Short Communication

Interventional Cardiology

The association of the triglyceride-glucose index with the risk of atrial fibrillation

Abstract

The Triglyceride-Glucose (TyG) index is a recognized surrogate for insulin resistance, yet its relationship with Atrial Fibrillation (AF) remains incompletely defined, with prior studies yielding conflicting results. In a recent UK Biobank study, Shi, et al investigated the association between baseline TyG index and long-term AF risk in 409,705 participants without prior arrhythmias. Over a mean follow-up of 13.9 years, 26,092 AF cases occurred. Participants were stratified by TyG tertiles (T1: Low, T2: Middle, T3: High). Multivariable Cox regression revealed a U-shaped association: Compared to T2, T1 (HR: 1.22, 95% CI: 1.17-1.27) and T3 (HR: 1.09, 95% CI: 1.05-1.14) groups showed elevated AF risk, independent of demographics, lifestyle, comorbidities, and polygenic risk score for AF. Restricted cubic spline analysis confirmed a significant non-linear relationship (P<0.001). This non-linear relationship remained consistent across subgroups stratified by type 2 diabetes status, heart valve disease, and genetic susceptibility to AF. The findings suggest that both low and high TyG index values are independent risk factors for AF, highlighting the potential of this simple metric for improving AF risk stratification in clinical practice.

Keywords: Triglyceride-glucose index • Atrial fibrillation • Insulin resistance • U-shaped association • Risk prediction

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Description

AF represents a pervasive clinical challenge and a leading cause of stroke, heart failure, and cardiovascular mortality worldwide [1-3]. Despite advances in management, its rising prevalence underscores the urgent need for enhanced risk prediction and preventive strategies. The TyG index serves as a straightforward and reliable surrogate marker for insulin resistance [4,5]. In previous studies, a high TyG index has been demonstrated to be associated with an increased risk of various cardiovascular diseases like coronary heart disease [6] and heart failure [7], but its specific association with AF has been inconsistent. Some studies suggest a linear positive correlation, particularly in non-diabetic populations [8], while others propose a U-shaped relationship [9]. These discrepancies, potentially stemming from limited sample sizes and varying adjustments, highlight the necessity for a definitive assessment in a large, well-phenotyped cohort. Against this backdrop, Shi, et al.'s prospective UK Biobank analysis [10], provides robust, large-scale insights into TyG's association with incident AF, accounting for extensive confounders, conducting thorough sensitivity analyses, and delving into TyG-AF relationships across diverse subpopulation.

Shi, et al.'s study represents an investigation into TyG's prognostic value for AF,

leveraging the UK Biobank's extensive dataset of 409,705 arrhythmia-free adults (mean age 56.4 years, 45.7% male and 95% white). Baseline TyG was calculated as Ln [Fasting plasma glucose (mg/dL) × Triglycerides (mg/dL) /2], with participants stratified into tertiles (T1: Lowest, T2: Middle, T3: Highest). Over a median follow-up of 13.9 years, 26,092 AF events were adjudicated via hospital and death records (ICD-10 code I48). The study employed Cox proportional hazards and Restricted Cubic Spline (RCS) models to comprehensively evaluate the relationship, adjusting for over 20 covariates including demographics, lifestyle (body mass index, smoking, alcohol, metabolic equivalent of task, sleep score), socioeconomic factors, comorbidities (hypertension, Type 2 Diabetes [T2D], hyperlipidemia, coronary disease, Heart Valve Disease [HVD], cardiomyopathy, stroke, hyperthyroidism, cancer), treatments, and notably, AF Polygenic Risk Score (PRS). Moreover, RCS analysis was employed to discern potential linear or nonlinear relationships between the TyG index and the risks of AF within these fully adjusted models. Furthermore, associations were examined in subgroups stratified by T2D, HVD, and genetic predisposition to AF.

Multivariable Cox models adjusted progressively: Model 1 (age, sex, ethnicity) showed a J-shaped pattern (T1 HR: 1.07, T3 HR: 1.26 vs. T2); Model 2 added lifestyle and socioeconomic factors, yielding T1 HR: 1.24, T3 HR: 1.11; Model 3 incorporated comorbidities, treatments, and PRS, confirming a U-shaped association (T1 HR: 1.22, 95% CI: 1.17-1.27; T3 HR: 1.09, 95% CI: 1.05-1.14). Consistently, the RCS curves showed that the associations between the TyG index and the risk of AF were presented as U-shaped patterns (P for non-linearity<0.001). In non-T2D participants, TyG levels were associated with AF risk in a U-shaped relationship. Among T2D participants, only the T3 group had an increased risk of AF (reverse "L" pattern). The U-shaped relationship between TyG levels and AF risk remained consistent across HVD and non-HVD patients, as well as different strata of genetic susceptibility to AF.

These findings align with the Atherosclerosis Risk in Communities (ARIC) cohort study of 11,851 individuals without known cardiovascular disease, which observed a U-shaped association between TyG index and AF incidence after adjustment.The range of TyG index with the lowest incidence of AF was approximately 8.80-9.20. Whereas the crude incidence of AF in the study increased with increasing TyG index, a U-shaped association was found only after adequate adjustment. Conversely, smaller studies in varied populations often supported linear relationships. In 356 cardiology inpatients, elevated TyG independently predicted AF in non-diabetics but not diabetics. A cross-sectional analysis of 3,244 diabetics reported a 40.6% AF risk increase per TyG standard deviation, supporting a linear and robust correlation between TyG and prevalent AF in the diabetic population [11].

The discrepancies between Shi, et al.'s findings and prior research may arise from several factors. Prior studies have been hampered by limited sample sizes and event numbers, which restrict statistical power and make results susceptible to extreme values. In the only study with longer follow-up, the TyG-AF relationship was inconsistent between unadjusted and fully adjusted models. Other studies, constrained by sample sizes, could not adequately evaluate subpopulations, reducing reliability and generalizability. By contrast, Shi, et al.'s study, bolstered by sufficient statistical power, followed 409,705 participants for up to 13.9 years and demonstrated that individuals in the baseline TyG Index tertile 1 and 3 groups had a 22% and 9% increased risk of AF, respectively, compared with the tertile 2 group. After adjusting for all potential covariates, the U-shaped relationship between TyG Index and the incidence of AF persisted in patients with different glucose metabolism status and HVD prevalence status. In addition, the author validated this for the first time in populations with different AF genetic risks, further clarifying that the relationship between TyG index and AF incidence is independent of AF genetic risk.

Regarding the mechanisms, previous studies have reported a nonsignificant association between the TyG index and the risk of developing AF in patients with T2D [12-14]. This may be because the well-established correlations between shared risk factors for AF and diabetes (e.g., hypertension, elevated BMI, and advanced age) and AF incidence, which could obscure the independent contribution of insulin resistance to AF pathogenesis [15]. Consequently, the persistently high levels of insulin resistance (reflected by elevated TyG values) in diabetic patients may attenuate the detectable association with AF risk.

The association between a diminished TyG Index values and a heightened incidence of AF might be mediated by hypoglycemic conditions. The underlying mechanisms could involve activation of the sympatho-adrenal system, leading to cardiac electrophysiological alterations, such as extended Q wave to T wave (QT) intervals, thereby amplifying the risk of arrhythmias [16,17]. Furthermore, electrolyte disturbances, especially hypokalemia, may have the potential to interfere with cardiac repolarization processes, introducing additional complexity to the cardiovascular system's response in various metabolic states [18]. Clinical research has consistently demonstrated an elevated risk of arrhythmia onset associated with lower blood glucose levels [19-21]. In contrast, a high TyG index, signifying pronounced insulin resistance, is also implicated in greater AF incidence. Insulin resistance is known to compromise the transport of glucose into the atrial cells and has been observed to predispose animal models to AF [22]. This state additionally disrupts intracellular calcium homeostasis and promotes structural remodeling of the atrial myocardium [23]. These findings underscore the complex bi-directional relationship between metabolic dysregulation and the propensity for cardiac

arrhythmias, necessitating a nuanced understanding of these mechanisms for improved clinical management.

Conclusion

In conclusion, this study identified U-shaped associations between the TyG index and the risks of AF. This simple index may help identify individuals at high risk of developing AF and emphasizes the importance of assessing the TyG index in clinical practice.

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