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REVIEW

Role of Triglyceride-Glucose Index in Type 2 Diabetes Mellitus and Its Complications

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Abstract: Insulin resistance (IR) is the major mechanism in the pathogenesis of type 2 diabetes mellitus (T2DM). Early identification of IR is of great significance for preventing the onset of T2DM and delaying the progression of the disease. Previous studies have shown that triglyceride-glucose (TyG) index can be used as an effective surrogate marker for IR. There is a significant correlation between TyG index and T2DM and its common complications. In addition, the predictive efficacy of TyG index is better than that of other IR surrogate indicators. TyG index may not only become an important marker to identify people at high risk of T2DM and its complications, but is also expected to become a strong predictor of the prognosis of these diseases. However, there are still some challenges in the widespread application of TyG index in clinical practice. In the future, more high-quality studies are needed to clarify the assessment methods of TyG index for the prognosis of T2DM and its complications. Further investigations of the relationship between TyG index and T2DM and its complications will be expected to provide new ideas and methods for the prevention and treatment of T2DM and its complications.

Keywords: triglyceride-glucose index, type 2 diabetes mellitus, complication, insulin resistance

Introduction

According to the 2021 IDF Diabetes Atlas,[1] the global adult population with diabetes had reached 537 million, accounting for 10.5% of the total adult population, with a global health expenditure estimated at US$966 billion. China has the largest number of diabetes patients in the world, with 140 million cases and approximately 1.4 million annual deaths from diabetes and its complications. Diabetes not only causes physical dysfunction and impaired quality of Iife, but also imposes a significant economic burden on individuals, families, and healthcare systems.

Type 2 diabetes mellitus (T2DM) accounts for 90–95% of all diabetes mellitus, and its primary pathogenesis is insulin resistance (IR).[2] Although the hyperinsulinemic euglycemic clamp technique is the gold standard for diagnosing IR, it is costly and time-consuming. Consequently, biomarkers including triglyceride-glucose (TyG) index, HOMA-IR, G/I, and QUICKI have been developed to assess IR more feasibly.[3] Among them, TyG index is considered an ideal alternative to IR because it does not require insulin measurement, is inexpensive and easy to obtain.[4] With the deepening of research, TyG index has gradually attracted wide attention as a promising surrogate marker of IR.[5]

TyG index was first proposed by Simental-Mendia et al in 2008, and is calculated by the formula Ln[fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2].[6] In recent years, a number of studies have found that TyG index can accurately identify IR, which may be related to its integrated consideration of both blood glucose and lipid factors, making it a more comprehensive reflection of the metabolic status of the body.

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Glucose and lipid metabolism disorders are key contributors to T2DM.[7] Typical diabetic dyslipidemia includes elevated triglycerides, decreased HDL-C, and a higher formation of sdLDLs.[8] Diabetes mellitus is associated with not only with altered concentrations of routinely measured lipid profile parameters but also with the presence of oxidatively modified lipoproteins not measured in everyday clinical practice with atherogenic may be altered.[9]

This review aims to discuss the correlation between TyG index and T2DM, along with its complications, and to evaluate the advantages and disadvantages of TyG index in clinical applications, thus providing valuable insights into the use of TyG index as a reliable tool in the early detection, prevention, and management of T2DM and its complications.

Methodology

A narrative review was conducted to assess the role of TyG index in T2DM and its associated complications. Relevant literature was identified through searches of the PubMed and Web of Science databases. The search terms were "Triglyceride-Glucose Index" OR "Triglyceride Glucose Index" OR "TyG Index" AND "Type 2 Diabetes Mellitus" OR "Diabetic Complications" OR "Cardiovascular Disease" OR "Diabetic Kidney Disease" OR "Diabetic Retinopathy" OR "Diabetic Neuropathy" OR "Diabetic Foot". This review focused on studies that examined the relationship between TyG index and T2DM or its complications, including cross-sectional, cohort, and case-control studies involving clinical populations.

Application of TyG Index in T2DM

TyG Index for T2DM Screening

The association between TyG index and the development of T2DM has been demonstrated in previous studies.[10–12] In individuals with visceral and/or ectopic fat obesity, as well as in those with a BMI below 25 kg/m^2, TyG index was found to have an independent association with the incidence of T2DM.[13] In overweight or obese children and adolescents, TyG index exhibits a significant correlation with IR, the AUC in ROC analysis was 0.839.[14] Even among individuals with normal body weight, TyG index still has the potential to identify high risk for T2DM.[15] Among Chinese elderly individuals aged 75 years and above, TyG index is independently associated with the risk of incident T2DM.[16] These findings suggest that TyG index may be an effective biomarker for diabetes risk assessment. This broad applicability underlines the index's utility in diverse populations and could lead to more individualized risk assessments. However, there are a few studies providing inconsistent opinions. For example, a research by the MONET group found that TyG index had only a relatively modest relationship with the hyperinsulinaemic-euglycaemic (HIEG) clamp in non-diabetic postmenopausal women and appeared to be less accurate in estimating IR in the population.[17]

Despite the widespread interest and research on the relationship between TyG index and T2DM risk, no consistent conclusion has been reached so far. Existing studies present different views: (A) a possible linear association between TyG index and T2DM risk;[18] (B) a steeper dose-response curve between TyG index and T2DM risk when TyG index exceeds 8.6;[19] and (C) a U-shaped relationship, with the lowest risk of T2DM occurring at a certain threshold (7.97 for men and 7.27 for women), with a positive association above and a negative association below this threshold.[20] Notably, a similar pattern was observed in a Chinese study, albeit with a different threshold value of 8.51.[21] Such discrepancies may be due to various factors, including study samples, population characteristics, or analytical methods. In addition, countries with different income levels differ in the association between TyG index and T2DM risk. A large-scale prospective cohort study involving 22 countries from five continents found that participants from middle- and low-income countries had a higher risk of diabetes with increasing TyG index.[22] Given the variation in the results of the current studies, more studies are needed to further verify and clarify it in the future.

TyG Index for T2DM Diagnosis

Although the Oral Glucose Tolerance Test (OGTT) is regarded as the gold standard for diagnosing diabetes, its application is limited by the need for multiple blood draws, resulting in poor patient compliance. Therefore, there is an urgent need to identify alternative, simple, and accurate diagnostic markers. In a German study, receiver operating characteristic (ROC) curves were used to evaluate the performance of TyG index in identifying prediabetes or diabetes, and the result showed that TyG index had high accuracy with an AUC of 0.762, and the thresholds were relatively stable and did not change with age.[23] This may provide new insights for the early diagnosis of diabetes.

TyG Index for T2DM Assessment

TyG index serves as a valuable marker for assessing long-term glycemic control in T2DM patients, demonstrating a strong correlation with both HbA1c levels and IR.[24] Regression analysis has confirmed that TyG index has significant predictive power for fasting plasma glucose.[25] TyG index exhibits an independent correlation with HbA1c and IR, and the ROC analysis showed that TyG had an AUC greater than 0.8,[26] suggesting that TyG index can also effectively be used to evaluate glycemic control. A cross-sectional study evaluating the correlation between TyG index and glycemic control and diabetes remission after metabolic surgery found that, compared with those without diabetes remission, patients with complete diabetes remission after surgery had Iower baseline TyG index levels, moreover, TyG index independently predicted diabetes remission and outperformed HOMA-IR in predictive efficacy.[27]

TyG Index for T2DM Follow-Up

TyG index may also predict mortality or risk of death in patients with diabetes. In a US cohort study of 3376 patients with T2DM who were followed for a median of 107 months, a higher TyG index was associated with an increased risk of all-cause/non-cardiovascular mortality only in T2DM patients younger than 65 years, but not in the older patients. Specifically, each unit increase in TyG index was associated with a 1.33 increase in hazard ratio (HR) after comprehensive adjustment for potential confounders.[28] However, no significant association was found between TyG index and cardiovascular or cancer-related mortality in the overall cohort or within the two age subgroups. These findings suggest that the TyG index may be more relevant in younger diabetic populations, but further research is needed to explore its predictive value across different age groups and to determine the underlying mechanisms influencing these age-specific associations.

Application of TyG Index and T2DM Complications

Chronic complications of type 2 diabetes mellitus refer to chronic damage to tissues and organs caused by long-term hyperglycemia, mainly including macrovascular disease (eg cardiovascular disease), microvascular disease (eg diabetic kidney disease, retinopathy), neuropathy,diabetic foot, etc.

Applications of TyG Index in Diabetic Cardiovascular Disease (DCVD)

TyG Index for DCVD Screening

Cardiovascular disease (CVD) is a significant contributor to the increasing global mortality rates, with T2DM and IR recognized as key factors in triggering cardiovascular events.[29] Therefore, early risk detection is crucial for preventing cardiovascular incidents. A longitudinal study targeting the Chinese middle-aged and elderly population from 2011 to 2018 revealed that an elevated TyG index increases the risk of future CVD caused by diabetes.[30] In a Chinese study with a median follow-up of more than 5 years, the risk of major adverse cardiovascular events (MACEs) in T2DM patients increased with the cumulative TyG index.[31] Similarly, another study with a mean follow-up of 7.7 years found that, after adjustment for traditional cardiovascular risk factors, for every 1 standard deviation increase in TyG index, the risk of MACEs in patients with T2DM increased by 19%.[32] Other studies found that TyG index is also an independent risk factor for T2DM with coronary heart disease.[33] In patients with T2DM, TyG index is independently associated with the number and severity of coronary artery stenoses, independent of classic risk factors.[34] However, ROC analysis showed that METS-IR had a higher AUC value and was more predictive than TyG index for identifying MACEs in diabetic population.[35] Anyway, TyG index may serve as a significant predictor of cardiovascular disease in patients with T2DM.

TyG Index for DCVD Follow-Up

In addition to its role in screening, TyG index is also recognized as an independent predictor of cardiovascular outcomes.[36] In patients with diabetes or pre-diabetes complicated by CVD, a U-shaped association between TyG index and all-cause and CVD mortality was observed, with thresholds of 9.05 and 8.84, respectively.[37] With increasing

TyG index, the cumulative incidence of major adverse cardiac and cerebral events (MACCEs), gastrointestinal bleeding, and all-cause mortality significantly increased in patients with T2DM complicated by ischemic cardiomyopathy.[38] Multivariate Cox proportional hazards analysis shows that the risk of major endpoints such as all-cause mortality, non-fatal myocardial infarction and ischaemia-driven revascularisation increases with increasing TyG index in patients with T2DM and non-ST-segment elevation acute coronary syndrome.[39] In older (≥80 years) diabetic patients with acute coronary syndrome (ACS), a dose-response relationship between TyG index and all-cause mortality was observed, with an HR (95% CI) of 1.44 for each one standard deviation (SD) increase in TyG index, with TyG index outperforming fasting blood glucose (FBG) and TG in predicting mortality risk.[40]

Applications of TyG Index in Diabetic Kidney Disease (DKD)

TyG Index for DKD Screening

DKD is one of the common microvascular complications of diabetes. According to statistics, the prevalence of DKD in Chinese patients with T2DM has reached 21.8%.[41] DKD is the leading cause of end-stage renal impairment.[42] Studies have demonstrated that T2DM patients with a high TyG index have a higher rate of microalbuminuria and an eGFR <60 mL/(min·1.73m^2), and an increased risk of developing DKD.[43] Two studies[44,45] have identified similar thresholds for TyG index in predicting DKD risk, with values of 9.66 (optimal threshold) and 9.05–9.09 (potential threshold), respectively. When patients' TyG index exceeds these values, their risk of developing DKD increases significantly. Furthermore, in T2DM patients, there is a strong correlation between TyG index and proteinuria, which is stronger than other surrogate markers of IR such as HOMA-IR, VAI, and LAP, and the study calculated a cut-off point of 9.39 for TyG index in diagnosing proteinuria.[46]

TyG Index for DKD Follow-Up

An 8.6-year follow-up study found that a higher TyG index was an independent predictor of chronic kidney disease (CKD) progression in T2DM patients, and this association may be mediated by pigment epithelium-derived factor.[47] RCS curves showed an inverted S-shaped relationship between TyG index and increased risk of CKD progression, which was more significant in patients with earlier stage CKD and those who had never used oral hypoglycemic agents.[48] In T2DM patients with CKD, 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.[49]

Applications of TyG Index in Diabetic Retinopathy (DR)

TyG Index for DR Screening

Diabetic retinopathy (DR) is an eye disease caused by diabetes-induced micro-vascular changes in the retina, resulting in pathological changes such as ischemia, edema, hemorrhage, and proliferation, which may eventually lead to visual impairment.[50] Several studies have consistently shown a significant correlation between TyG index and the risk of developing DR, with TyG index being recognized as an independent risk factor or reliable predictor of DR. For example, a prospective cohort study in Singapore found a significant association between TyG index and the prevalence and incidence of DR in patients with T2DM, after adjustment for confounders.[51] Another large population-based study found an independent association between TyG index and DR after adjustment for age, sex, blood pressure, etc.[52] A nested case-control study showed a significant association between TyG index and DR of varying severity.[53] In a cross-sectional analysis of adult patients with diabetes mellitus based on the NHANES data, TyG index was associated with the risk of DR in a U-shaped manner.[54]

Applications of TyG Index in Diabetic Neuropathy (DN)

TyG Index for DN Screening

Studies have shown that TyG index and HbA1c levels are significantly higher in T2DM patients with cardiac autonomic neuropathy (CAN) than in T2DM patients without CAN.[55,56] In another study of 500 patients with T2DM, patients with combined diabetic polyneuropathy (DPN) had a significantly higher TyG index than those without DPN.[57] Therefore, TyG index may serve as an important marker for the early identification of patients at high risk for diabetic neuropathy.

Applications of TyG Index in Diabetic Foot (DF)

TyG Index for DF Assessment

Diabetic foot (DF) is one of the most serious and costly chronic complications of diabetes mellitus, which in severe cases can lead to amputation and death. Unfortunately, current treatment options for diabetic foot ulcers (DFUs) remain limited, highlighting the importance of early detection and prevention. A higher TyG index is independently associated with the severity of DFUs in patients with diabetes, and this association is more significant in patients who are male, aged ≥65 years, have had diabetes for ≥10 years, and do not have peripheral artery disease.[58] Therefore, monitoring TyG index could be particularly valuable in tailoring preventive and therapeutic strategies to those patients at greatest risk.

TyG Index for DF Follow-Up

A 9-year follow-up study of elderly female patients with diabetic foot ulcers found a strong positive correlation between TyG index and all-cause mortality in these patients.[59] Despite preliminary evidence suggesting an association between TyG index and DFUs, research in this area remains limited. Further in-depth studies are needed to clarify these associations and to explore how TyG index can be used effectively in clinical practice to improve patient outcomes in diabetic foot management.

Discussion

Advantages of TyG Index for Clinical Application

Currently, studies on the correlation between TyG index and T2DM and its complications have focused on disease screening and disease follow-up, and TyG index has demonstrated high accuracy and reliability. In the future, TyG index may be more suitable as an important indicator for risk assessment and prognosis prediction of T2DM and its complications. Its simplicity, accessibility and cost-effectiveness make it highly applicable in primary health care settings. More importantly, the predictive efficacy of TyG index is superior to other indicators. Comparison with the gold standard HIEG clamp test fully demonstrated the high sensitivity and specificity of TyG index in detecting IR, reaching 96.5% and 85.0%, respectively.[60] TyG index also performed better than HOMA-IR in assessing IR, with sensitivity and specificity of 89% and 67%, respectively.[61] TyG index also shows the ability to predict the prevalence and incidence of T2DM beyond HOMA-IR.[62] ROC analysis showed that TyG index was superior to HOMA-IR in identifying T2DM (AUC value: 0.839 vs 0.645).[14] In a German study, TyG index surpassed VAI and LAP in terms of accuracy in identifying pre-diabetes or diabetes.[24]

Deficiencies of TyG Index for Clinical Application

However, there are still some knowledge gaps in the practical application of TyG index. For example, the relationship between the two variables of TyG index and T2DM risk has not yet yielded a relatively well-recognized result. Some studies suggest a linear relationship between TyG index and T2DM risk, while others propose a more complex relationship. These inconsistencies could be due to differences in population demographics, sample sizes, and methodological approaches. Standard TyG index thresholds have not yet been established for populations of different age, ethnicity, and sex. Therefore, more high-quality, large-scale studies are needed in the future to clarify the functional relationship between TyG index and T2DM risk and the optimal TyG index threshold in different patient subgroups. Besides, in many countries and regions, there is currently no recommendation content of TyG index in the clinical diagnosis and treatment guidelines of diabetes.[2,63–66] This may be due to the fact that TyG index is a relatively new evaluation index, and the guiding significance and application range of TyG index in actual clinical operation still need to be further studied and explored. After rigorous scientific demonstration and real-world verification, TyG index may have the potential to become a reference index in future clinical guidelines for the management of diabetes. Furthermore, combining TyG index with obesity-related indicators may improve predictive accuracy. Compared to the TyG index, TyG-BMI[67] was found to be more effective in assessing insulin resistance, and TyG-WHtR performed better in predicting metabolic syndrome risk.[68]

Proposed Directions for Future Research

Future research should focus on several key areas to better understand and utilize TyG index (Figure 1). Standardizing thresholds through large-scale, multi-ethnic studies is crucial for determining cut-off values applicable across diverse

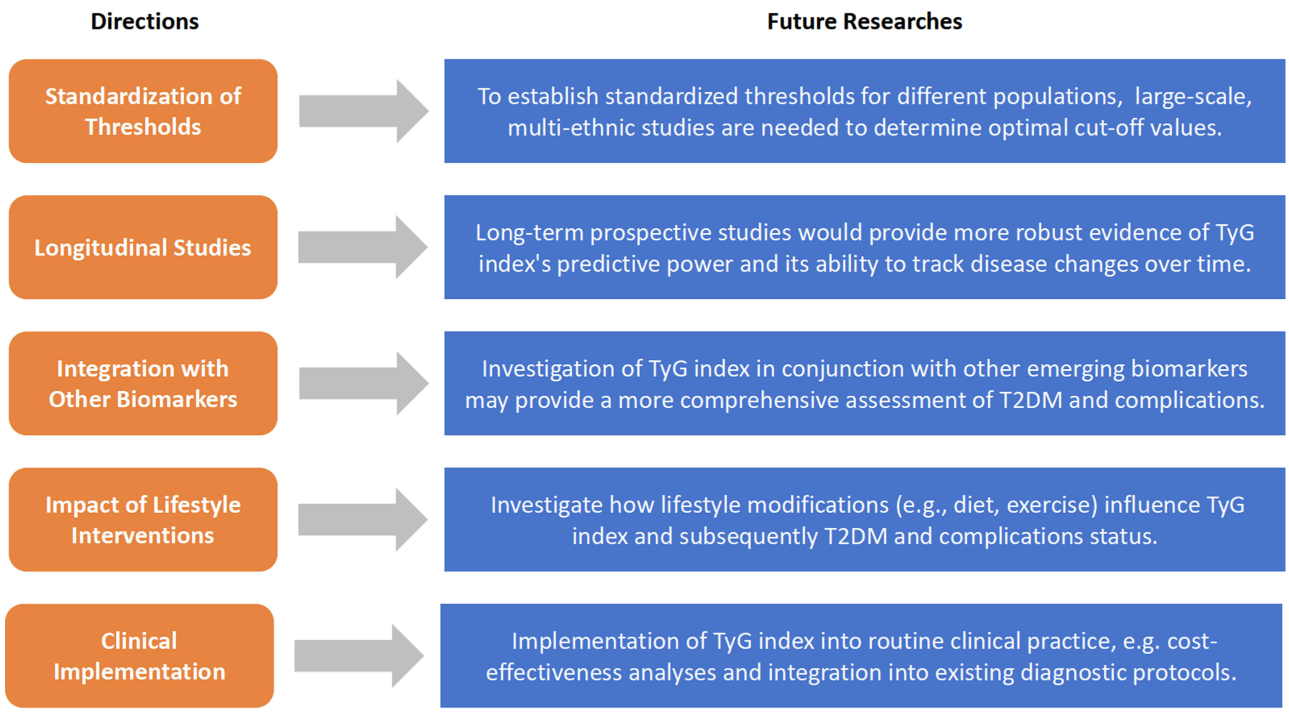

Figure 1 Suggested Directions for Future Research.

populations. Longitudinal studies are needed to validate TyG index's predictive power and track progression of T2DM and complications over time. Integrating TyG index with other biomarkers could offer a more comprehensive assessment of metabolic health. Researches should also explore how lifestyle changes like diet and exercise affect TyG index and related outcomes, aiding personalized T2DM management. Finally, studies should evaluate the index's cost-effectiveness, scalability, and integration into clinical practice, with guidelines to support its routine use in healthcare.

Limitations of This Study

Despite the positive findings of this review, there are some limitations. 1) Most of the studies included in the analysis were observational studies, including cohort studies and cross-sectional studies, which have a lower level of evidence than randomized controlled trials. 2) There is heterogeneity in these studies, and different analysis methods and different patient characteristics may cause differences in the analysis results. 3) There are many confounding variables affecting the relationship between TyG index and diabetes, and different studies adjusted for different variables, which may have affected the results. 4) It is not sufficient to establish a causal relationship between TyG index and the risk of diabetes and its complications based on the results of observational studies. Therefore, more high-quality research are needed to provide more reliable evidence.

Conclusion

As a unique and innovative indicator, TyG index incorporates blood glucose and triglyceride levels, providing physicians with a new perspective to understand the comprehensive metabolic status of patients. This index not only replaces the assessment of insulin resistance, but also effectively reflects the development of T2DM and its complications. However, further research is essential to establish standardized thresholds, validate its predictive efficacy across diverse populations, and explore its integration into clinical practice. In the future, through continuous scientific exploration and rigorous research, TyG index is expected to play an important role in the risk assessment and prognosis prediction of T2DM and its complications. This will not only help high-risk groups to receive early intervention and preventive treatment in time, thereby reducing the incidence and severity of T2DM and its complications, but also guide physicians to understand the development trend of the disease, adjust the treatment plan in time, and achieve more efficient allocation and optimization of medical resources.

Abbreviations

TyG, triglyceride-glucose; IR, insulin resistance; T2DM, type 2 diabetes mellitus; IDF, International Diabetes Federation; G/I, glucose/insulin ratio; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; sdLDLs, small dense low-density lipoproteins; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; DCVD, diabetic cardiovascular disease; DR, diabetic retinopathy; DF, diabetic foot; DKD, diabetic kidney disease; CKD, chronic kidney disease; DN, diabetic neuropathy; DPN, diabetic polyneuropathy; FBG, fasting blood glucose; OGTT, Oral Glucose Tolerance Test; VAI, Visceral adiposity index; LAP, lipid accumulation product; ROC, receiver operating characteristic; AUC, area under the curve; RCS, restricted cubic spline; CVD, cardiovascular disease; ACS, acute coronary syndrome; METS-IR, metabolic score for insulin resistance; MACEs, major adverse cardiovascular events; MACCEs, major adverse cardiac and cerebral events; IS, ischemic stroke; CAN, cardiac autonomic neuropathy; NHANES, National Health and Nutrition Examination Surveys; DFUs, diabetic foot ulcers; SD, standard deviation; HR, Hazard Ratio; CI, confidence interval; WHtR, waist-to-height ratio.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest related to this review article.

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