The Association of Triglyceride Glucose index for Coronary Artery Disease in Postmenopausal Women

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Abstract
This study aimed to explore the association between the triglyceride glucose (TyG) index and coronary artery disease (CAD) in postmenopausal women. This study enrolled 869 postmenopausal women and classified them into two groups: CAD group (n = 538) and control group (n = 331). The TyG index was significantly higher in patients with CAD than in controls (P < 0.05). Receiver operator characteristic curves showed that the TyG index was more discriminative for CAD than for control group, and after adjusting for the traditional clinical prognostic factors, including age (>60 years), diabetes, ischemic stroke, systolic blood pressure (≥140), and ejection fraction (<50%), we found that the TyG index could be an independent risk factor for CAD (P < 0.05). The risk of increased TyG index was greater in the <50 years subgroup than in the >50 years subgroup (P < 0.05). The TyG index may be a valuable clinical predictor of CAD risk in postmenopausal women.

Keywords
triglyceride glucose index, coronary artery disease, Gensini score, postmenopausal women

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Introduction
Globally, coronary artery disease (CAD) is a major cause of morbidity and mortality, especially in postmenopausal women. The postmenopausal phase has been considered an important factor for developing metabolic syndrome. Insulin resistance (IR) is regarded as a decline in insulin in promoting glucose uptake and utilization, which is a marker of metabolic imbalance. Previous research has shown that IR is strongly related to the development and progression of coronary atherosclerosis, plaque characteristics, and cardiovascular (CV) outcomes. In addition, IR is involved in inflammation, endothelial dysfunction, and cardiac autonomic function, which is reported to play a vital role in the pathogenesis of CAD. Increasing evidence in postmenopausal women suggests a protective effect of endogenous estrogen against CAD, whereas its deficiency exacerbates the process of CAD after menopause.

The triglyceride glucose (TyG) index is a novel, simple, and inexpensive alternative index of IR and has been proven to be a good marker for predicting subclinical CAD in the absence of traditional risk factors. The formula is ln [TG (mg/dL) × fasting glucose (mg/dL)/2] to calculate TyG index. However, the association between the TyG index and CAD in postmenopausal women remains unclear. Therefore, this study aimed to examine whether the TyG index is a valuable biomarker for predicting the presence and severity of CAD in postmenopausal women.

Methods
Participants
This is a single center, retrospective, observational study. A total of 869 inpatients with suspected CAD were consecutively enrolled in this study, between December 2015 and January 2016.

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2019, at the Affiliated Hospital of Chengde Medical College. They were divided into two groups based on coronary angiography (CAG): the CAD group (n = 538) and the control group (n = 331). The inclusion criteria for the CAD group included postmenopausal women and suspected CAD with any stenosis of coronary arteries or ≥50% stenosis of the left main, left anterior descending, left circumflex, right coronary, or their main branches. The exclusion criteria were as follows: (1) infections, malignancies, hematopoietic or immune system disease of any form, or coronary embolism (2) hypertrophic cardiomyopathy and (3) connective tissue disease combined with coronary artery vasculitis. The Gensini score is a comprehensive score that assesses the extent of CAD burden on angiography. This score is calculated as the sum of the severity scores assigned depending on the degree of angiographic luminal stenosis in each segment of the coronary artery, exponentially increasing by the severity of lesions (25%, 50%, 75%, 90%, 99%, and 100% coronary stenosis), with a cumulative effect according to multiple lesions and lesion location. The study complies with the Declaration of Helsinki.

**Statistical Analyses**

Statistical analyses were performed using the SPSS (version 26.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze continuous data with normal or skewed distributions. Mean ± standard deviation and quartile median were used to express normal and skewed continuous data, respectively. To investigate differences between the groups, the t-test was applied for normally distributed continuous variables, the Mann-Whitney U-test for continuous variables with abnormal distribution, and the Chi-squared test for categorical variables.

Bivariate correlations between the TyG index and risk factors were calculated using Spearman’s rank correlation, and Pearson correlation was used to prove the association of TyG index and other continuous data, including demographics, risk factors, and biomarkers. Gensini score according to the maximum Yorden index through ROC curve to divided into 2 groups. Logistic regression analysis was performed to investigate unadjusted and multivariable-adjusted associations of the TyG index with CAD. A two-tailed P value of <0.05 was considered statistically significant.

**Results**

**Baseline Characteristics of the CAD and Control Groups**

The prevalence of hyperlipidemia, hypertension, diabetes mellitus, ischemic stroke, current smoker, and family history were higher in CAD group than control group. Furthermore, age, heart rate, systolic blood pressure (SBP), AI, AIP, LCI, and TyG index were significantly higher in the CAD group as compared to the control group (all \( P < 0.05 \)). Similarly, the left ventricle end-systolic diameters and Gensini score were higher in the CAD group than in the control group; however, the ejection fraction was lower in the CAD group (all \( P < 0.001 \)). The proportion of calcification of the aorta and abnormal ventricular wall motion were common in the CAD group. Moreover, levels of TC, TG, LDL-C, and blood glucose were higher in the CAD group than in the control group (all \( P < 0.05 \)) (Table 1).

**TyG index According to Different Coronary Artery Severity**

AI, LCI, and TyG index were significantly higher in the Gensini ≥ 38.75 group than the Gensini < 38.75 group (all \( P < 0.05 \)). Although AIP was no significant difference between the two groups, we also found AIP in the Gensini ≥ 38.75 group was greater than the Gensini < 38.75 group. (Table 2).

**Association of the TyG index with CAD Risks Factors**

Table 3 demonstrated that the TyG index had a significant positive correlation with hyperlipidemia, hypertension, diabetes mellitus, TC, TG, LDL-C, AI, AIP, LCI, blood glucose, and Gensini score (Rs = 0.352, 0.117, 0.360, 0.230, 0.666, 0.080, 0.336, 0.623, 0.518, 0.107, 0.476, and 0.199, respectively; all \( P < 0.05 \)). Moreover, the TyG index was negatively correlated with HDL-C (Rs = -0.191; \( P < 0.05 \)).

**Receiver-Operating Characteristic Curve Analyses of the CAD and Control Group Subjects**

The area under the curve (AUC) of the AI, AIP, LCI and TyG index were 0.578, 0.570, 0.583 and 0.615, respectively. The
optimal diagnostic cut-off point for AI, AIP, LCI and TyG index were found to be 2.793, 0.029, 13.687 and 9.432, respectively. Surprisingly, the AUC of TyG was higher than that of AI, AIP, and LCI (Table 4).

### Univariate Logistic Regression Analysis of CAD Risk Factors

Univariate associations with CAD were examined for the baseline demographic and clinical characteristics, and increasing age, SBP, TC, TG, LDL-C, AI, AIP, LCI, and TyG were found to have a significant univariate association. The following variables were shown to be statistically significant in the univariate associations: hyperlipidemia, hypertension, diabetes mellitus, ischemic stroke, calcification of the aorta, and ejection fraction <50% (Table 5).

### Multiple Logistic Regression Analysis of CAD Risk Factors

The multivariate logistic regression model showed that age of >60 years, diabetes mellitus, ischemic stroke, SBP of ≥140, ejection fraction of <50%, and TyG of ≥9.432 were independent risk factors for CAD, and the odds ratios of these factors were 2.031 (1.465, 2.815), 1.625 (1.080, 2.445), 1.782 (1.104, 2.877), 1.933 (1.409, 2.651), 3.736 (2.068, 6.748), and 1.876 (1.299, 2.710), respectively (all *P* < 0.05). (Table 6).
and 2 with different adjusted CAD risk factors. The association was consistent after further adjustment for hypertension, diabetes mellitus, and ischemic stroke. When adjusting for ejection fraction of <50%, SBP of ≥140, as well as for hypertension, diabetes mellitus, and ischemic stroke, a necessary association between the TyG index and CAD was predominant (all \( P < 0.05 \), Table 7).

### Discussion

To the best of our knowledge, at present, there is limited information about the TyG index and its association with CAD in postmenopausal women. In the present study, we found that the TyG index was prominently associated with the prevalence of CAD in postmenopausal women. In addition, we also found that the TyG index could predict CAD in women at different menopausal ages.

CAD is the leading cause of morbidity and mortality worldwide.\(^1^5\) In the view of CAD progression, numerous conditions such as postmenopausal status,\(^1^6\) dyslipidaemia, diabetes mellitus have been regarded as high-risk factors.\(^1^7\) For this reason, it is necessary to discover new indicators for predicting CAD in postmenopausal women. In previous studies, the AI was a classical index to measure the degree of atherosclerosis. It is the ratio of a series of risk factors to protective factors involved in the process of atherosclerosis and possesses more clinical value than any other single index.\(^1^8\) Furthermore, \( et al. \) reported that the LCI was higher in acute coronary artery disease patients than in non-CAD patients.\(^1^9\) However, there was no association between AI, LCI, and CAD in postmenopausal women who underwent CAG. AIP is correlated with the atherosclerosis burden.\(^2^0\) In previous study, AIP was positively related to the severity of CAD in elderly individuals and was superior to other lipid profiles.\(^2^1\) So we compared the differences between AIP and TyG for coronary artery disease in postmenopausal women. In addition, Wang \( et al. \) demonstrated that the AIP, as a biomarker, assists in the prevention of CAD in the Chinese population.\(^1^2\) Guo \( et al. \) and Wu \( et al. \) observed that AIP could be a powerful independent predictor of CAD risk in postmenopausal women.\(^1^3,2^2\)

A recent study showed that the TyG index was an inexpensive clinical surrogate marker for IR, which expresses a noticeable underlying disorder contributing to CAD.\(^2^3\) IR causes atherosclerosis due to chronic hyperinsulinemia. Chronic hyperinsulinemia increases the synthesis of very low-density lipoprotein cholesterol, proliferation of vascular smooth muscle cells, transport of LDL cholesterol into arterial smooth muscle cells, and activation of inflammation genes.\(^2^4\) In addition, IR stimulates the progression of CAD by disrupting glucose metabolism, weakening systemic lipid metabolism, and causing endothelial dysfunction.\(^2^5\) There are connections between the TyG index and a fair amount of CAD risk, including arterial stiffness and coronary artery calcification.\(^2^6-2^8\) A series of reports have shown that the TyG index predicts CAD severity\(^2^9\) and CV outcomes in patients with non-ST-segment elevation ACS\(^3^0\) and myocardial infarction.\(^3^1,3^2\) Moreover, the TyG index could be a valuable predictor of adverse CV outcomes after PCI in patients with type 2 diabetes mellitus and ACS.\(^3^3\)

Epidemiological studies have mentioned that the rates of morbidity and mortality due to CAD are markedly higher in postmenopausal women than in premenopausal women.\(^3^3\) The onset of heart disease in women reportedly occurs much later than that in men, and young women suffer less from heart disease due to the vascular protective action of estrogen, which prevents atherosclerosis.\(^3^4,3^5\) Mazzuca found that estrogen binding to estrogen receptors (ERs) could promote vasodilation\(^3^6\) and reduce the response of blood vessels to the progression of atherosclerosis.\(^3^7\) Loss of estrogen early in life might destroy vascular

### Table 3. Correlation Between the Triglyceride Glucose Index and Other Variables.

| Factors                  | Rs    | \( P \)-value |
|--------------------------|-------|---------------|
| Hyperlipidemia           | 0.352 | <0.001        |
| Hypertension             | 0.117 | <0.001        |
| T2DM                     | 0.360 | <0.001        |
| TC                       | 0.230 | <0.001        |
| TG                       | 0.666 | <0.001        |
| LDL                      | 0.080 | 0.019         |
| HDL                      | -0.191| <0.001        |
| AI                       | 0.336 | <0.001        |
| AIP                      | 0.623 | <0.001        |
| LCI                      | 0.518 | <0.001        |
| Blood glucose            | 0.476 | <0.001        |
| Gesini score             | 0.199 | <0.001        |

AI, atherosclerosis index, AIP, Atherogenic index of plasma, HDL-C, high-density lipoprotein cholesterol, LCI, lipoprotein combine index, LDL-C, low-density lipoprotein cholesterol, Rs, ratio scale, T2DM, type-2 diabetes mellitus, TC, total cholesterol, TG, triglyceride, TyG, triglyceride glucose.

### Table 4. The Receiver Operating Characteristic Curves of the Triglyceride Glucose Index, Atherosclerosis Index, Atherogenic Index of Plasma, and Lipoprotein Combine Index.

| Variables | AUC | SE  | \( P \)  | \( 95\% \) CI  | Se (%) | Sp (%) | Cut off |
|-----------|-----|-----|----------|----------------|--------|--------|---------|
| TyG       | 0.615 | 0.020 | <0.001  | 0.577–0.654    | 40.5   | 78.1   | 9.432   |
| AI        | 0.578 | 0.020 | <0.001  | 0.539–0.617    | 56.0   | 60.5   | 2.793   |
| AIP       | 0.570 | 0.020 | 0.001   | 0.530–0.609    | 71.6   | 40.8   | 0.029   |
| LCI       | 0.583 | 0.020 | <0.001  | 0.544–0.622    | 55.6   | 58.3   | 13.687  |

AI: atherosclerosis index, AIP: Atherogenic index of plasma, AUC: area under the curve, CI: confidence interval, LCI: lipoprotein combine index, SE: Standard Error, Se: sensitivity, Sp: specificity, TyG: triglyceride glucose.
function and promote the expression of inflammatory factors at a younger age, which could further damage vascular function.\(^3\)\(^8\) Androgen and sex hormone-binding globulin are also associated with the risk of CV disease.\(^3\)\(^9\) Androgen and sex hormone-binding globulin are associated with both postmenopausal major adverse cardiovascular events\(^4\)\(^0\) and serious CAD risk factors. Menopause is a complex physiological process resulting from the declined production and secretion of ovarian hormones, with increasing age, estradiol levels decrease until menopause, when they are of the same level as seen in men (5-20 pg/ml).\(^4\)\(^1\) Endothelial function provides the mechanisms leading to the development and progression of atherosclerosis with menopause, and coronary endothelial function is impaired by both traditional and non-traditional CAD risk factors that predict future CV events.\(^4\)\(^2\)\(^4\)\(^3\) Lambrinoudaki et al demonstrated that the TyG index was relevant to arterial stiffness, mainly in lean postmenopausal women.\(^4\)\(^4\) In a recent study, Nakagomi et al\(^4\)\(^5\) studied sex differences in the association between the TyG index and arterial stiffness, and in contrast to previous studies, our study showed that the TyG index was of more predictive value for CAD in postmenopausal women than AI, AIP, and LCI. In this retrospective cohort study, we also found that the TyG index was a strong and independent risk factor for CAD in postmenopausal women, providing incremental diagnostic value compared to the well-known, traditional CV risk factors. Additionally, the TyG index is prominently associated with well-known CV risk factors.

Menopause age might be regard as a crucial factor in the risk stratification of CV disease in women.\(^3\)\(^8\) According to the SWAN study’s methodology, using 50 to differentiate premenopause and postmenopause.\(^1\)\(^7\) In our study, we observed a subgroup of CAD patients and found that the TyG index was a crucial predictor of CAD, independent of the traditional CV risk factors, which might support the hypothesis that the TyG index may predict CAD in postmenopausal women.

**Limitations**

Our study has several potential limitations. First, the sample size of the patients in this study was relatively small. We need a larger sample size to compare such parameters between pre- and postmenopausal CAD subjects and subanalyse the CAD group based on disease severity. Second, this was a single-center study, and patient selection may have been subject to bias.

| Variables | OR  | 95% CI       | P    |
|-----------|-----|--------------|------|
| Age > 60(years) | 2.800 | 1.720–4.559  | <0.001 |
| Hyperlipidemia | 1.482 | 1.112–1.976  | 0.007 |
| Hypertension | 2.210 | 1.365–3.581  | 0.001 |
| T2DM | 2.340 | 1.311–4.175  | 0.004 |
| Ischemic stroke | 2.596 | 1.225–5.504  | 0.013 |
| SBP≥140mm Hg | 1.719 | 1.063–2.780  | 0.027 |
| EF<50% | 2.778 | 1.154–6.688  | 0.023 |
| Calcification of the aorta | 2.436 | 1.513–3.920  | <0.001 |
| TC > 5.2 (mmol/L) | 1.733 | 1.234–2.434  | 0.001 |
| TG > 1.7 (mmol/L) | 1.392 | 1.005–1.837  | 0.019 |
| LDL-C > 3.4 (mmol/L) | 1.846 | 1.179–2.890  | 0.007 |
| AI≥2.793 | 1.939 | 1.468–2.561  | <0.001 |
| AIP≥0.029 | 1.527 | 1.157–2.015  | 0.003 |
| ICI≥13.687 | 1.830 | 1.387–2.415  | <0.001 |
| TyG≥9.432 | 2.788 | 1.607–4.835  | <0.001 |

Cl: confidence interval, EF: Ejection fraction, OR: odds ratio, SBP: systolic blood pressure, T2DM: type-2 diabetes mellitus, AI: atherosclerosis index, AIP: Atherogenic index of plasma, CI: confidence interval, EF: Ejection fraction, OR: odds ratio, SBP: systolic blood pressure, T2DM: type-2 diabetes mellitus, TyG: triglyceride glucose.

| Factor | OR  | 95% CI       | P    |
|--------|-----|--------------|------|
| Age > 60(years) | 2.031 | 1.465–2.815  | <0.001 |
| T2DM | 1.625 | 1.080–2.445  | 0.020 |
| Ischemic stroke | 1.782 | 1.104–2.877  | 0.018 |
| SBP≥140(mm Hg) | 1.933 | 1.409–2.651  | <0.001 |
| EF<50% | 3.736 | 2.068–6.748  | <0.001 |
| TyG≥9.432 | 1.876 | 1.299–2.710  | 0.001 |

Cl: confidence interval, EF: Ejection fraction, OR: odds ratio, SBP: systolic blood pressure, T2DM: type-2 diabetes mellitus, TyG: triglyceride glucose.

| Age≥50 (N = 583) | Non-CAD Group (n = 214) | 95% CI       | P    |
|------------------|-------------------------|--------------|------|
| CAD Group (n = 369) | Unadjusted | 2.062 | 1.455–2.923  | <0.001 |
|                 | Model1-adjusted | 1.779 | 1.220–2.595  | 0.003 |
|                 | Model2-adjusted | 1.615 | 1.074–2.431  | 0.021 |

Model 1: Hypertension, T2DM, Ischemic stroke.
Model 2: Model1 + EF<50%, SBP≥140mm Hg.

| Age<50 (N = 286) | CAD Group (n = 169) | 95% CI       | P    |
|------------------|---------------------|--------------|------|
| Non-CAD Group (n = 117) | Unadjusted | 3.230 | 1.823–5.724  | <0.001 |
|                 | Model1-adjusted | 2.602 | 1.415–4.787  | 0.002 |
|                 | Model2-adjusted | 2.882 | 1.484–5.977  | 0.002 |
Conclusion
We found that the TyG index was a strong, independent CV risk factor, providing important, novel insights into the diagnosis of CAD in postmenopausal women. In particular, menopausal age of <50 years was a much stronger predictor than menopausal age >50 years for the diagnosis of CAD.

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Author Contributions
JY.L. contributed to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and drafting of the manuscript. YX.G. contributed to the methodology and validation. HW.B., ZJ.D., Y.Z., and YJ.C. contributed to the data acquisition. YX.G. contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication.

Authors’ Note
Ethical approval to report this case was obtained from the Institutional Review Board of The Affiliated Hospital of Chengde Medical University. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval
The protocol was approved by the Institutional Ethics Committee of the Affiliated Hospital of Chengde Medical University (Number: CYFYLL2022150).

Informed Consent
Participants provided informed consent.

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