An Overview on Triglyceride-Glucose Index (TyG)

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Abstract:

The Triglyceride-Glucose (TyG) index is a simple, low-cost surrogate marker widely used to estimate insulin resistance (IR). It is calculated from fasting plasma triglycerides and fasting plasma glucose using the formula: TyG index = ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) ÷ 2]. Insulin resistance plays a central role in the development of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular diseases. While the gold-standard hyperinsulinemic-euglycemic clamp test directly measures insulin sensitivity, it is laborious and impractical for large clinical or epidemiological studies. The TyG index, on the other hand, has been validated as a reliable and accessible alternative that correlates strongly with clamp-measured insulin resistance.

Keywords: Triglyceride-Glucose Index, TyG index, Insulin resistance, Metabolic syndrome, Cardiovascular risk, Type 2 diabetes mellitus.

Introduction:

Insulin resistance is a key mechanism underlying the development of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease. Identifying a simple and reliable surrogate marker for insulin resistance is essential for early diagnosis and prevention strategies **(1).**

The triglyceride-glucose (TyG) index, calculated from fasting triglycerides and fasting glucose, has been validated as a cost-effective and accurate indicator of insulin resistance compared to the hyperinsulinemic-euglycemic clamp and HOMA-IR **(2).**

Recent studies have shown that elevated TyG index levels are strongly associated with an increased risk of type 2 diabetes and cardiovascular events, making it a valuable predictive tool in clinical practice **(3).**

Furthermore, the TyG index has also been linked with the presence of non-alcoholic fatty liver disease (NAFLD), hypertension, and chronic kidney disease, expanding its role beyond diabetes risk prediction **(4).**

plasma triglycerides are transported in chylomicrons and very-low-density lipoproteins (VLDLs), collectively referred to as Triglyceride-Rich Lipoprotein (TGRLs). Although TGRLs are generally too large to cross the endothelium, they can significantly affect certain aspects of atherosclerotic lesion development. TGRLs contain high levels of cholesterol and undergo remodeling during intravascular lipolysis. This process produces free fatty acids and monoglycerides, which can increase the concentration of cytotoxic free fatty acids, particularly saturated fatty acids. TGRLs and their remnants can lead to endothelial dysfunction, activate the coagulation cascade, and enhance platelet aggregation, The TyG index is a composite measure that assesses insulin resistance (IR) by analyzing fasting triglyceride (TG) and fasting glucose (FG) levels. The index was computed using the formula TyG index = logarithm (triglycerides (mmol/l) × glucose level (mg/dl)/2). **(5).**

Insulin resistance (IR) is a metabolic condition in which insulin levels are elevated due to insensitivity to insulin and associated with elevated triglyceride levels. Hypertriglyceridemia leads to increased transport of free fatty acids to the liver, which increases liver sugar production. The Triglyceride-glucose index (TyG index) was first proposed in 2008, and the formula for calculating the TyG index is TyG index = Ln [fasting triglyceride (mg/dl) × fasting glucose (mg/dl) /2]. It is a composite indicator consist of fasting triglyceride (TG) and fasting

plasma glucose (FPG) levels , With high sensitivity and specificity, the TyG index can serve as an alternative biomarker for IR due to its simple calculation and few constraints on time or cost (**6**).

TyG index has a linear dose-response association with IR risk. TyG index was significantly correlated with the incidence of multiple diseases. The TyG threshold predicts an increased risk of death in a large, homogeneous general population. Therefore, summarizing and analyzing the connection among the TyG index and different diseases is of positive significance for clinical treatment and basic experimental research. The different diseases in which TyG is involved are shown in Fig. 1 (**7**).
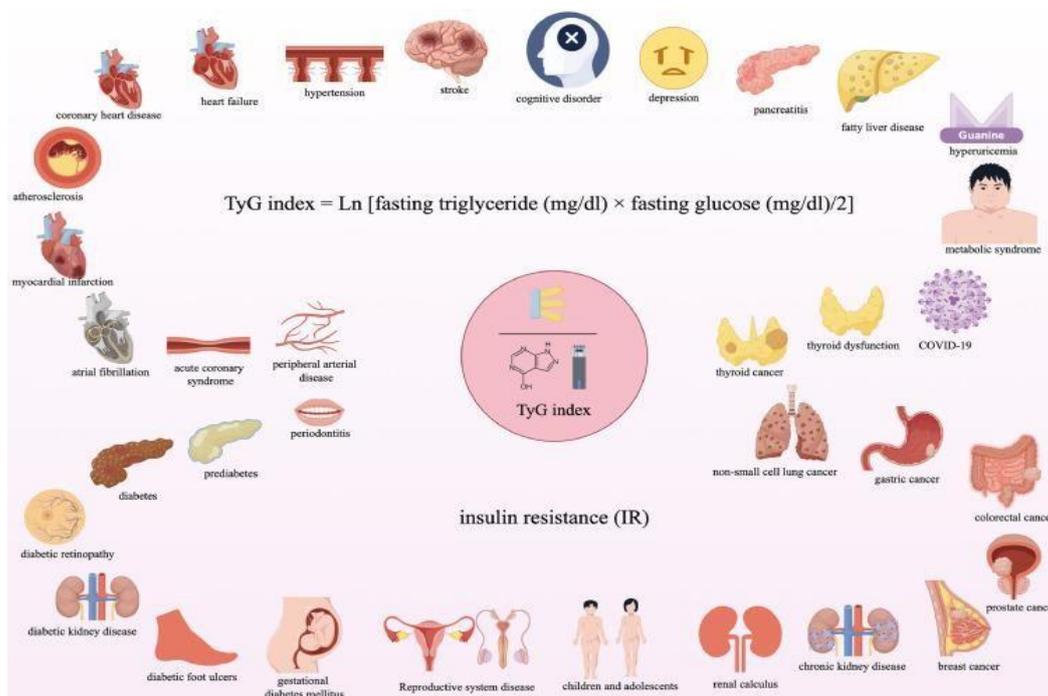

Fig. 1. Association of TyG index with different diseases. (**7**).

Relationship between TyG index and different diseases :

Prediabetes

Data from the International Diabetes Federation (IDF) indicate a year-onyear rise in the prevalence of diabetes, highlighting the importance of delaying the progression from prediabetes to diabetes. Study reveals that the TyG index can forecast prediabetes with impaired glucose tolerance; regardless of glucose metabolism status, the TyG index can identify the risk of early and late β cell dysfunction (**8**).

A multicenter randomized controlled trial (RCT) involving eight countries, focusing on lifestyle interventions for prediabetes, indicated that personalized approaches based on TyG could prevent the progression to T2DM , thereby aiding in the differentiation of prediabetes/diabetes patients. The aforementioned researchers have elucidated the influential role of the TyG index in the context of prediabetes. Furthermore, it may serve as a strategic intervention to mitigate the progression to T2DM, thereby playing a crucial role in the management and treatment of prediabetes. (**9**).

Diabetes mellitus

Type 2 diabetes constitutes a substantial proportion of the total incidence of diabetes mellitus. Each incremental unit in the TyG index is correlated with nearly a tenfold increase in the risk of T2DM, with a direct correlation between the TyG index and T2DM risk and the most valuable biomarker. Extensive population-based studies have underscored the predictive ability of the TyG index in assessing T2DM risk. A longitudinal study spanning 12 years on nonobese adults has confirmed the TyG index's involvement in T2DM pathogenesis

(**10).**

Early identification and monitoring of the TyG index are pivotal in managing T2DM comprehensively, aiding in clinical decision-making and patient care. Given the gradual onset of hyperglycemia and the low diagnosis rate of T2DM, early screening of the TyG index can partially address this diagnostic challenge. Research indicates a strong interconnection between elevated TyG index levels before pregnancy, during the first trimester, and throughout pregnancy, and the increased risk of GDM (**11).**

Cardiovascular disease

Cardiovascular disease (CVD) represents the foremost cause of mortality on a global scale. According to a report from the World Health Organization, fatalities attributed to cardiovascular diseases constitute a significant health risk to human populations. The TyG index's capability to pinpoint individuals at heightened risk of cardiovascular events. Notably, baseline TyG index levels have been linked to an elevated cardiovascular risk. Moreover, an escalation in the TyG index has shown a close linkage with an increased susceptibility to cardiovascular diseases (**12),** enabling the prediction of CVD risk within populations. This increase in TyG index has also been correlated with amplified risks of all-cause mortality and cardiovascular death among individuals at high CVD risk, as well as a positive correlation with 28-day and 90-day mortality rates in CVD patients. Furthermore, individuals exhibiting higher baseline TyG index levels and a trajectory of sustained or progressive increase in early adulthood have displayed significantly heightened rates of CVD events and all-cause mortality in later life. (**9).** So, under equivalent total cumulative exposure, the risk of CVD and all-cause mortality stemming from early TyG index accumulation surpasses that of late accumulation, underscoring the significance of early TyG index management. The TyG index can serve as a straightforward supplementary indicator for CVD screening and the early identification of vascular disease severity. It is imperative to leverage the TyG index's potential in the context of CVD to mitigate mortality rates and enhance patient prognosis. (**13).**

Hypertension

Hypertension constitutes a significant global health concern. Its prevalent nature presents substantial challenges to healthcare systems and carries considerable socio-economic ramifications on a global scale. A significant correlation between elevated TyG index levels and the incidence of hypertension, with a linear positive correlation observed between the TyG index and the risk of developing hypertension and the TyG index has been independently linked to branch artery and aortic diastolic blood pressure (BP), The TyG index plays a crucial role in identifying and managing prehypertension and hypertension, influencing various stages, phenotypes, and progression of the condition. In the initial stages of pregnancy, the TyG index demonstrates a significant correlation with the incidence of hypertensive disorders of pregnancy (HDP) as well as negative pregnancy outcomes Analysis of patients with grade 1–3 hypertension reveals a stronger correlation in patients with grade 1–2 hypertension compared to those with grade 3 hypertension . The TyG index of hypertensive patients exhibits an L-shaped relationship with all-cause mortality (**9).**

Metabolic syndrome

A growing prevalence of adults is being identified as meeting the diagnostic criteria for metabolic syndrome (MetS). Recent research indicates a concerning increase in the incidence of MetS among younger populations, implying that these conditions are no longer confined to adults and the elderly. The TyG index exhibits a direct association with multiple metabolic risk factors, thereby serving as an important instrument for the identification of populations at elevated risk for metabolic disorders. Research suggests that the TyG index is a more reliable predictor of MetS compared to HOMA-IR and other metabolic indicators, MetS constitutes a multifaceted array of metabolic disorders that serve as risk factors for numerous diseases. Emphasizing the strong association between the TyG index and MetS may facilitate the mitigation of both the incidence and progression of this syndrome. (**14).**

Hyperuricemia

There exists a direct association between hyperuricemia (HUA) and various medical conditions, including hypertension, diabetes, severe obesity, hyperlipidemia, renal failure, and other related disorders. The TyG index

demonstrated a notable correlation with HUA, exceeding the obesity index in its efficacy for identifying HUA. Moreover, an increase in baseline TyG levels and associated indicators has been associated with a heightened risk of HUA. TyG and its derivative indicators have demonstrated potential as sensitive biomarkers for the prediction of HUA. While the overall prognosis for HUA is generally favorable, a subset of patients may still experience complications; thus, early detection and prompt intervention utilizing the TyG index are crucial. **(15).**

Thyroid disease

The study involved the determination of serum thyrotropin (TSH) and free thyroxine (FT4) levels in the participants. Research findings suggest that the TyG index is a dependable measure for assessing the relationship between thyroid function. It was noted that the TyG index demonstrated a substantial negative correlation with levels of FT4, while showing a positive correlation with TSH levels and anti-thyroglobulin antibodies (TgAb). This indicates a significant association between the TyG index and thyroid function **(16).**

Among individuals with normal thyroid function, the log-transformed TSH (LnTSH) was notably linked to the TyG index in females. Furthermore, both hyperthyroidism and hypothyroidism demonstrated associations with the TyG index **(17)** .

Stroke

Stroke has emerged as a predominant cause of mortality and disability. As a major chronic noncommunicable disease, it presents a substantial risk to public health and demonstrates a troubling increasing trend. One study conducted on extensive populations have demonstrated that elevations in the baseline level and long-term cumulative mean TyG index autonomously forecast stroke , including analyses of the general population, young adults, and middle-aged and elderly individuals. The progression, recurrence, and prognosis of stroke are significantly intertwined with the survival and quality of life of patients. A plethora of studies have underscored that the TyG index is linked to an escalated risk of stroke recurrence and fatality **(10).**

Patients who received dual antiplatelet therapy (DAPT) were assessed. The findings indicated that an increase in the TyG index was associated with enhanced platelet reactivity and a higher incidence of high residual on-treatment platelet reactivity (HRPR), serving as an independent risk factor for assessing aspirin HRPR. Given that the sequelae of stroke can result in prolonged cognitive impairment for patients, the early identification and intervention based on the prognostic value of the TyG index are of considerable importance. **(18).**

Kidney disease

Extensive research involving large populations has indicated that an increased TyG index is associated with a greater risk of CKD, which can significantly enhance the predictive capacity of CKD. It is notably correlated with the severity of CKD, serving as a valuable indicator for identifying the risk of CKD progression. The early identification of elevated TyG index and renal hyperfiltration (RHF) may have the potential to prevent the future development of CKD in relatively healthy young adults **(19).**

The likelihood of acute kidney injery (AKI) increases in direct correlation with the elevation of the TyG index, and patients with critical AKI exhibiting higher TyG index levels face an elevated risk of all-cause mortality . Moreover, the TyG index demonstrates a significant independent positive association with the decline in renal function among the elderly population. The TyG index serves as a mediating factor in the relationship between overweight and ESRD . A dose-response analysis indicated a positive association between the TyG index and the risk of developing kidney stones, implying its potential applicability as a biomarker for the prediction of kidney stone formation **(20)**.

Cancer

The TyG index demonstrates a significant correlation with the risk of non-small cell lung cancer (NSCLC). The escalation of the TyG index is notably associated with gastric cancer, serving as an independent prognostic factor for gastric cancer and elevating the risk of gastrointestinal system cancer **(21).**

An elevated TyG index is connected to a higher risk of colorectal adenoma occurrence and recurrence, with a stronger association observed with recurrence . The TyG index is correlated with prostate cancer (PCa) risk and a lower PCa survival rate. Research has validated the TyG index's ability to identify high-risk groups for thyroid papillary carcinoma. Notably, an elevated TyG index is linked to an increased incidence of female reproductive tissue tumors and serves as a biomarker for endometrial carcinoma (EC). There is a notable association between the TyG index and the survival outcomes of patients with renal cell carcinoma (RCC), The incidence of cancer in all systems is increasing year by year, and the mortality rate is extremely high, which brings huge economic and health burden to all mankind. Although the continuous development of chemotherapy, radiotherapy, immunotherapy and targeted therapy can prolong the progression-free survival (PFS) and overall survival (OS) of patients, the early diagnosis and intervention of cancer are still very important, and the TyG index can play a predictive role. **(22).**

Triglyceride-glucose index as prediction of chronic kidney disease development in all blood pressure subtypes:

 Hypertension and insulin resistance are known as risk factors for chronic kidney disease (CKD). The triglyceride-glucose (TyG) index has been reported as a simple indicator of insulin resistance. Previous several studies have investigated the relationship between TyG index and the risk of CKD, and recently a meta-analysis has shown that higher TyG index was associated with increased risk of CKD, independently of established risk factors (**23).**

Sakoda et al., (24) investigates the association between TyG index and new onset of CKD using health checkup data of 41,811 middle-aged Japanese men. TyG index can be a good indicator for early prediction of future CKD development this study reveals that high TyG levels are associated with new onset of CKD, regardless of BP subtype. Interestingly, this association is also confirmed in isolated diastolic hypertension (IDH) and normotensive subjects

The association between TyG index and CKD have also been recently reported by others, **Ren et al (25).** demonstrated that higher TyG index was associated with increased risk of CKD, independently of established risk factors based on the data of longitudinal study including 10498 participants. Furthermore, Ren et al. conducted a meta-analysis including twelve published articles and their study, and confirmed the significant associations between TyG index and CKD

Isolated diastolic hypertension (IHD) is the most common type of hypertension in young to middle-aged men and is often overlooked and unaware as hypertension. It is a very significant finding that high TyG levels are associated with the risk of future CKD development even in people with normal BP and IDH. **(26).**

the underlying mechanisms of the association between the TyG index and CKD are yet to be fully understood. The TyG index is composed of factors related to lipid metabolism and glucose, which are closely related to insulin resistance. Hyperinsulinemia induces renal vasodilation, which leads to glomerular hypertension and hyperfiltration . Glomerular hyperfiltration contributes to glomerulosclerosis and renal impairment. Insulin plays a predominant role in the metabolism and function of podocytes.

Hyperinsulinemia could contribute to the lesion of podocytes and proteinuria through some molecular mechanisms. Hyperglycemia can also provoke inflammation, which results in tubulointerstitial damage. Furthermore, Insulin resistance induces overproduction of reactive oxidative stress by activating the mitochondrial electron transport chain, resulting in renal tissue fibrosis. **(27).**

In recent years, in addition to conventional treatment centered on RAS inhibitors, new treatment options, such as SGLT2 inhibitors and mineralocorticoid receptor antagonists, have emerged for CKD treatment . The TyG index is considered to be a highly significant CKD prediction index for early therapeutic intervention in CKD. **(28).**

It has been reported that SGLT2 inhibitors and GLP1 agonists have a renal protective effect as hypoglycemic agents. Conventional fibrates used as TG-lowering therapy are excreted by the kidneys, and their use is contraindicated in patients with severely impaired renal function. Recently, selective peroxisome proliferator-activator receptor alpha (PPARα) modulator "Pemafibrate", which is excreted by bile, has been released and can

now be used in patients with severe renal function decline, and its use in CKD patients is attracting attention **(29).**

CKD is associated with increased mortality, and one of the factors contributing to increased mortality is IR. IR is present in patients with early CKD and progressively worsens as the disease progresses to end-stage renal disease. IR may participate in the occurrence and development of CKD through such mechanismsas a hyperinsulinemic reaction. induction of oxidative stress. Activation sympathetic renin-angiotensin-aldosteronesystem, activation of inflammatory factors. andinhibition of insulin signaling pathway. **(30).**

Microalbuminuria is an early manifestation of hypertensive renal injury and can be used as an early indication of renal injury. Urinary microalbumin cannot pass the glomerular filtration membrane under physiological conditions, and its content is extremely low. When the glomerulus is damaged,the protein filtration barrier will be damaged, with increased permeability and excretion of microalbumin in urine. Hence,microalbuminuria is one of the sensitive indicators of earlyglomerular injury.**(31).**

IR is an underlying condition for hypertension onset. The current gold standard for IR measurement is the normal blood glucose clamp test. However, due to the time-consuming, expensive, and complex nature of glucose clamp testing, it is difficult to apply in large-population research and clinical settings. **(32).**

A TyG index derived from fasting triglyceride and glucose concentrations as an IR index and validated it against the normoglycemic clamp test in a Mexican population, showing its superiority over HOMA-IR. Studies have confirmed that the TyG index predicts the development of hypertension in Chinese populations and may reflect cardiac remodeling, dysfunction, and atherosclerosis. **(33)**

The pathophysiological mechanisms underlying the association between the TyG index and CKD are modulated by IR, which affects the metabolic processes in the body. Insulin signaling is essential for podocyte function and the maintenance of glomerular integrity within the kidney, multiple insulinsensitive cell types express insulin receptors, and specific knockdown of these receptors in podocytes or proximal tubules results in proteinuria, renal pathology, and hyperglycemia. **(34).**

Shimobayashi et al. (30), demonstrated that IR triggers adipose tissue inflammation by inhibiting insulin signaling pathways and increasing the production of monocyte chemoattractant protein 1. The inflammatory activation of M2 macrophages in the adipose tissue induces the release of proinflammatory cytokines, which cause glomerular endothelial dysfunction and ultimately lead to CKD.

KHAN et al. (35), found a high positive correlation between the TyG index and urine albumin creatine ratio in a cross-sectional study that included227 patients with metabolic syndrome.

Fritz et al. (36), found thatthe TyG index appeared to be associated with ESKD risk and mediates nearly half of the total association between BMI and ESRD in the general population.

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