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Progress of Triglyceride Glucose Index in Lesion Severity and Prognosis of Acute Coronary Syndromes

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Abstract

Background: In response to the escalating burden of cardiovascular diseases (CVDs) worldwide, exacerbated by lifestyle changes and socioeconomic shifts, acute coronary syndromes (ACS) stand out as a leading cause of morbidity and mortality. The pivotal role of insulin resistance in the pathogenesis of atherosclerosis, independent of traditional risk factors, has garnered significant interest. **Objective:** This review aims to synthesize the recent advancements in the utilization of the triglyceride glucose index (TyG index) as a biomarker for assessing the severity and predicting the prognosis of ACS lesions. **Methods:** A systematic search was conducted across PubMed, Embase, and Scopus databases, incorporating keywords such as "triglyceride glucose index", "TyG index", "acute coronary syndrome", "cardiovascular disease", "insulin resistance", "coronary artery calcification", "SYNTAX score", "Gensini score", and "major adverse cardiac events". Studies were included from the inception of each database up to July 2024. Selection criteria encompassed observational studies, case-control studies, and randomized controlled trials, with a particular emphasis on evaluating the diagnostic and prognostic value of the TyG index in patients with acute coronary syndromes. Ultimately, 46 publications met the inclusion criteria. Data extraction and quality assessment were performed in accordance with established guidelines. **Results:** Evidence suggests that the TyG index, reflecting insulin resistance, blood glucose, and lipid levels, is significantly associated with lesion severity in ACS, including coronary artery calcification, SYNTAX score, and Gensini score. Moreover, it demonstrates predictive power for major adverse cardiovascular events, underscoring its potential as a valuable tool in clinical decision-making. **Conclusion:** The review highlights the emerging role of the TyG index in the assessment and prognosis of ACS, advocating for its incorporation into clinical practice as a complement to existing diagnostic modalities.

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However, the establishment of standardized reference ranges and further validation across diverse populations are warranted to refine its applicability in personalized medicine. The interdisciplinary approach is essential to advance our understanding of the complex interplay between insulin resistance and cardiovascular disease, paving the way for the development of more effective prevention and treatment strategies.

Keywords

Triglyceride Glucose Index, Insulin Resistance, Acute Coronary Syndrome

1. Introduction

Cardiovascular disease (CVD) stands as a paramount cause of rising morbidity and mortality rates globally, with its impact intensifying alongside socioeconomic advancement and shifts in lifestyle patterns [1]. Among these conditions, acute coronary syndrome (ACS) holds particular significance, encompassing a spectrum of clinical presentations ranging from asymptomatic individuals to critically ill patients experiencing persistent angina pectoris or cardiogenic shock [2]. The pathophysiological mechanisms underlying ACS involve the instability of atherosclerotic plaques, including erosion, rupture, and subsequent thrombosis [3]. Of note, insulin resistance, a cardinal feature of type 2 diabetes mellitus, has been substantiated as an independent risk factor for the formation and progression of atherosclerotic plaques, even after adjustments for hypertension, dyslipidemia, and glycemic control [4]-[6]. In recent years, the triglyceride glucose index (TyG index), an emerging biomarker, has distinguished itself for its simplicity and efficacy in quantifying insulin resistance [7]. This index not only mirrors the state of insulin resistance but also integrates considerations of both glucose and lipid levels [8]. The correlation between the TyG index and the severity of lesions and prognosis in ACS has become a focal point of investigation, with its potential clinical utility gradually coming to light. This study endeavors to comprehensively review the latest advancements regarding the TyG index within the realm of ACS research, with a concentrated examination of its association with the severity of coronary artery disease and patient outcomes, along with its implications for clinical practice. Through a systematic literature review, we will analyze the performance of the TyG index in relation to coronary artery calcification, SYNTAX score, Gensini score, and its independent predictive value for the prognosis of ACS patients. By conducting this review, we aspire to offer clinicians an updated perspective on the role of the TyG index in assessing the severity of coronary artery lesions and forecasting outcomes, thereby facilitating optimized management strategies for ACS patients.

2. Methodology

A systematic literature search was conducted utilizing electronic databases such

as PubMed, Embase, and Scopus. Search terms encompassed "Triglyceride Glucose Index," "TyG index," "Acute Coronary Syndrome" (ACS), "Cardiovascular Disease," "Insulin Resistance," "Coronary Artery Calcification," "SYNTAX Score," "Gensini Score," and "Major Adverse Cardiovascular Events." Studies were included from the inception of each database up to July 2024. Selection criteria encompassed observational studies, case-control studies, and randomized controlled trials, with a particular emphasis on evaluating the diagnostic and prognostic value of the TyG index in patients with acute coronary syndromes. Ultimately, 46 publications met the inclusion criteria. Data extraction and quality assessment were performed in accordance with established guidelines.

3. Insulin Resistance and Cardiovascular Disease Progression

3.1. Relationship between Insulin Resistance and Cardiovascular Disease

Insulin resistance (IR), which is prevalent in patients with type 2 diabetes (T2D), extends beyond glucose homeostasis disruption to multifaceted effects on cardiac function. IR can trigger disturbances in cardiac calcium ion metabolism, mitochondrial dysfunction, and reduced metabolic flexibility, leading to a cascade of cardiopathological changes, including abnormal interactions between cardiomyocytes and endothelial cells, impaired diastolic function, increased cardiomyocyte apoptosis, and accelerated fibrosis [9]. Globally, numerous studies have explored the clinical link between IR and cardiovascular disease (CVD). In recent years, scholars both domestically and internationally have conducted extensive research on the clinical association between IR and CVD. For example, Lee, Jong Hee *et al.* conducted a cross-sectional study involving 3597 participants from the Korean Genome and Epidemiology Study (KoGE), revealing a significant positive correlation between IR and CVD risk, with a hazard ratio (HR) of 1.37 and a 95% confidence interval (CI) of 1.01 to 1.84 [10]. Similarly, another cohort study, which followed 6755 adults aged 40 to 69 years for 9.83 years, showed that changes in IR status were significantly associated with the occurrence of cardiovascular events and their adverse outcomes, with a hazard ratio of 1.37 and a 95% CI of 1.01 to 1.84, after adjusting for age, sex, body mass index (BMI), diabetic status, and lipid levels [11]. Wang, Tiange *et al.*, using data from the China Heart Metabolic Disease and Cancer (CHMC) cohort study, which included 111,576 eligible participants nationwide, further confirmed the positive association between IR and CVD risk, with a hazard ratio of 1.04 and a 95% CI of 0.92 to 1.18. Notably, impaired glucose tolerance increased the risk of cardiovascular adverse events by approximately 12% [12]. Louie, Judy Z *et al.*, through a prospective cohort study utilizing data from 3645 middle-aged and older adults (median age 68 years) from the Malmö Preventive Project (MPP) in Sweden, excluding those with pre-existing CVD or diabetes and incomplete data, found a significant association between IR and the incidence of CVD, providing further direction for investigating the mechanisms linking IR and CVD [13]. IR is not

only a hallmark of T2D but also a potential driver in the development of CVD. This finding provides a new perspective for the prevention and treatment of CVD, emphasizing the importance of early identification and intervention of IR status in clinical practice. However, the complex and subtle relationship between IR and CVD still requires further elucidation through more high-quality prospective studies.

3.2. Relationship between Insulin Resistance and Atherosclerosis

Insulin resistance, as a central element in metabolic disorders, has implications far beyond simple glucose regulation, deeply embedding itself within the framework for the prevention and control of cardiovascular disease [14] [15]. Even when lipid and glucose levels are within normal ranges, molecular mechanisms of insulin resistance act as independent and critical drivers in the progression of atherosclerosis [16] [17]. Although compensatory mechanisms are initiated by the body in response to insulin resistance—primarily through increased insulin secretion—the efficacy of these mechanisms is often insufficient. It is within this pathological context that a series of interrelated events promote the development of CVD, which primarily include:

1) Dyslipidemia and Lipotoxicity: Abnormal phosphorylation of insulin receptor substrate 1 (IRS-1) impairs insulin's regulatory capacity over lipolysis and lipid storage in adipose tissue. This leads to an excess of low-density lipoprotein cholesterol (LDL-C) entering the arterial wall, forming lipid-laden foam cells, and accelerating the formation of atherosclerotic plaques.

2) Inflammation and Oxidative Stress: Insulin resistance promotes the synthesis of pro-inflammatory mediators and oxidative stress products, such as oxidized LDL (ox-LDL), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), endothelin-1 (ET-1), and plasminogen activator inhibitor-1 (PAI-1). These substances exacerbate inflammation, stimulate the proliferation of vascular smooth muscle cells, and collectively contribute to the progression of atherosclerosis.

3) Endothelial Dysfunction: Insulin resistance leads to reduced production of nitric oxide (NO) in endothelial cells while promoting the accumulation of reactive oxygen species (ROS). This results in accelerated degradation of NO and diminished synthesis and release of vasodilatory prostacyclin (PGI2), along with increased synthesis of the potent vasoconstrictor endothelin-1 (ET-1). This imbalance disrupts normal vascular regulation and accelerates the progression of atherosclerosis [18]-[20]. Through this exposition, we clearly recognize that insulin resistance is not only a hallmark of type 2 diabetes but also a catalyst for the development of atherosclerosis and subsequent cardiovascular disease. Therefore, elucidating the mechanisms of insulin resistance is crucial for developing effective preventive and therapeutic strategies.

3.3. Relationship between Triglyceride Glucose Index and Insulin Resistance

In 1979, DeFronzo and colleagues pioneered the "gold standard" for measuring

insulin resistance—the hyperinsulinemic-euglycemic clamp (HIEC) technique—which laid the foundation for understanding the physiological mechanisms of insulin resistance [21]. However, due to its complex operational procedures, high costs, and time-consuming nature, the HIEC technique is challenging to implement in clinical practice and large-scale epidemiological studies. Subsequently, researchers have developed alternative indicators to assess insulin resistance, with the homeostatic model assessment for insulin resistance (HOMA-IR) becoming the preferred simple method. Nonetheless, with deeper research, an emerging biomarker—the triglyceride glucose index (TyG index)—has emerged, utilizing its unique calculation method: Ln (fasting triglycerides (mg/dL) × (fasting glucose (mg/dL)/2)), which not only reflects the state of insulin resistance but also provides a comprehensive assessment of both glucose and lipid levels [22]. A cross-sectional study comparing different methods found that the TyG index displayed higher sensitivity and specificity compared to the cumbersome HIEC technique, highlighting its superiority in assessing insulin resistance [23]. Despite these advantages, the TyG index is not without limitations; it is not a perfect marker of insulin resistance [24]. The latest systematic review indicates that although the TyG index can only serve as an effective marker of insulin resistance, its practicality and cost-effectiveness make it a valuable tool in clinical and epidemiological research [25]. In the future, with a deeper understanding of the mechanisms of insulin resistance, the application scope and clinical value of the TyG index are expected to expand.

4. Triglyceride Glucose Index (TyG Index) Correlates with Acute Coronary Syndrome

4.1. Relationship between Triglyceride Glucose Index (TyG Index) and Lesion Severity in Acute Coronary Syndromes

4.1.1. Triglyceride Glucose Index (TyG Index) and Coronary Artery Calcification (CAC)

Coronary artery calcification (CAC), quantified using multi-detector computed tomography (CT), has been established as a sensitive indicator for the early detection of coronary atherosclerosis, closely related to atherosclerotic processes [26]. A cross-sectional study involving 4319 eligible participants in Korea revealed a significant association between the triglyceride glucose index (TyG index) and the prevalence of coronary artery calcification, with an area under the receiver operating characteristic curve (AUC) of 0.629 (95% CI: 0.598 - 0.660, P = 0.016) [27]. Even after adjusting for conventional cardiovascular risk factors such as gender, age, blood pressure, and lipid levels, the association between the TyG index and CAC prevalence remained significant (odds ratio OR = 1.95, 95% CI: 1.23 - 3.11, P = 0.01). Another cohort study involving 1175 Korean subjects, with an average follow-up period of 4.2 ± 2.2 years, further confirmed the independent predictive value of the TyG index for the progression of coronary artery calcification, with an odds ratio OR of 1.82 (95% CI: 1.20 - 2.77, P ≤ 0.01) [28]. The study also noted a positive correlation between the TyG index and annual

changes in the coronary artery calcification score (CACS) (β = 0.066, P = 0.036) [29]. A systematic review and meta-analysis of 26 observational studies, including 87,307 subjects, further validated these findings, demonstrating a significant association between elevated TyG index and increased risk of coronary artery calcification, with an odds ratio OR of 1.66 (95% CI 1.51 - 1.82, I^2 = 0%). This suggests that every one-unit increase in the TyG index corresponds to a 73% increase in the risk of coronary calcification (95% CI 1.36 - 2.20, I^2 = 51%) [30]. These studies indicate that the TyG index is closely linked to the degree of coronary artery calcification and can serve as a predictor of coronary calcification progression, offering a new perspective for early identification and intervention in cardiovascular disease. These findings also underscore the potential value of the TyG index in cardiovascular health monitoring, particularly as a supplementary tool for assessing the risk of coronary artery calcification. However, future research needs to further explore the applicability and thresholds of the TyG index in different populations to more precisely guide clinical practice.

4.1.2. Triglyceride Glucose Index (TyG Index) and SYNTAX Score Correlation

The SYNTAX score, a comprehensive angiographic tool that considers anatomical risk factors, is an authoritative scoring system guiding percutaneous coronary intervention (PCI) strategy and a key indicator of the severity of coronary artery lesions [31]. A large-scale cohort study conducted domestically, involving 1007 subjects, demonstrated that the triglyceride glucose index (TyG index) is an independent predictor of high SYNTAX scores (>22 points), with an odds ratio (OR) of 2.6452 (95% CI: 1.9020 - 3.6786, P < 0.0001) [32]. Even after controlling for potential confounders such as age, body mass index (BMI), hypertension, and diabetes, the TyG index, as a categorical variable, remained a significant independent risk factor for high SYNTAX scores (OR = 2.645, 95% CI 1.902 - 3.679, P < 0.001). Another study focused on 791 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) treated at Xinqiao Hospital, Third Military Medical University, Chongqing, China, between January and September 2017. The results indicated that the TyG index might be an effective marker of the severity of coronary artery stenosis and was significantly and independently correlated with the SYNTAX score (OR = 6.055, 95% CI 2.915 - 12.579, P < 0.001) [33]. The close association between the TyG index and the SYNTAX score underscores the potential value of the TyG index in assessing the complexity of coronary lesions and guiding clinical decision-making. As an easily accessible biomarker, the TyG index could play a crucial role in risk assessment, disease monitoring, and treatment planning in cardiovascular disease, especially in evaluating the severity of coronary artery lesions. However, further prospective studies are needed to validate its stability and predictive accuracy across different populations.

4.1.3. Triglyceride Glucose Index (TyG Index) and Gensini Score Association

The Gensini score, based on images obtained from coronary computed tomog-

raphy angiography (CCTA) in patients with acute coronary syndrome, is a quantitative measure of the overall burden of coronary atherosclerosis [34] [35]. A multicenter retrospective cohort study conducted in China, involving 1491 patients with ST-segment elevation myocardial infarction (STEMI) between 2015 and 2019, revealed a significant positive correlation between the triglyceride glucose index (TyG index) and the extent of coronary artery stenosis (correlation coefficient $r = 0.262$, $P < 0.001$) [36]. This indicates that the TyG index is a reliable indicator of the severity of coronary artery stenosis and, independently of other traditional risk factors, serves as an independent risk factor for severe coronary artery stenosis (OR = 2.003, 95% CI: 1.633 - 2.458, $P < 0.001$). This finding further highlights the potential value of the TyG index in risk assessment for cardiovascular disease, particularly for patients with acute coronary syndrome, where it may serve as a powerful tool for predicting the degree of coronary atherosclerosis and assessing disease prognosis. However, given the complexity of cardiovascular disease, future research should aim to validate the applicability of the TyG index in broader populations and explore its specific role in personalized treatment planning.

4.2. Relationship between Triglyceride Glucose Index (TyG Index) and Prognosis of Acute Coronary Syndrome

Although the Global Registry of Acute Coronary Events (GRACE) score is recognized as a powerful tool for predicting long-term mortality and reinfarction rates in patients with acute coronary syndrome (ACS), the high incidence of major adverse cardiovascular events (MACE), including all-cause death, non-fatal myocardial infarction (MI), and unplanned repeat revascularization, highlights the limitations of existing predictive models [37] [38]. Against this backdrop, the triglyceride glucose index (TyG index)—an effective and practical surrogate marker of insulin resistance—has emerged as a predictor closely tied to the prognosis of ACS patients. The TyG index has been demonstrated to be an independent predictor of adverse cardiovascular events in both diabetic and non-diabetic patients (hazard ratio HR = 1.6542, 95% confidence interval CI: 1.1555 - 2.3681, $P = 0.006$). When combined with the GRACE score, it significantly improves the predictive accuracy of MACE (C-statistic from 0.735 to 0.744, 95% CI: 0.682 - 0.788 and 0.6889 - 0.800, respectively, $P < 0.01$; net reclassification improvement NRI = 0.282, 95% CI: 0.028 - 0.426, $P = 0.02$; integrated discrimination improvement IDI = 0.019, 95% CI: 0.004 - 0.046, $P = 0.01$) [38]. Additionally, the TyG index, through the SYNTAX score, a mediator reflecting the complexity of coronary artery lesions, is associated with the prognostic prediction of ACS patients (attributable risk percentage of 11.53%, 95% CI: 2.80 - 28.64%, $P < 0.05$; hazard ratio HR = 1.9674, 95% CI: 1.4346 - 2.6979, $P = 0.0001$) [39]. Systematic reviews and meta-analyses further support the role of the TyG index in predicting MACE. One meta-analysis of 41 studies showed that higher levels of the TyG index in ACS patients were significantly associated with increased MACE (HR = 2.09, 95% CI: 1.68 - 2.62, $I^2 = 87\%$, $P < 0.00001$) when

considered as a categorical variable; similarly, when viewed as a continuous variable, ACS patients had a strongly correlated risk of MACE (HR = 2.28, 95% CI: 1.44 - 3.63, I^2 = 95%, P = 0.0005) [40]. Another meta-analysis of 17 studies similarly confirmed that ACS patients with the highest TyG index had a significantly increased risk of MACE following percutaneous coronary intervention (PCI) (HR = 1.54, 95% CI: 1.27 - 1.86, P < 0.001); this association was consistent in continuous variable analysis (HR = 1.74, 95% CI: 1.47 - 2.05, P < 0.001) [41]. Regardless of whether considered as a continuous or categorical variable, the TyG index is independently associated with major adverse cardiovascular events (MACCE) in ACS patients who have undergone PCI for coronary artery bypass grafting (CABG) (HR 1.42, 95% CI 1.09 - 1.86, P = 0.009; HR 1.53, 95% CI 1.16 - 2.01, P = 0.003) [42]. Specifically, a retrospective study of 101,113 patients demonstrated that, after adjusting for all relevant factors, the TyG index (>10.013) was an independent predictor of in-hospital MACE (HR = 1.604, 95% CI = 1.437 - 1.791, P < 0.001), particularly in ST-segment elevation myocardial infarction (STEMI) patients, where it was significantly associated with adverse cardiovascular events (HR = 1.670, 95% CI = 1.464 - 1.904, P < 0.001) and more pronounced in women, older individuals, and those with renal insufficiency [43]. In patients with ACS undergoing emergency PCI, the prognostic value of the TyG index was also confirmed, with a median follow-up of 47 months showing an independent association with MACE (HR = 1.493, 95% CI: 1.230 - 1.812, P < 0.001) [44]. Notably, even as the best marker of insulin resistance, the TyG index still significantly predicts the prognosis of diabetic patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (HR = 3.208, 95% CI: 2.400 - 4.289, P < 0.001) [45]. Finally, the predictive capability of the TyG index in elderly ACS patients has also been affirmed (HR = 1.64, 95% CI: 1.06 - 2.54, P < 0.05) [46]. In summary, the TyG index plays a key role in the prognostic assessment of ACS and demonstrates predictive value in various clinical scenarios, including short-term adverse cardiovascular event prediction during hospitalization, post-emergency PCI prognosis, and prognostic evaluation in specific high-risk subgroups such as diabetic patients and the elderly. These findings underscore the potential of the TyG index as a tool in cardiovascular disease management and provide a scientific basis for more personalized and precise medical decision-making in clinical practice.

5. Discussion

5.1. The Triglyceride Glucose Index (TyG Index) and Cardiovascular Disease: Where Theory Meets Practice

The triglyceride glucose index (TyG index), emerging as a novel biomarker for insulin resistance, has garnered considerable interest due to its close association with cardiovascular disease, particularly acute coronary syndrome (ACS). Insulin resistance, a cornerstone component of metabolic syndrome, not only intertwines with the development of type 2 diabetes but also plays a pivotal role in the

pathogenesis of atherosclerosis. The uniqueness of the TyG index lies in its ability to simultaneously reflect the body's insulin resistance status, blood glucose, and lipid levels through a straightforward mathematical formula—namely, ln(Triglycerides × (Glucose/2)). This characteristic endows it with significant practical value in clinical settings.

5.2. Clinical Relevance of the TyG Index in ACS

Within this review, we have thoroughly examined the link between the TyG index and the severity of ACS lesions as well as its prognostic value. Ample empirical data support the significant correlation of the TyG index with key cardiovascular indicators such as coronary artery calcification, SYNTAX score, and Gensini score, indicating its potential clinical applicability in assessing the severity of coronary artery lesions. Moreover, the TyG index has proven to be an independent predictor of adverse cardiovascular events, offering a new perspective on risk stratification and prognosis evaluation for ACS patients.

5.3. Limitations of the TyG Index and Directions for Future Research

Despite the immense potential of the TyG index in the field of cardiovascular disease, its application still faces certain challenges. Current research often categorizes the TyG index based on the median, tertiles, or quartiles of the study population, lacking standardized reference ranges and cut-off values. This limitation hinders its widespread adoption in clinical practice. Additionally, the applicability of the TyG index needs to be further validated in diverse populations across different races, genders, and age groups to ensure its predictive accuracy and generalizability.

6. Summary and Future Directions

Starting from the intersection of type 2 diabetes mellitus and cardiovascular disease (CVD): insulin resistance, this review comprehensively comprehends that the TyG index, an emerging biomarker of insulin resistance, has demonstrated a unique advantage in assessing the lesion severity and predicting the prognosis of ACS due to its simplicity, validity, and practicality. Its significant correlation with key indicators such as coronary artery calcification, the SYNTAX score, and the Gensini score further demonstrates its potential value and clinical significance in cardiovascular disease management. Looking toward the future, in-depth interdisciplinary collaboration will be a key driving force to promote the deepening of TyG index research. Integration of resources from genetics, molecular biology, clinical medicine, epidemiology, and artificial intelligence technology will open a new era in the development of cardiovascular disease risk prediction models based on the TyG index. Such models are expected to provide highly personalized and accurate disease risk assessment by integrating multiple biomarkers and clinical parameters, laying a solid foundation for clinicians to develop more accurate and effective preventive and therapeutic plans. Through

this approach, the application of the TyG Index will not only improve the overall level of cardiovascular disease management but will also directly benefit patients and help achieve more efficient and personalized healthcare services.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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