

The Triglyceride-Glucose Index and Coronary Artery Disease

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Abstract

Background: Insulin resistance is a fundamental pathophysiological defect underlying a constellation of metabolic disorders, most notably type 2 diabetes mellitus and cardiovascular disease. While the hyperinsulinemic-euglycemic clamp is the gold standard for measuring insulin resistance, its complexity and invasiveness render it impractical for large-scale epidemiological studies and routine clinical use.

Review content: The Triglyceride-Glucose (TyG) index, calculated from fasting triglycerides and fasting glucose, has emerged as a particularly promising tool. Its efficacy is rooted in the deep physiological interconnection between lipid and glucose metabolism, orchestrated by insulin. The association between the TyG index and cardiovascular disease is particularly robust, reflecting the role of insulin resistance as a key driver of atherosclerosis.

Conclusion: The TyG index uses two cheap, routinely measured, and widely available biomarkers. It has been validated against the gold standard and hard clinical outcomes across diverse populations. However, lack of universal cutoff points remains the primary limitation for widespread clinical adoption, and the TyG index remains a surrogate rather than a direct measure of insulin resistance.

Keywords: Triglyceride-glucose index; insulin resistance; coronary artery disease; atherosclerosis; coronary angiography; SYNTAX score.

Introduction

Insulin resistance (IR) is a fundamental pathophysiological defect underlying a constellation of metabolic disorders, most notably type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). As a key component of metabolic syndrome, IR is a silent driver of a global epidemic of chronic diseases. Furthermore, IR promotes a pro-atherogenic environment—characterized by dyslipidemia, endothelial dysfunction, hypertension, and a prothrombotic state—significantly elevating the risk for atherosclerotic cardiovascular disease [1].

While the hyperinsulinemic-euglycemic clamp is the gold standard for measuring IR, its complexity and invasiveness render it impractical for large-scale epidemiological studies and routine clinical use. This has spurred the search for simple, accurate, and cost-effective surrogate markers. The Triglyceride-Glucose (TyG) index, calculated from fasting triglycerides and fasting glucose, has emerged as a particularly promising tool. Its strong predictive power for incident T2DM, CVD, non-alcoholic fatty liver disease, chronic kidney disease, and mortality has been examined [2].

Coronary artery disease (CAD), also known as ischemic heart disease, is a condition characterized by narrowing or blockage of the coronary arteries, the primary vessels supplying oxygen-rich blood to the myocardium. This impairment is almost universally caused by atherosclerosis, a chronic inflammatory process leading to plaque buildup within the arterial walls [3]. The consequent reduction in blood flow can manifest in various clinical syndromes, most notably angina, myocardial infarction, heart failure, and sudden cardiac death.

This review describes the pathophysiological relationship between insulin resistance and coronary atherosclerosis, the derivation and calculation of the TyG index, its associations with cardiovascular and metabolic disease, and its potential applications and limitations in cardiovascular risk assessment.

Coronary Artery Disease and Atherosclerosis

Pathophysiology of Atherosclerosis

The development of CAD is a slow, progressive process that often begins at a younger age and remains asymptomatic for decades. The widely accepted model for atherogenesis is the response-to-injury hypothesis. The initial step involves endothelial dysfunction. The endothelium is not a mere barrier, but a dynamic organ responsible for regulating vascular tone, inflammation, and thrombosis.

Once the endothelium is compromised, a cascade of events follows [3]. Injured endothelium becomes more permeable, allowing LDL cholesterol to infiltrate the intimal layer of the artery wall. Within the intima, LDL undergoes oxidation, becoming oxidized LDL, which is highly atherogenic. Oxidized LDL triggers endothelial cells to express adhesion molecules that recruit circulating monocytes and T-lymphocytes to the site of injury [4].

Monocytes migrate into the intima and differentiate into macrophages. These macrophages engulf oxidized LDL particles, leading to massive cholesterol ester accumulation and transforming them into lipid-laden foam cells. This is the hallmark of the earliest atherosclerotic lesion, the fatty streak [5]. Smooth muscle cells migrate into the intima and proliferate. They produce extracellular matrix, forming a fibrous cap that overlies a core of lipids, necrotic debris, and calcium. This structure is a mature atherosclerotic plaque or fibroatheroma [6].

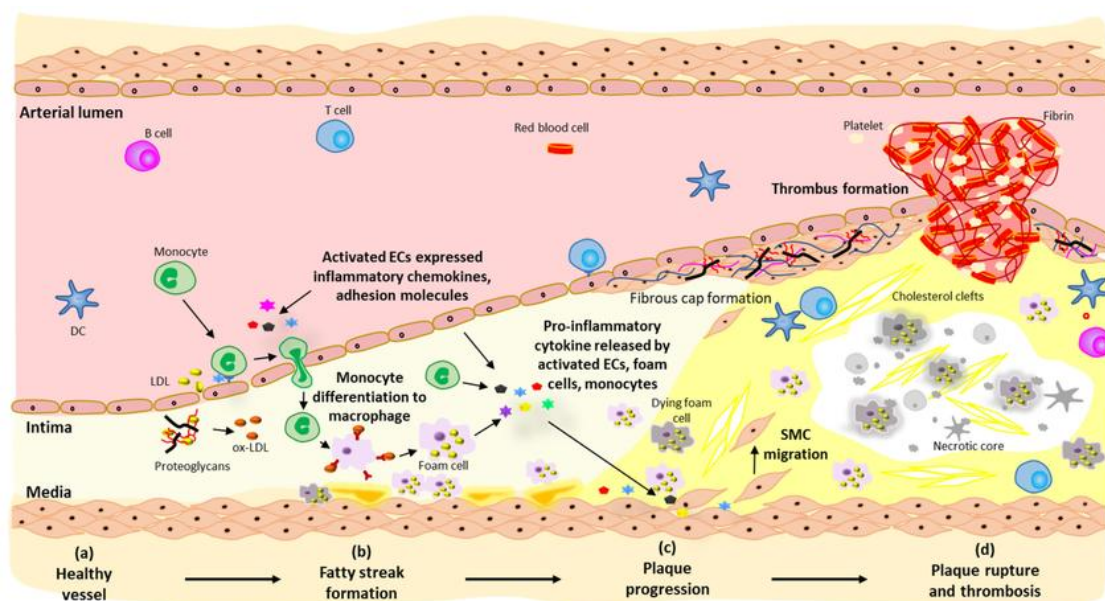


Figure 1. The Atherogenic Cascade (Nguyen et al., 2022) [7].

The most catastrophic events occur when a vulnerable plaque ruptures or erosions form on its surface. This exposes thrombogenic material, prompting the rapid formation of an intraluminal thrombus. This clot can abruptly and severely occlude the artery, leading to an acute coronary syndrome [8].

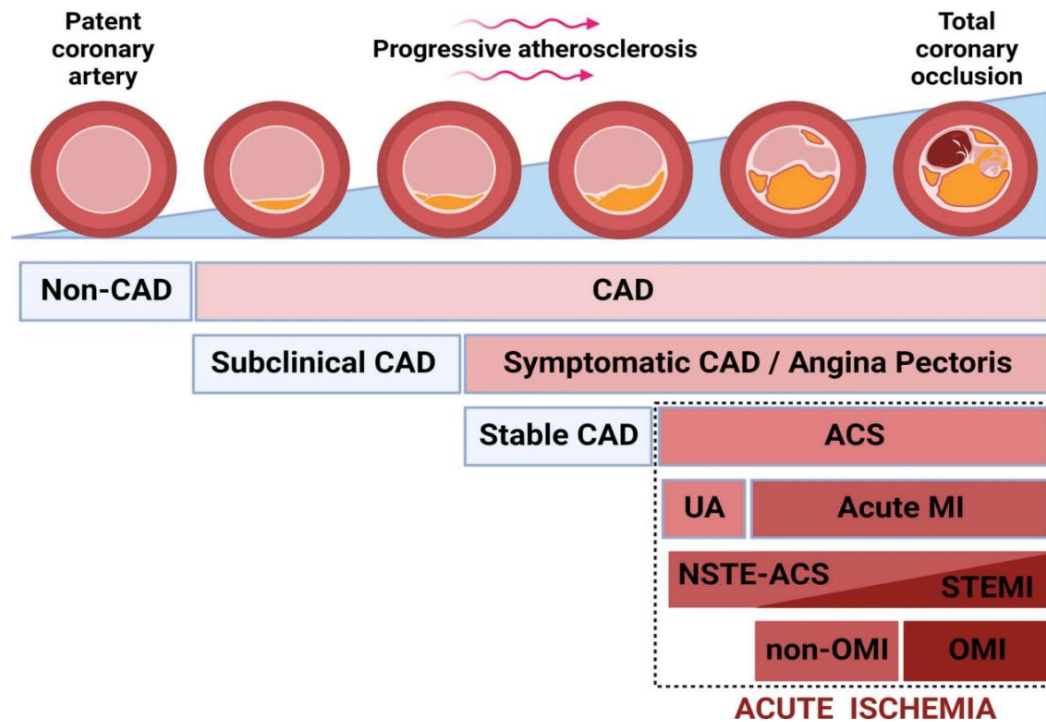


Figure 2. The spectrum of coronary artery disease as a function of severity and extent of atherosclerotic plaque progression, ranging from patent coronary artery to total coronary occlusion (Al-Zaiti et al., 2023) [9].

Risk Factors for Coronary Artery Disease

CAD is a multifactorial disease. Risk factors are characteristics that increase the probability of developing the disease. They are broadly classified as non-modifiable and modifiable [10]. Dyslipidemia, hypertension, cigarette smoking, diabetes mellitus, insulin resistance, obesity, and sedentary lifestyle are major modifiable risk factors.

Elevated LDL-C is the central causal agent in atherosclerosis. Low levels of high-density lipoprotein cholesterol and elevated triglycerides are also independent risk factors [11]. Diabetes mellitus and insulin resistance are closely related to CAD. Chronic hyperglycemia causes advanced glycation end-products that damage vessels and promote inflammation [12]. Central obesity is strongly linked to insulin resistance, dyslipidemia, hypertension, and a pro-inflammatory state [13].

Table 1. Risk factors for coronary artery disease (Bays et al., 2021) [14]

Category	Risk Factors
Non-Modifiable	Age (advanced), Sex (Male > Female), Family History (Genetics), Race/Ethnicity
Modifiable	Dyslipidemia (High LDL/Low HDL), Hypertension, Tobacco Smoking, Diabetes/Hyperglycemia, Obesity/BMI, Physical Inactivity/Sedentary Lifestyle
Emerging/Contributory	Chronic Kidney Disease (CKD), Psychosocial Stress/Depression, Inflammation (high-sensitivity C-reactive protein - hs-CRP), Thrombogenic factors, Sleep Apnea, Metabolic Syndrome

Coronary Angiography and Assessment of CAD Severity

Coronary angiography and percutaneous coronary intervention represent the cornerstone of invasive cardiology's approach to CAD. The direct visualization of the coronary arterial tree is achieved through coronary angiography, a fluoroscopic procedure that remains the definitive method for assessing the presence, location, and severity of coronary stenoses [15].

The interventional cardiologist analyzes the angiographic cine films to define coronary anatomy, identify lesion location, estimate stenosis severity, assess lesion characteristics, and identify collateral circulation. A stenosis of $\geq 70\%$, or $\geq 50\%$ for the left main coronary artery, is generally considered hemodynamically significant and potentially eligible for revascularization.

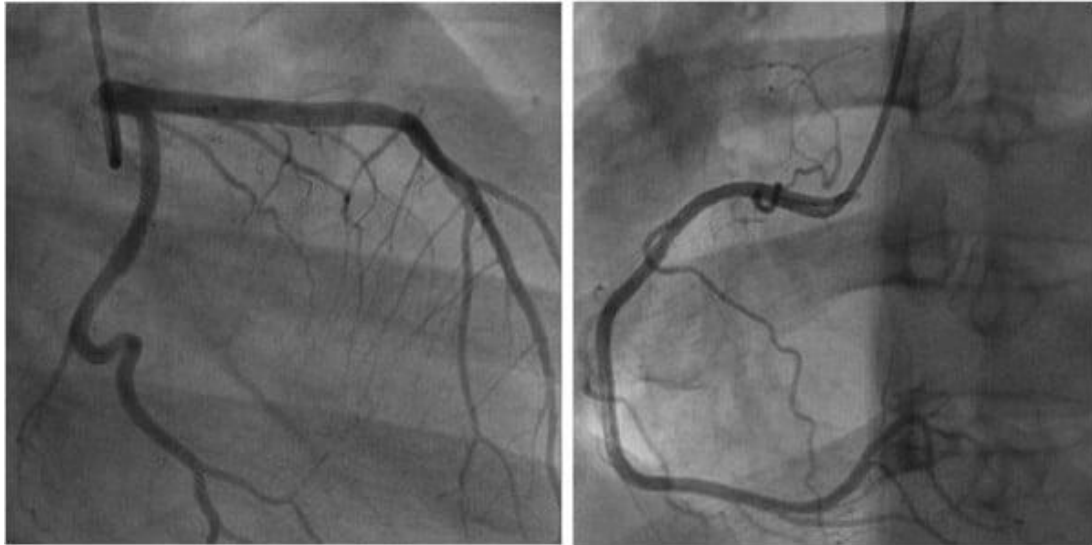


Figure 3. Example of left and right coronary artery angiography (Shin et al., 2013) [16].

A fundamental limitation is that angiography shows the outline of the blood-filled lumen, not the vessel wall. It can underestimate the overall burden of atherosclerosis, where the wall expands outward, preserving the lumen until the disease is advanced [17]. Visual estimation of stenosis can also be subjective.

The SYNTAX Score

The SYNTAX Score is a comprehensive angiographic scoring system used to quantify the complexity of coronary artery disease [18]. It helps guide heart teams in deciding whether a patient with complex CAD is better treated with PCI or coronary artery bypass grafting. The score is calculated from a patient's coronary angiogram and assigns points for each coronary lesion causing $\geq 50\%$ stenosis in a vessel ≥ 1.5 mm in diameter.

Coronary segments are weighted based on the amount of myocardium they supply. Points are added for complex features that make PCI more difficult and riskier, including bifurcations, chronic total occlusions, heavy calcification, long lesions, thrombus, and severe vessel tortuosity [19]. The final score is the sum of points from all lesions and is commonly interpreted as low (0–22), intermediate (23–32), or high (>32) [20].

While a valuable tool, the SYNTAX Score has inherent limitations. The score is based on visual assessment of the angiogram, which leads to interobserver variability. The original score also does not account for clinical factors such as age, kidney function, or diabetes, which strongly influence outcomes.

Insulin Resistance and the TyG Index

The Centrality of Insulin Resistance

Insulin resistance is a state of diminished biological response to insulin in its target tissues, primarily the liver, skeletal muscle, and adipose tissue. It is the precursor to the development of T2DM, as pancreatic beta-cells eventually fail to compensate for the increased insulin demand. Furthermore, IR promotes a pro-atherogenic environment characterized by dyslipidemia, endothelial dysfunction, hypertension, and a prothrombotic state [1].

The accurate identification of individuals with IR is crucial for early intervention and prevention strategies. However, direct measurement of IR is challenging. The hyperinsulinemic-euglycemic clamp is labor-intensive, time-consuming, and requires specialized expertise. HOMA-IR is more widely used but relies on insulin

measurement, an assay that is not standardized across laboratories and is not routinely ordered in many clinical practices [21].

Table 2. Comparison of insulin resistance assessment methods (Sharma et al., 2020) [21]

Method	Description	Advantages	Limitations
Hyperinsulinemic-euglycemic clamp	Gold standard for IR measurement	Highly accurate	Complex, expensive, and impractical
HOMA-IR	Based on fasting insulin and glucose	Widely used in research	Requires a non-standardized insulin assay
TyG index	Based on fasting triglycerides and glucose	Simple, cost-effective, and widely available	Surrogate marker with no universal cutoff

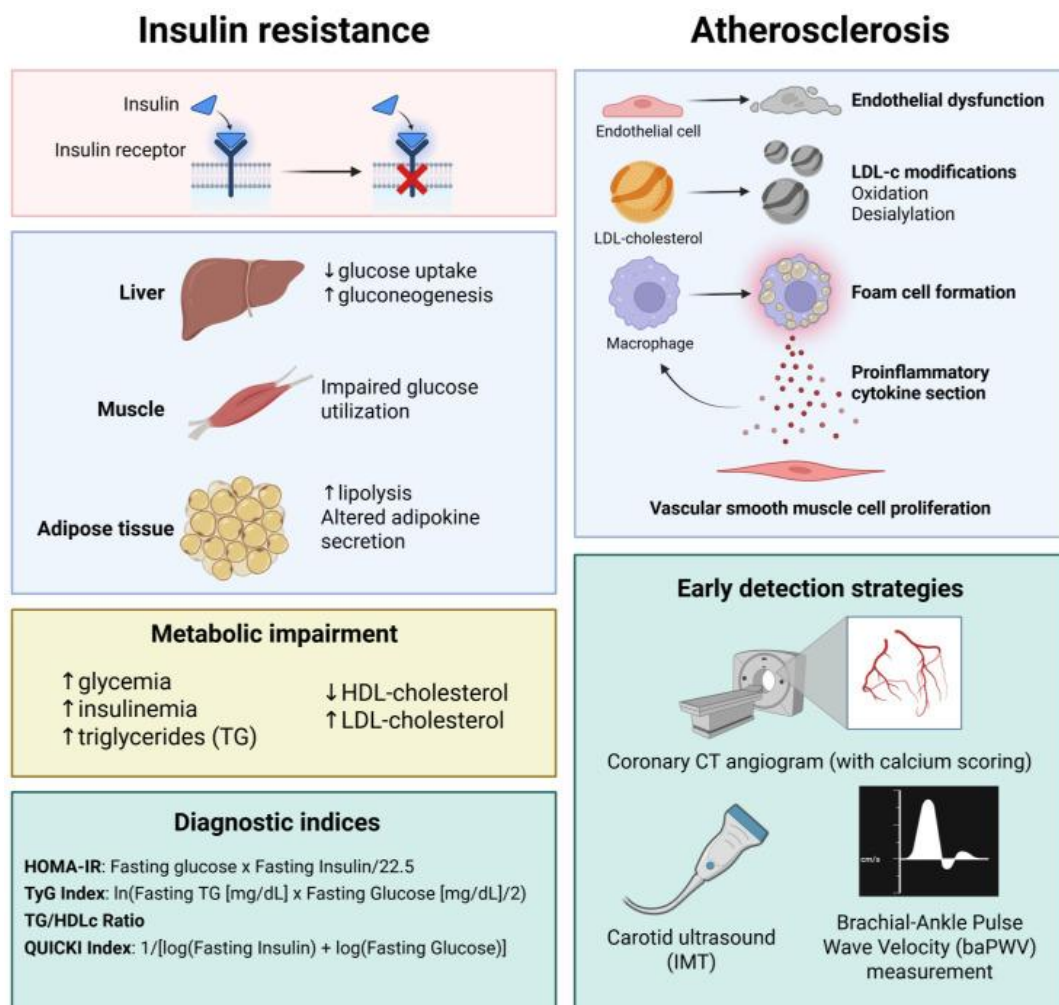


Figure 4. The connection between insulin resistance and atherosclerosis development and progression (Brie et al., 2025) [22].

The Physiological Link Between Triglycerides and Glucose

The TyG index is not an arbitrary combination of biomarkers; its efficacy is rooted in the deep physiological interconnection between lipid and glucose metabolism, orchestrated by insulin. Insulin is a master anabolic hormone. After a meal, it promotes glucose uptake into skeletal muscle and adipose tissue, promotes *de novo* lipogenesis in the liver, and inhibits the breakdown of stored triglycerides in adipose tissue [23].

In insulin resistance, the body's tissues become less responsive to these signals, setting off a cascade of metabolic disturbances [24]. Skeletal muscle fails to efficiently take up glucose, leading to postprandial hyperglycemia. The liver becomes resistant to insulin suppression of glucose production, leading to fasting hyperglycemia, while loss of insulin suppression of VLDL production results in hypertriglyceridemia.

In adipose tissue, the anti-lipolytic effect of insulin is blunted. This leads to continuous release of free fatty acids into the circulation. These fatty acids are taken up by the liver, further driving triglyceride and VLDL synthesis and exacerbating hepatic insulin resistance [25].

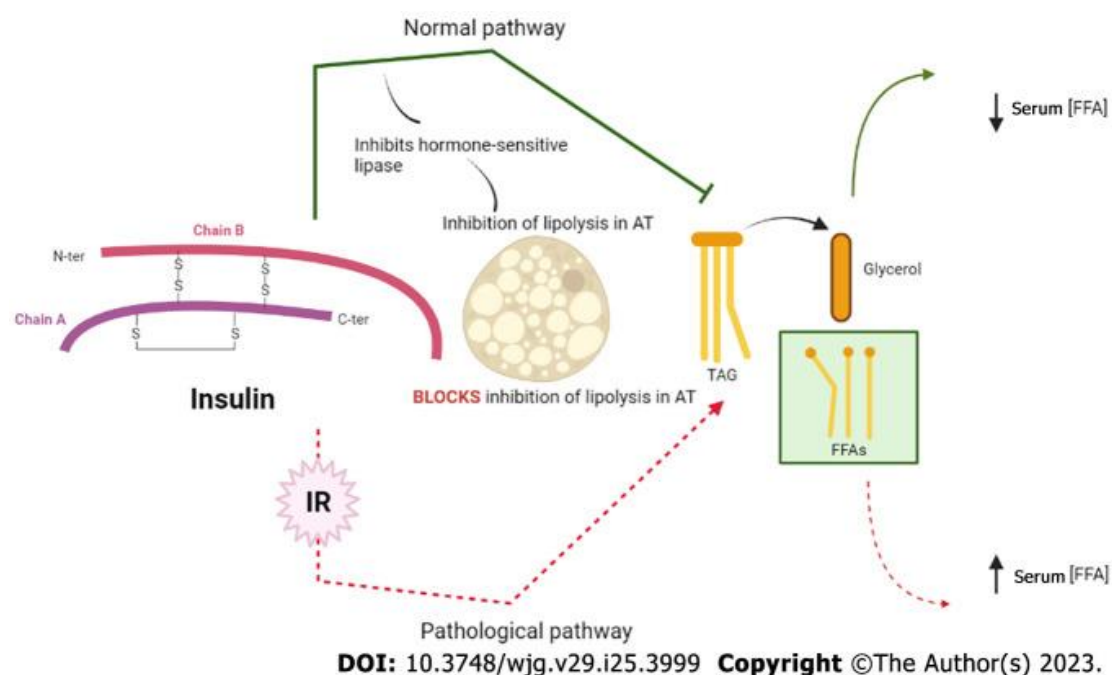


Figure 5. Effect of insulin resistance on adipose tissue lipolysis (Pal et al., 2023) [25].

Thus, hypertriglyceridemia and hyperglycemia are not just correlated; they are direct, intertwined consequences of the same underlying insulin-resistant state. The TyG index, by combining these two key biomarkers, effectively captures the essence of this dysmetabolism.

Derivation and Calculation of the TyG Index

The Triglyceride-Glucose Index was first proposed and validated by Simental-Mendía et al. in 2008. The researchers identified a strong correlation between the product of fasting triglycerides and fasting glucose and the results from the hyperinsulinemic-euglycemic clamp [26].

$$\text{TyG Index} = \text{Ln} [\text{Fasting Triglycerides (mg/dL)} \times \text{Fasting Glucose (mg/dL)} / 2]$$

The natural logarithm is used to normalize the skewed distribution of triglyceride values. This simple calculation can be performed manually or automated in electronic health records, making it instantly accessible.

The TyG Index and Cardiovascular Disease Risk

The association between the TyG index and CVD is particularly robust, reflecting the role of IR as a key driver of atherosclerosis. The TyG index encapsulates the essence of atherogenic dyslipidemia: high triglycerides, low HDL-C, and the presence of small, dense LDL particles, a highly atherogenic profile characteristic of IR [27].

Insulin resistance promotes endothelial dysfunction, vascular inflammation, and oxidative stress. A high TyG index is associated with increased levels of inflammatory markers such as hs-CRP and adhesion molecules, providing a biological pathway for its link to CVD. Insulin resistance also promotes a pro-inflammatory state, with increased production of inflammatory cytokines and reduced production of anti-inflammatory adiponectin. This inflammatory milieu promotes endothelial dysfunction, monocyte adhesion, and plaque formation [28].

The TyG index appears to be a marker of the residual risk that persists even after managing conventional risk factors such as LDL-C, highlighting the importance of addressing metabolic health. A meta-analysis by da Silva et al. confirmed that a high TyG index is significantly associated with an increased incidence of cardiovascular events, including coronary artery disease, stroke, and myocardial infarction [29].

The TyG Index in Other Metabolic Conditions

Given its strong association with insulin resistance, the TyG index is a powerful predictor of future T2DM development. The Korean Genome and Epidemiology Study found that participants in the highest quartile of the TyG index had a significantly higher risk of developing T2DM over a 10-year follow-up period compared with those in the lowest quartile, even after adjustment for multiple confounders including HOMA-IR [30].

The reach of the TyG index extends beyond diabetes and CVD to other insulin resistance-related pathologies. The TyG index shows a strong correlation with ultrasound-diagnosed hepatic steatosis and more advanced measures of liver fat content [31]. Multiple cohort studies have also found that a higher TyG index is associated with decline in estimated glomerular filtration rate, onset of albuminuria, and development of chronic kidney disease [32].

Table 3. TyG index and associated conditions

Condition	Mechanism of association	Evidence summary
Type 2 diabetes mellitus	Reflects beta-cell strain and lipotoxicity	Strong predictive value in cohort studies
Cardiovascular disease	Captures atherogenic dyslipidemia and inflammation	Associated with increased ASCVD risk
Non-alcoholic fatty liver disease	Indicates hepatic IR and triglyceride accumulation	Correlates with steatosis and fibrosis
Chronic kidney disease	Linked to inflammation and glomerular stress	Predicts eGFR decline and albuminuria

Advantages and Limitations of the TyG Index

The TyG index uses two cheap, routinely measured, and widely available biomarkers. Unlike insulin assays, measurements of glucose and triglycerides are highly standardized across laboratories. It requires no extra blood draws or costs if a standard lipid panel and glucose are already being checked. It has been validated against the gold standard and hard clinical outcomes across diverse populations [33].

Lack of universal cutoff points is the primary limitation for widespread clinical adoption. Proposed optimal cutoffs for identifying insulin resistance vary between studies and populations; ethnicity-, age-, and sex-specific cutoffs may be needed [34]. The TyG index remains a surrogate marker and infers insulin resistance from its metabolic consequences rather than measuring tissue-specific insulin sensitivity directly.

Acute factors such as recent excessive alcohol intake or very high carbohydrate intake can transiently elevate triglycerides, artificially inflating the index. It should be measured in a true fasting state [35]. The index also does not provide information on beta-cell function.

Table 4. Advantages and limitations of the TyG index

Advantages	Limitations
Simple and inexpensive	No universal cutoff values
Uses standardized laboratory tests	Surrogate rather than direct IR measurement
Strong predictive power for metabolic diseases	Affected by acute dietary changes
Suitable for large-scale screening	Does not assess beta-cell function

Conclusion

Hypertriglyceridemia and hyperglycemia are direct, intertwined consequences of the same underlying insulin-resistant state. The TyG index, by combining these two key biomarkers, effectively captures the essence of this dysmetabolism. Its association with cardiovascular disease is particularly robust, reflecting the role of insulin resistance as a key driver of atherosclerosis.

The TyG index uses two cheap, routinely measured, and widely available biomarkers and requires no extra blood draws or costs if a standard lipid panel and glucose are already being checked. However, it remains a surrogate marker, and lack of universal cutoff points is the primary limitation for widespread clinical adoption.

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