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REVIEW ARTICLE

Evaluation of Role of Triglyceride Glucose Index as a Marker for Predicting severity of Coronary Artery Disease

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ABSTRACT

One trustworthy substitute biomarker of insulin resistance (IR) has been found to be the triglyceride glucose (TyG) index. The development and prognosis of cardiovascular disease (CVD) have been linked to the triglyceride glucose index, according to a significant number of recent research that have produced strong statistical support for this theory. However, there is even less data available about the underlying mechanisms linked to cardiovascular illness, and the use of the triglyceride-glucose index as a marker of cardiovascular disease has not been thoroughly examined. In light of this, we provide a brief overview of the development of the triglyceride-glucose index as a stand-in marker for insulin resistance in this review. In order to increase the triglyceride glucose index's usefulness for cardiovascular disease and offer more thorough and accurate supporting data, we set out to demonstrate the index's application value for a range of cardiovascular disease types and investigate any potential drawbacks associated with its use as a predictor of cardiovascular events.**Conclusion:** The results suggest that while fasting and postprandial triglyceride glucose indices may not be independent predictors of CAD severity in non-diabetic patients, The TyG index was not independently relevant to adverse cardiovascular events in nondiabetic patients who underwent PCI. However, in subjects with LDL-C lower than 70 mg/dl, it may predict adverse cardiovascular prognosis.

Keywords: Triglyceride glucose index, cardiovascular disease, insulin resistance.

INTRODUCTION

The TyG index is a composite indicator made up of fasting glucose (FG) and fasting triglyceride (TG) levels. It is computed as TyG index = ln [Fasting triglyceride (mg/dl) × fasting glucose (mg/dl)]/2. 2008 saw the initial proposal of it. The TyG score was found to be a better proxy (sensitivity 84.0% and specificity 45.0%) to diagnose IR than the HOMA-IR index in a large cross-sectional investigation of people who appeared to be in good health [1]. Large-scale clinical trials have demonstrated the validity and accessibility of the TyG index as a tool for assessing IR in high-risk people. Impairment of glucose tolerance (IR) is a major factor in the development of diabetic mellitus (DM). 5,354 middle-aged Koreans who were not diabetics were included in a study by Lee *et al*. in 2014 for a long-term follow-up to determine their diabetes status. Relative risk, 4.095; 95% CI 2.701–6.207, showed that the risk of diabetes onset was more than four times higher in the highest quartile of the TyG index than in the lowest, indicating that the TyG index could be a valuable tool for identifying subjects who are at high risk of acquiring the disease. Furthermore, this research demonstrated that the TyG index had

a higher predictive power for IR evaluation than the HOMA-IR index [2].

However, their conclusions about the TyG index's reliability in predicting the occurrence of DM were hampered by the lack of favorable comparisons for diagnosing DM. Then, in 2016, a study by David *et al*. found that among 4820 people, the TyG index had a higher predictive potential for DM diagnosis than fasting blood glucose (FBG) test and TG levels. In order to give early therapies for those who may be at risk of developing DM in the future, the TyG index may be able to assist [3].Apart from diabetes mellitus, insulin resistance (IR) is a noteworthy indicator of obesity, hypertension, dyslipidemia (higher triglyceridemia and decreased HDL), and additional symptoms associated with the metabolic syndrome (MetS). It has been established that these metabolism-related parameters are separate CVD risk factors [4, 5].

The TyG index, a helpful proxy for IR, has been progressively associated with the onset of CVD and unfavorable results. With a large sample from the Vascular Metabolic CUN cohort (VMCUN cohort) and a median follow-up period of 10 years, Laura *et al*. first proposed an independent positive correlation between the TyG index and CVD events, such as peripheral arterial disease, cerebrovascular disease, and coronary heart failure (CHD), without taking into account confounding variables. Since then, the connection between various forms of CVD and the TyG index has been gradually revealed [6] (Figure 1).

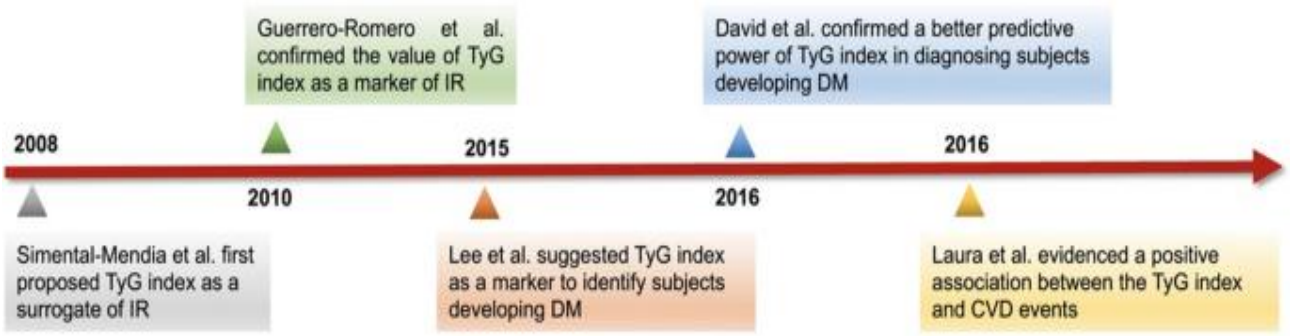

Figure 1: The useful history of triglyceride-glucose index (TyG) [7].

TyG: triglyceride-glucose index; IR: insulin resistance; DM: diabetic mellitus; FBG: fasting blood glucose; CVD: cardiovascular disease.

Role of TyG index in metabolic syndrome:

The TyG-Index is computed as follows: log fasting glucose (mg/dl) X log fasting triglycerides (mg/dl). 2. Even after controlling for all conventional cardiovascular risk variables, the TyG-Index showed a substantial correlation with carotid atherosclerosis, in contrast to the HOMA-Index. In fact, even after the metabolic syndrome's components or existence were eliminated from model 24, the TyG-Index persisted [8] (Figure 212).

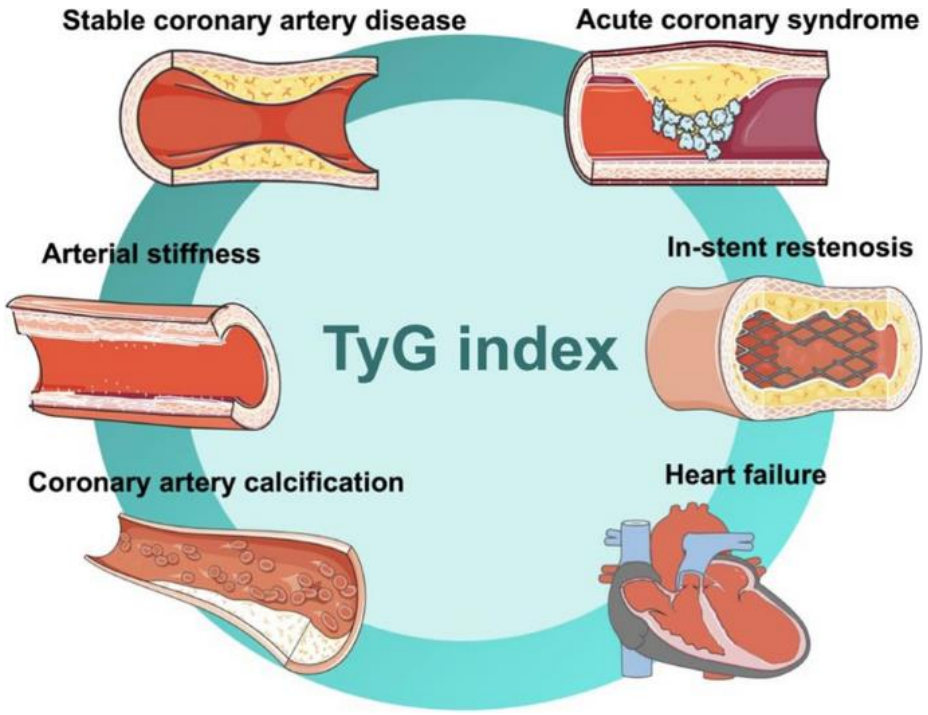

Figure 21: The application of triglyceride-glucose (TyG) index in cardiovascular diseases[7].

TyG: triglyceride-glucose index.

TyG index in cardiovascular diseases:

Acute coronary syndrome (ACS)

A variety of myocardial ischemic diseases, such as unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI), and ST-elevated myocardial infarction (STEMI), are referred to as acute coronary syndrome (ACS), the most severe kind of ischemic heart disease[9]. Some patients with ACS are still at high risk for recurrent cardiovascular events (CVEs) even after using the current guidelines-recommended therapeutics, such as optimal drug treatments and coronary artery bypass grafting (CABG) or PCI, which are techniques for revascularizing coronary arteries. Therefore, in order to give intensive measures, it is imperative to identify ACS patients who are at a 9high risk of CVEs [10].

According to studies, the TyG index may be a helpful tool for risk assessment and prognostic prediction for individuals with or without diabetes who have ACS. A retrospective cohort research included 2531 patients with diabetes who were enrolled consecutively. Due to ACS, these individuals underwent coronary angiography (CAG) and finished a three-year clinical follow-up. Whether invasive or non-invasive therapy were employed, the TyG index remained a reliable predictor of MACEs after standard CVRFs were adjusted for, the researchers found. The TyG index tertiles increased in lockstep with the prevalence of MACEs [11]. Furthermore, to determine the risk of MACEs, Mao *et al.* assessed 438 patients with NSTE-ACS and monitored them for a year following admission. The findings showed that the TyG index has good diagnostic potential for CVRFs, such as metabolic syndrome and glucose metabolism disorders. Moreover, it was discovered that the TyG index independently predicted both the incidence of MACEs and a high SYNTAX score. These two studies provided evidence in favor of the TyG index's potential utility in predicting clinical outcomes in patients belonging to various ACS groups [12].

Nevertheless, only patients with a confirmed diagnosis of diabetes mellitus or impaired glucose tolerance were included in these earlier investigations. Does the prognosis of patients without glucose metabolic problems also depend on the TyG index? The TyG index, as was previously mentioned, has been shown to be helpful in early detection of patients who appear healthy but are at high risk of developing cardiovascular disease. It may therefore be of therapeutic interest to determine whether the TyG index can forecast the clinical fate of ACS patients in the absence of known risk factors. Zhang et al. analyzed 1655 ACS patients without diabetes and found that a high TyG index level was associated with a greater incidence of AMI

(21.2% vs. 15.2%), larger infarct size, and higher incidence of revascularization (8.9% vs. 5.0%) compared with ACS patients with LDL-C values below 1.8 mmol/L. It's interesting to note that patients with a high TyG index were more likely to get diabetes during follow-up, suggesting that multivessel CAD, which may contribute to the higher incidence of revascularization, may be more common in these patients [13].

Apart from obstructive ACS, nonobstructive coronary artery disease (MINOCA) patients who have an increased TyG index also have an independent bad prognosis. A unique clinical entity, MINOCA accounts for 5–10% of all MI cases and displays a heterogeneous diagnosis of many causes, including spontaneous dissection, thrombosis, supply/demand mismatch, plaque erosion, and coronary spasm. After controlling for multivariate risk variables, Gao *et al.* observed that MACEs were more common in patients in the higher TyG index tertiles. 1179 MINOCA patients with a median follow-up of 41.7 months were recruited for the study. Notably, the TyG index continued to be a strong risk factor for all patients with MINOCA or its subsets, such as those with or without diabetes and those whose LDL-C levels were above or below 1.8 mmol/l. This suggests that the TyG was a valid indicator for prognosticating outcomes in MINOCA patients regardless of their glucose-lipid metabolic status [14].

Potential explanations of the TyG index as a marker for predicting cardiovascular disease

It is still unclear what precise mechanism underlies the association between CVD and the TyG index. Lipid-related and glucose-related risk factors for CVD, which are indicative of IR in the human body, make up the TyG index, which is evidently an index. One possible explanation for this link could be the TyG index, which has been found to be a valid marker of IR in recent research. In addition to being a risk factor for CVD in the general population and in individuals with diabetes, IR also indicates the cardiovascular prognosis of CVD patients. The following is a description of the probable mechanisms causing IR and CVD [15, 16] (Figure3).

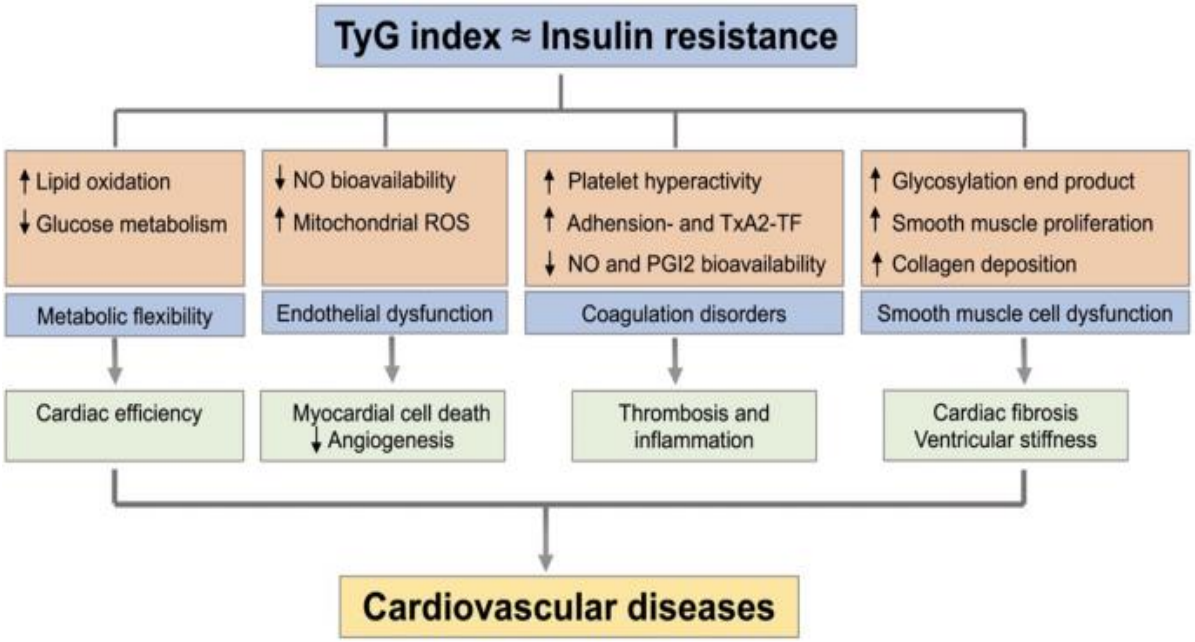

Figure3: Potential molecular mechanisms that contribute to the predictive role of the triglyceride-glucose (TyG) index in cardiovascular diseases (CVD). Insulin resistance (IR) is a hallmark of metabolic syndrome and has been evidenced as a risk factor for CVD. The TyG index has been identified as a reliable alternative marker of IR, which may explain the association between the TyG index and CVD. The molecular mechanisms underlying IR and CVD include metabolic flexibility, endothelial dysfunction, coagulation disorders and smooth muscle cell dysfunction[16].

TyG: triglyceride-glucose; CVD: cardiovascular diseases; IR: insulin resistance; NO: nitric oxide; ROS: reactive oxidative stress; TxA2: thromboxane A2; TF: tissue factor; PGI2: prostaglandin I2.

First, IR can lead to an imbalance in the metabolism of glucose, which can exacerbate hyperglycemia and cause oxidative stress and inflammation. Atherosclerosis may start because of systemic lipid abnormalities, which have also been documented. These include decreased HDL levels, high TG, small dense LDL, and postprandial lipedema levels [17].

Furthermore, decreased insulin activity in the established ischemic myocardium restricts the bioavailability of glucose and induces a switch to the metabolism of fatty acids, which in turn raises cardiac oxygen consumption and decreases the compensatory potential of the non-infarcted myocardium. The evolution of CAD is made worse by these pathological metabolic abnormalities [18].

Second, research indicates that IR can cause a rise in free radical and glycosylated product formation, which can inactivate nitric oxide (NO). Endothelium-dependent vasodilation results from vascular endothelium damage brought on by aberrant NO production associated with IR. Moreover, IR causes an excess of reactive oxidative stress (ROS) and stimulates the mitochondrial electron-transport chain, both of which contribute to compromised endothelial function [19]. Diabetic patients exhibit aberrant endothelial function that affects cardiac energy metabolism and coronary microcirculation. A decreased density of collaterals in response to cardiac ischemia is a result of the negative relationship between IR and median colony forming unit endothelial cells in individuals with cardiac ischemia [20].Furthermore, numerous experimental investigations have unequivocally demonstrated that the insulin receptor can facilitate associated signaling, hence sensitizing platelets to prostaglandin I2 (PGI2) and NO's antiaggregating properties. On the one hand, platelet hyperactivity may be exacerbated by IR. Conversely, adhesion-induced and thromboxane A2 (TxA2)-dependent tissue factor expression in platelets can be enhanced by it. These occurrences have been linked to inflammation and thrombosis, which helps to explain why some patients experience non-obstructive coronary thromboembolism or obstructive ACS [7].

Furthermore, earlier research has shown that IR, which is typically associated with hyperglycemia, causes excessive glycosylation, which can encourage the growth of smooth muscle cells as well as the crosslinking and deposition of collagen. Cardiac fibrosis, elevated diastolic left ventricular stiffness, and ultimately heart failure are all caused by these pathological events [16].Lastly, IR contributes significantly to hyperlipidemia in addition to hyperglycemia. Research has indicated that increasing TG levels may cause an increase in free fatty acid (FFA) levels and facilitate the flow of FFAs from adipose tissue to non-adipose tissue, which may occur in conjunction with IR. More significantly, the pathophysiology of atherosclerosis may be connected to the retention of TG- and cholesterol-rich ApoB-containing fragments within the coronary wall [21, 22].Therefore, TG level reduction seems to be an extra goal for patients with a high risk of CVD. Moreover, renin-angiotensin system activation and reduced cardiac calcium processing capacity could potentially be factors [23].

Limitations of the TyG index as a marker in cardiovascular diseases:

An additional method for detecting insulin resistance (IR) in extensive studies or evaluating groups at elevated risk of diabetes is the TyG index, a composite metric composed of fasting TG and FG. Interestingly, several research have shown that the TyG index outperformed the HOMA-IR index in terms of anticipating the development of atherosclerosis and adverse consequences, like as increased risk of carotid atherosclerosis and the progression of CAC, as measured by the CAC score [24]. Furthermore, prior research indicates that the alternative test, which is derived from fasting TG and FBG, is more widely available and less expensive than the direct measurement of blood insulin levels, which is unavailable in the majority of developing country cities. Furthermore, exogenous insulin may affect the HOMA-IR index's value because quantification is required. As a result, people with diabetes on insulin treatment may not be

able to use the HOMA-IR index's current assessment of IR. The TyG index can be applied to all diabetic patients receiving insulin treatment because it is a formula made up of fasting TG and FG, which does require the quantification of insulin. In conclusion, TyG is thought to be a useful and trustworthy measure for IR in those who have a high risk of CVD, particularly in developing nations [7].

Nonetheless, a number of observations continue to refute the link between CVEs and the TyG index. Firstly, the TyG index was initially used in 2008 with the justification that IR frequently causes elevated TG and glucose levels in healthy individuals [25]. Thus, diabetes and hyperlipidemia may have an impact on how the TyG index is applied to CVD patients. In order to validate the TyG index's efficacy as a biomarker, it is imperative that hypertriglyceridemia and glucose metabolic disorders are adequately managed. However, a number of patients with abnormally high TGs or FBSs were included in earlier clinical trials, which precluded investigating reverse causality when the TyG index was applied to these CVD patients. For instance, Laura *et al*. did not discover a correlation between the TyG index and CVD in individuals who had baseline hypertension or T2DM. The possibility that patients with a history of diabetes or hypertension were receiving treatment or had changed to better lifestyles could account for their results and ensure that their analytical parameters were under control. After controlling for conventional CVRFs, Cho *et al*. were unable to discover a significant correlation between the TyG score and the existence of CAD or obstructive CAD in 996 individuals with established diabetes [25].

Furthermore, the majority of studies on the use of TyG in CVD have been conducted on middle-aged or older participants, and there are currently no data on the effectiveness of TyG in younger participants. The TyG index was discovered by Dikaiakou *et al*. to have a positive connection with IR in both children and adolescents; however, there is a lack of information about the TyG index's predictive power in determining whether these younger people will have CVD in the future. Disparities in the TyG index between the sexes remain unclear, in addition to the dearth of data on various age groups. Men are more at risk for metabolic illnesses than women are. Men, for instance, have lower estimated glomerular filtration rates (eGFR), higher serum levels of homocysteine and uric acid, and are more prone to smoke and drink [26, 27].

CONCLUSION:

The results suggest that while fasting and postprandial triglyceride glucose indices may not be independent predictors of CAD severity in non diabetic patients , The TyG index was not independently relevant to adverse cardiovascular events in nondiabetic patients who underwent PCI. However, in subjects with LDL-C lower than 70 mg/dl, it may predict adverse cardiovascular prognosis. More large-scale prospective research should be carried out in the future to explore the predictive effect of this index in nondiabetic patients who receive PCI, especially patients with well controlled LDL-C.

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