 versus quartile 1 TyG index. This association was still maintained when reviewed using the mean TyG index (derived from baseline and follow-up visits) with HR 1.58 (95%CI 1.18–2.12) supporting the robustness of a single baseline measurement. The authors also reported a 42% higher risk of MI per one unit increase in baseline TyG index (HR 1.42; 95% CI 1.33–1.53) with higher hazard risks reported in women versus men [55]. A further study undertaken in the Kailuan cohort reviewed the longitudinal association between baseline and mean TyG index with the incidence of cardiovascular disease over a median 9-year follow-up. The highest tertiles of baseline and mean TyG index were each associated with a higher incidence of CVD when compared to the lowest tertile with adjusted hazard ratios of 1.25 and 1.40 respectively [56].

A study utilizing a Chinese cohort examined the utility of the TyG index as an independent predictor of major adverse cardiovascular events (MACEs) in a population with ACS. At the 3-year follow-up, Kaplan- Meier curves showed significant differences in event-survival rates per TyG index tertiles. The TyG index was demonstrated to be an independent predictor of MACE on multivariate Cox proportional hazards regression analysis [57].

In a community-based prospective study utilizing data from the Shanghai Suburban Adult Cohort, 42,651 participants without previous ASCVD were followed for a median of 4.7 years. The study reported a one-unit incremental increase in TyG index to be associated with HR 1.16 (95%CI 1.04–1.29) for the development of CVD [58].

Many of the prospective studies examining the association of TyG index with cardiovascular disease have been undertaken in Asian countries; there are a smaller number that have been performed in other regions of the world. A fairly large prospective study ($n=5014$) in a Spanish population demonstrated a significantly increased independent risk of CVD with a higher TyG index. The authors reported a relative risk of 2.32 (1.65–3.26) for those individuals in the higher TyG index quintile in comparison to those in the lowest TyG index quintile 1.52 (1.07–2.16) [59]. Another European cohort study examined the TyG index as a potential cardiovascular disease risk factor utilizing participants from the UK Biobank. The primary outcome of this study was the incident of fatal or non-fatal coronary heart disease or stroke. Following a median follow-up of 8.1 years, 4.1% of individuals developed CHD. Raised TyG index values were associated with a higher risk of CVD following adjustment for other common risk factors. Those in the highest TyG index quartile were reported to have a 1.19-fold increased risk of CVD when compared to the lowest TyG index quartile. The association of raised TyG index and stroke was reported as not significant in this study. This study also examined the association of the TyG index with the TG/HDL-C ratio and demonstrated a significant correlation between both indices. Mediation analyses were also performed to determine the effect of dyslipidemia, type 2 diabetes, and hypertension on the TyG index. All three of these traditional risk factors contributed significantly to the total effect of the TyG index on CVD and CHD. Thus, illustrates the utility of the TyG index as a single composite marker for predicting CVD [60]. One of the few prospective studies to have examined the TyG index as a predictive marker outside Asia and Europe was the Isfahan Cohort Study. This study followed 5432 Iranian adults over a median period of 11.2 years. Their findings were supportive of those performed in other populations showing and increased risk of CVD with a higher TyG index with a HR of CVD for 1.48 (95% 1.22–1.79) after adjustment for multiple confounders [61].

The PURE (Prospective Urban Rural Epidemiology) study is a large-scale prospective study ($n=141243$) with participants from 22 countries across five continents. Baseline fasting triglycerides and plasma glucose were performed on all individuals and primary outcomes of mortality or major cardiovascular events (defined as death from cardiovascular causes, non-fatal myocardial infarction, or stroke) were followed for a median period of 13.2 years. The study reported that after adjusting for confounding variables the risk of developing cardiovascular diseases increased across tertiles of the baseline TyG index. Following adjustment for relevant variables, the highest tertile TyG index group HRs for the composite outcome; myocardial infarction and stroke were respectively 1.21 (955 CI 1.13–1.30); 1.24 (1.12–1.38) and 1.16 (1.05–1.28) [28], . Interestingly, the authors reported that associations between the TyG index and outcomes differed by country income level. Low-income and middle-income countries had significantly higher HRs for the primary outcomes with increasing TyG index tertiles in comparison to high-income countries [28].

Reflecting on the findings reported in the aforementioned studies, there was no association between the TyG

index and non-cardiovascular mortality. Table 3 depicts the prospective studies relating to ASCVD.

In summary, the totality of the evidence supports the role of the TyG index in predicting ASCVD in several population groups.

The TyG index and heart failure

Heart failure (HF) causes significant morbidity and mortality worldwide. Insulin resistance has also been shown to play an etiological role in the development of HF [62, 63].

A 31-year follow-up study of 4992 young adults assessed the association between the TyG index and congestive HF (CHF). 1.3% of participants developed CHF during the period. An increased risk of CHF was associated with a unit increase in the TyG index with a reported HR of 2.8 (1.7–4.7). Participants in the highest TyG index quartile demonstrated a higher risk for CHF development than those in the lowest quartile [64].

Data from a NHANES study cohort for over 13,000 individuals was analyzed to determine the relationship between the TyG index and HF. Those participants with HF had higher levels of the TyG index compared with those without HF. However, after adjustment for all covariates, the highest quartile of the TyG index did not demonstrate a statistically significant association with risk for HF when compared to the lower TyG index quartile [65].

The TyG index has also been demonstrated to be a prognosticator of HF. Patients with heart failure with preserved ejection fraction (HFpEF) were reviewed after a median of 3 years with regard to all-cause mortality, CV deaths, and HF re-hospitalizations. Those in the highest TyG index tertile displayed the greatest susceptibility to ACM with HR of 1.53 (95%CI 1.19–1.98) and CV death HR of 1.52 (95%CI 1.19–1.96) [66]. The Atherosclerosis Risk in Communities (ARIC) study followed 12,374 participants free of HF and CHD over a median follow-up period of 22.5 years. This study also confirmed the association with a higher baseline TyG index and increased risk of HF development, HR 1.15 (95%CI 1.10–1.21). Additionally, a greater baseline TyG index was associated with unfavorable left ventricular modeling and dysfunction [67]. As discussed earlier, the TyG index has been shown to be a useful predictor of MACEs such as heart failure. TyG index has been demonstrated to be a useful predictor of MACEs in diabetic patients with ischemic cardiomyopathy. Abuduaini et al. reported for Cox proportional hazards regression, a HR of 7.334 (3.424–15.708) for the development of heart failure [68].

TyG index and arrhythmia

Arrhythmias are associated with increased cardiovascular morbidity and mortality with atrial fibrillation being the most commonly occurring problem. Obesity and insulin resistance have been previously demonstrated to be associated with the risk of AF development [69]. In a prospective study, utilizing the Atherosclerosis Risk in Communities (ARIC) cohort a U-shaped association with baseline TyG index and atrial fibrillation (AF) was reported. The study consisted of 11851 American participants without known CVD with a median follow-up of 24.26 years. Cox proportional hazards analysis demonstrated an adjusted HR of 1.15 (1.02–1.29) for the lower TyG index group and an adjusted HR of 1.18 (1.03–1.37) for the upper TyG index group but no increase for the middle group [70]. A further prospective study in the aforementioned Kailuan cohort followed 1979 participants over a median follow-up of 5.31 years. In this study, multivariate Cox proportional hazards regression analysis indicated that a higher TyG index was significantly associated with MACE in patients with AF (HR 2.103 (1.107–3.994) [71]. Risk of ventricular arrhythmias have also been associated with increases in the TyG index [72].

Thus, in summary, prospective studies provide valuable information on the association of the TyG index with ASCVD, risk factor development, risk stratification, outcome, and mortality prediction. The evidence supports the use of the TyG index as a valuable tool in the assessment and management of cardiovascular disease.

Pathogenic mechanisms

Insulin resistance as evidenced by the TyG index predisposes to Metabolic Syndrome, T2DM, and Hypertension as reviewed above. Furthermore, insulin resistance by increasing the risk for T2DM, Hypertension, and Dyslipidemia (manifesting as elevated TG levels, low levels of HDL-C, and a preponderance of small dense LDL particles) also increases the risk for ASCVD [1, 2, 11]. This is not surprising since it used measures of dysregulation of both carbohydrate and lipid metabolism [11]. Pathogenic mechanisms that have been advanced to explain this increased risk include endothelial dysfunction, increased oxidative stress, a pro-inflammatory state, and increased thrombosis [1, 2, 11, 73, and 74]. There is a serious paucity of studies examining the relationship of the TyG index specifically with these mediating mechanisms. Some groups have shown a relationship with the prototypic downstream marker of inflammation, C-reactive protein (CRP) [5, 74,]. Vasquez et al. also showed an inverse correlation with plasma adiponectin [5].

A study in a small group of patients ($n=30$) with Klinefelter syndrome (KS) a sex chromosomal disorder with hypogonadism examined TyG index and endothelial dysfunction [75]. KS is associated with increased morbidity and mortality related to cardiovascular diseases. Asymmetric dimethylarginine (ADMA), an inhibitor of endothelial nitric oxide synthase resulting in a

Table 3 Prospective studies showing that TyG index predicts ASCVD

Study	Year	Country	Participants	Follow up (median)	Incident ASCVD diagnosis	TyG index Quartiles/ tertiles	ROC AUC/ other
Moon et al.	2023	Korea	*N* = 8511 40–70 years old 47.5% males	15.6 years	10.9%	1.00 1.12 (0.91–1.38) 1.17 (0.95–1.44) 1.36 (1.10–1.68)	0.578 vs. HOMA-IR 0.543
Park et al.	2020	Korea	*N* = 16,455 ≥ 20 years 51% males	50 months	2.0%	1.00 1.61 (1.05–2.48) 1.85 (1.21–2.81) 2.29 (1.50–3.51)	
Tian et al.,	2021	China	*N* = 98,849 18–98 years old 79.75% male	11 years	1.57%	1.00 1.26 (1.01–1.51) 1.60 (1.36–1.89) 2.08 (1.77–2.45)	
Li et al.	2022	China	*N* = 49,579 ≥ 18 years 76.6% male	9 years	4.9%	1.00 1.22 (1.09–1.37) 1.25 (1.11–1.42)	
Wang L et al.	2020	China	*N* = 2531 66.3 ± 6.8 years 55.9% males	3 years	11.4%	1.00 1.591 (0.939–2.697) 1.709 (1.006–2.903)	
Wan et al.	2023	China	*N* = 42,651 20–74 years 41.3% male	4.7 years	3.3%	1.00 0.95 (0.80–1.13) 1.06 (0.89–1.25) 1.18 (0.98–1.41)	
Sanchez-Inigo et al.	2016	Spain	*N* = 5014 18–90 years 61.1% male	10 years	9.25%	1.00 1.19 (0.83–1.71) 1.32 (0.93–1.88) 1.52 (1.07–2.16) 2.32 (1.65–3.26)	0.719 (0.70–0.74) combined Framingham and TyG index model
Che et al.	2023	UK	*N* = 403,335 56.2 (SD 8.1 years) 54.5% male	8.1 years	4.9%	1.00 1.07 (1.01–1.13) 1.09 (1.03–1.15) 1.25 (1.18–1.32)	
Rafiee et al.	2024	Iran	*N* = 5432 ≥ 35 years 48.75% males	11.2 years	15%	1.00 1.14 (0.93–1.38) 1.48 (1.22–1.79)	For CVD 0.611 (0.590–6.33) not compared to HOMA IR
Lopez- Jaramillo et al.	2023	Multinational	*N* = 141,243 35–70 years 41% male	13.2years	4.5%	1.00 1.04 (0.94–1.15) 1.24 (1.12–1.38)	

Tertile or Quartile 1 was assigned a referent value of 1.0

Confidence Intervals in parenthesis ()

decrease in nitric oxide (NO) levels is a valid surrogate marker of endothelial dysfunction, was also measured in both the patients with KS, and matched controls. In the KS patients, the TyG index was positively correlated with both plasma ADMA levels ($r=0.48$, $p<0.001$) and HOMA- IR ($r=0.36$, $p=0.011$). The study demonstrated that the TyG index was an independent determinant of endothelial dysfunction as reflected in ADMA levels in this group of individuals [75]. A study by Li et al. investigated the association between the TyG index and endothelial dysfunction directly [76]. In this study, flow-mediated dilation (FMD) of brachial arteries was used as a marker for endothelial function. A decreased FMD, which is nitric oxide-mediated, suggests endothelial dysfunction and represents early nascent atherosclerosis promoting leukocyte recruitment and entry, trapping, and modification of atherogenic lipoproteins resulting in the fatty streak lesion [77]. The authors reported lower FMD values with each unit increase of the TyG index following the adjustment of covariates. However, this association between the TyG index and endothelial dysfunction was evident only in female patients under 60 years of age without diabetes [76]. The authors acknowledged that multiple confounders including therapies could have influenced their aberrant findings. In their prospective cohort study, Yang et al. investigated the relationship between oxidative stress, the TyG index, and risk of CVD. The study consisted of 6131 adults from the NHANES group who were followed for a median period of 106 months. They described a J- shaped relationship between the TyG index CVD and all-cause mortality. In addition, they described the mediation of this association with the relationship to increased levels of surrogate markers of oxidative stress such as gamma-glutamyl transferase (GGT), a precursor of glutathione, and uric acid a potent water-soluble antioxidant [78]. It should be noted that GGT and uric acid are non-specific markers of oxidative stress and are affected by several confounders including alcohol ingestion and the presence of several other diseases. An interpretation of their data is that the increased levels are a response to an increase in oxidative stress.

In a recent report in a cohort in which smoking, macro-inflammation T2DM, and ASCVD were excluded, using a wide repertoire of biomarkers they showed that there was a significant relationship between the TyG index and increased oxidative stress as evidenced by elevated levels of direct footprints of oxidative/nitrative stress, plasma nitrotyrosine and oxidized-LDL levels [79]. Furthermore, they showed an association with both circulating biomarkers of inflammation (CRP, endotoxin, chemerin, and interleukin-6) and cellular biomarkers (monocyte toll-like receptors 2 & 4 and their downstream cellular signaling). However, since this was a cross-sectional study of 102 individuals these important findings need to be replicated in larger prospective studies. Finally with respect to increased thrombosis, in 468 individuals with ST- elevation myocardial infarction who underwent percutaneous coronary intervention (PCI) the TyG index was significantly higher with the larger thrombus burden (LTB) and in multivariate analysis was an independent predictor of LTB [80]. However no pathogenic mechanisms were provided.

Thus, it is imperative to focus on pathogenic mechanisms in prospective studies to clearly define the exciting role of the TyG index.

Correct calculation of the Tyg index

A major concern with respect to cut points is the confusion created by the initial investigators claiming their original reports had the incorrect formula [4, 6]. In a subsequent letter to a concern raised by another group, they stated that there was an error in the original formula used in their 2008 and 2010 papers and that the correct formula was:

Ln [fasting triglycerides (mg/dl) x fasting plasma glucose (mg/dl)]/2 [81].

They failed to provide any plausible scientific explanation for this recommendation.

In our report of the NHANES data set in 5380 Individuals aged 20–80 years we showed that the TyG index, in this cross-sectional study, was superior to HOMA-IR in predicting prevalent MetS in this general and representative US adult population with an excellent ROC-AUC of 0.87 [95% Confidence Intervals (CI) of 0.85–0.88] [13]. We have now re-analyzed our data using both formulas and arrived at identical ROC-AUCs of 0.87 (95% CI of 0.85–0.88) for both since the product of the same analytes is used. The major issue with using the two formulae is that the values for the TyG index are different. The best TyG index cut point, the Youden index, was 8.6 with the first formula and 4.7 with the second formula. To further underscore this disparity in our NHANES study, values for the TyG index using the first formula for the median and (inter-quartile range) are 8.5(8.1-9.0) and 4.6(4.4–4.8) for the second formula respectively [82]. Needless to say, this has created considerable confusion in the published literature and is well illustrated in the review of 21 studies by Kurniawan in which cut-offs ranging from 4.5 to 9.5 are reported with the vast majority of studies reporting values ≥ 8.0 [12]. Since they provide no scientific plausibility for this suggestion like Alizagar et al. we recommend based on our expertise in clinical biochemistry and biomarker research, that investigators adhere to the original formula to derive cut points and reference ranges [82, 83]. A recent review by Avagimyan et al. obfuscated the area further by using both mmol/L for

TG and mg/dl for glucose levels in their formula without rationale [84].

There is an urgent need to develop a consensus document on this issue to facilitate further research with this promising biomarker.

Strengths and limitations

The major strengths of the present review are the following. It focused on the role of the TyG index as a biomarker of the commonest cardio-metabolic syndromes. In addition, it clearly differentiates the data from cross-sectional studies and prospective studies since the latter allows us to infer possible causality. This review suggests that the TyG index is a valid biomarker for MetS, T2DM, hypertension, and ASCVD. Furthermore, we discuss plausible pathogenic mechanisms, making a plea for more prospective studies investigating mechanisms, and finally make recommendations on the correct formula to use to end the present confusion.

A possible perceived weakness is the failure to discuss the evolving role of the TyG index in Obstructive Sleep Apnea and Non-alcoholic fatty liver disease (NAFLD). In addition, our discussion of mechanisms was limited by the scanty studies on TyG and mechanisms since the focus of the majority of authors is epidemiological relationships.

Conclusion

Overall, this review supports the utility of the TyG index as a reliable surrogate marker of insulin resistance that is useful as a predictive marker of cardio-metabolic disease. We would support the introduction of the TyG index in clinical practice, as it will provide valuable additional information in assessing risk for cardio-metabolic disease. Further studies are required in more diverse populations as most studies have been performed in Asian nations with a smaller number of studies in European or US populations. Additionally, further consideration of the addition of the TyG index to existing risk predictors may improve their utility. Future studies should explore mechanistic links between the TyG index and clinical syndromes since this can usher in novel therapies.

Abbreviations

ACM	All-Cause Mortality
ASCVD	Atherosclerotic Cardiovascular Disease
AMI	Acute Myocardial Infarction
AUC	Area Under the Curve
CI	Confidence Interval
CV	Cardiovascular
CVD	Cardiovascular Disease
DN	Diabetic Nephropathy
DR	Diabetic Retinopathy
GDM	Gestational Diabetes Mellitus
GIR	Glucose Infusion Rate
HF	Heart Failure
HOMA-IR	Homeostasis Model Assessment Insulin Resistance
HR	Hazard Ratio
IR	Insulin Resistance
M	Glucose Metabolism Rate
MD	Mean Difference
MetS	Metabolic Syndrome
NHANES	National Health and Nutrition Examination Study
OGTT	Oral Glucose Tolerance Test
RR	Risk Ratio
T2DM	Type 2 Diabetes
TyG	Triglyceride Glucose Index
RR	Risk Ratio
ROC	Receiver Operator Curve

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IJ generated the idea for this publication following invitation by the Reviews Editor. IJ, SD and VG drafted the manuscript. All authors read numerous iterations and approved final version for submission. VG formatted manuscript.

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

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