# The Correlation of Atherosclerosis and Triglyceride Glucose Index: A Secondary Analysis of a National Cross-Sectional Study of Japanese

**xingping yang**
The First Affiliated Hospital of Guangdong Pharmaceutical University
**Zhao Gao**
Guangdong Sports Science Research Institute
**Xuming Huang**
The First Affiliated Hospital of Guangdong Pharmaceutical University
**Mingxing Zhang**
The First Affiliated Hospital of Guangdong Pharmaceutical University
**Yihua Shi**
The First Affiliated Hospital of Guangdong Pharmaceutical University
**Zhuoming Chen** ( zm_chen120@126.com )
The First Affiliated Hospital of Jinan university （Guangdong）

**Research**

**Keywords:** Triglyceride glucose index, Brachial ankle pulse wave velocity, Atherosclerosis

**Posted Date:** October 8th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-952543/v1

# The correlation of atherosclerosis and triglyceride glucose index: A Secondary Analysis of a National Cross-Sectional Study of Japanese

Xingping Yang,[1,2] Zhao Gao,[3] Xuming Huang,[2] Mingxing Zhang,[2] Yihua Shi,[2] Zhuoming Chen[1,*]

[1] Department of Rehabilitation Medicine, The First Affiliated Hospital, Jinan University, Guangzhou 510630, China.

[2] Department of Rehabilitation Medicine, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou 510080, China.

[3] Guangdong Institute of Sports Science, Guangzhou, China, Guangzhou, 510663, China.

*Corresponding author:

Zhuoming Chen, Department of Rehabilitation Medicine, The First Affiliated Hospital, Jinan University, No.601, West Huang pu Avenue, Guangzhou 510630, China.

Email: zm_chen120@126.com

## Abstract

**Background:** The triglyceride/glucose index (TyG index) has been suggested as a simple and reliable surrogate insulin resistance (IR) marker for years. However, the association between the TyG index and arterial stiffness in adults is controversial. Therefore, we evaluated this relationship, as measured based on the brachial ankle pulse wave velocity (baPWV), in Japanese adults.

**Methods:** This study selected a total of 912 participants from the NAGALA (NAfld in Gifu Area, Longitudinal Analysis) study conducted from 2004 to 2012.The relationship between TyG index and baPWV was estimated through a logistics model. Subgroup analyses by gender, age, body mass index (BMI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), and fatty liver were performed. The formula for TyG index was ln [½fasting triglyceride level (mg/dL) × fasting plasma glucose level (mg/dL)].

**Results:** After adjusting for underlying confounders, a linear relationship between TyG and baPWV was discovered. After adjusting for gender, age, body mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, fatty liver, and eGFR, TyG, as a continuous variable, was related to an increased risk of baPWV (adjusted odds ratio [adj OR], 1.57; 95% confidence interval [95% CI], 1.14–2.18). Compared with the the TyG index in the first tertile, the probabilities of subjects in the third tertile that developed to baPWV were 1.78-fold higher (adj OR 1.78, 95% CI 1.08–2.95; P for trend 0.024). Stable associations were also observed between the TyG index and baPWV in different variables through subgroup analyses.

**Conclusions:** The TyG index was positively and linearly related to subclinical atherosclerosis in Japanese adults and may be valuable as a predicted marker.

**Keywords:** Triglyceride glucose index, Brachial ankle pulse wave velocity, Atherosclerosis

## Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide [1]. Arterial stiffening increases vascular and cardiovascular morbidity [2]. The brachial ankle pulse wave velocity (baPWV) is a candidate measure to estimate arteriosclerosis progression quantitatively noninvasively [2]. In clinical practice, the baPWV values indicate the degree of systemic arteriosclerosis and vascular disorders [3,4].

Insulin resistance (IR) is among the most important risk factors for the development of arterial stiffening [5]. IR may require routine assessment in clinical practice. The homeostasis model assessment of insulin resistance (HOMA-IR) index is the most common method used to evaluate IR in clinical practice [6]. However, this method is complex, invasive, and expensive [7]. Recently, studies have demonstrated a significant correlation between the triglyceride-glucose (TyG) index (calculated as ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2]) and HOMA-IR [8]. The TyG index was adopted to evaluate IR with the sensitivity and specificity of 84.0% and 45.0%, respectively[9]. Thus, the TyG index could serve as a simple and credible surrogate marker of IR [10–11]. Clinical approaches have traditionally been used to measure IR [12–14]. However, the relationship between the TyG index and baPWV is controversial [15-19]. In clinical practice, baPWV is used as a simple and reliable tool to measure arterial stiffness because of its high reproducibility [20-24].

Therefore, the present study evaluated the association between the TyG index and arterial stiffness measured using baPWV in a relatively healthy Japanese population.

## Materials and Methods

### Data Source

The secondary use of datasets was explored through the DATADRYAD database (http://www.Datadryad.org/), which provides free access to the original research data (Fukuda Takuya et al. (2014)) (dataset: https://doi.org/10.5061/dryad.m484p). The database provided messages on variables including: gender, age, body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), alanine aminotransferase (ALT),aspartate aminotransferase (AST), gamma-glutamyl transferase (γGTP), fasting plasma glucose (FOG), uric acid (UC), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), ankle-brachial index (ABI,) brachial-ankle pulse wave velocity (baPWV).

### Study Population

A physical examination research project from the Murakami Memorial Hospital (Gifu, Japan) was performed aiming for the early detection of chronic diseases and evaluation of their underlying risk factors to improve public health.

With the database, Fukuda et al. [25] reported that serum γGTP affected the risk of developing atherosclerosis in women. The participants underwent an examination between March 2004 and December 2012. A total of 1,445 participants (897 men and 548 women) were chosen based on the following exclusion criteria: (1) taking exogenous hormone supplementation at baseline; (2) hepatitis B(HBV) or C virus (HCV) infection; (3) fetation; and (4) ABI <0.95. A total of 912 participants (592 men and 320 women) were included in the full analysis (Figure 1). The study was approved by the ethics committee of Murakami Memorial Hospital, and all participants provided informed consent before entering the research project.

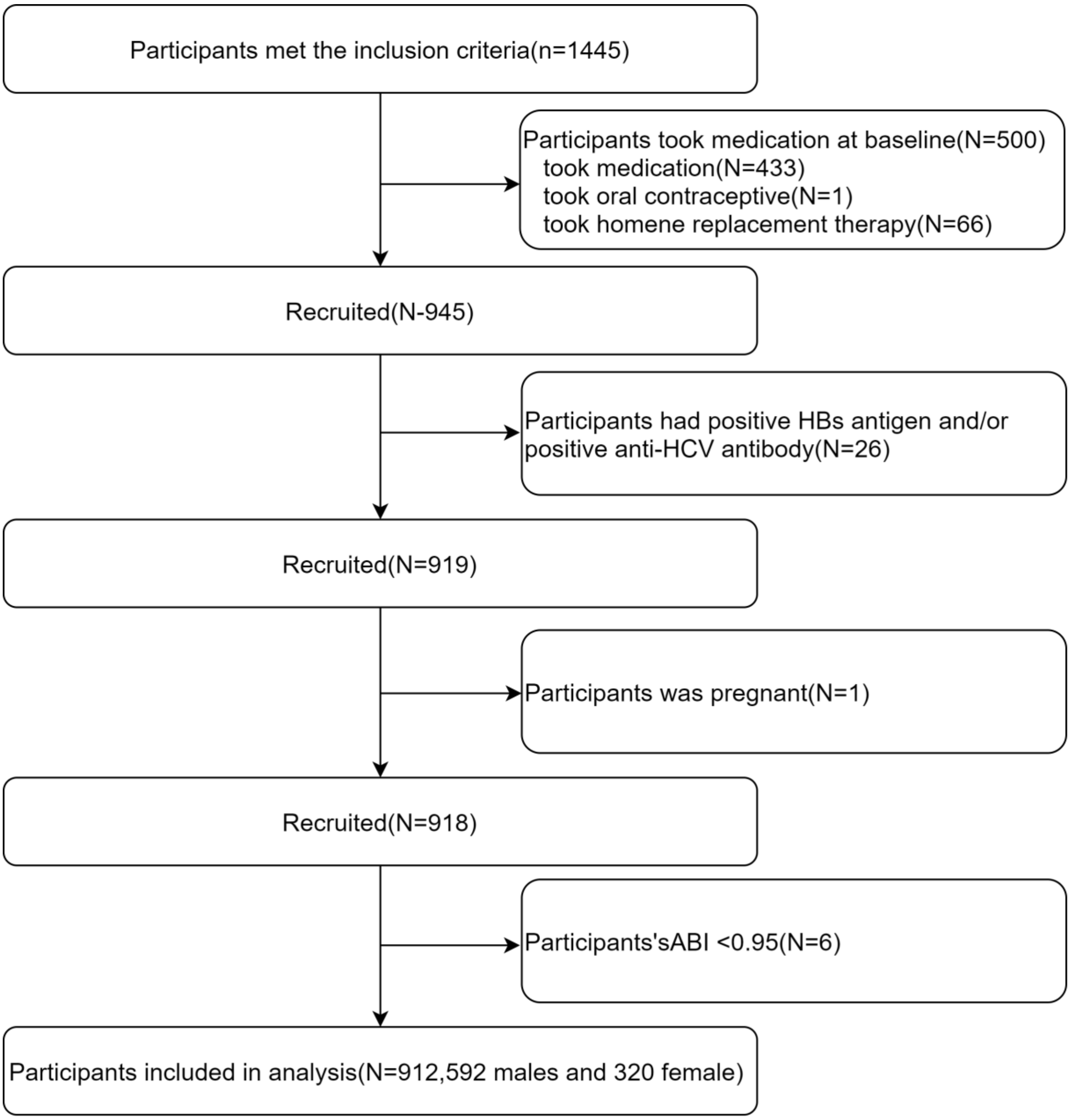


Figure 1 Flow diagram of the screening and enrollment of study participants.
Abbreviations:HBs,hepatitis B surface;HCV,hepatitis C virus;ABI,ankle-brachial index.

**Data Collection and Measurements**

The database contains information on participants' demographic characteristics, biochemical indices, abdominal ultrasonography, baPWV, ABI, and lifestyle factors. Taken as an example, the type of alcohol consumed and the average weekly amount of alcohol consumed during the latest month were recorded and then classified into four categories: no or minimal (<40 g/week), light (40-140 g/week), moderate (140-280 g/week), or heavy (> 280 g/week) [26]. Likewise, the participants were divided into never smokers, former smokers, or current smokers. Exercise that lasts long enough to cause sweating for more than 1 week, such as jogging, cycling, and swimming, is perceived to be normal [27]. Abdominal ultrasound detection together with artificial diagnosis by gastroenterologists were used for confirmation of suffering from fatty liver. Among the four criteria (liver/kidney echo contrast, liver luminance, deep attenuation, and vascular obscurity), subjects with liver brightness and liver/kidney contrast are judged with fatty liver disease [28]. After rested in the supine position for 5 minutes, the baPWV and ABI of the patient were measured using an automatic waveform analyzer (Colin Medical Technology, Komaki, Japan) in a room with a temperature of about 25°C. Electrocardiogram (ECG) electrodes are placed on both wrists and the heart sound microphone is placed on the left edge of the sternum edge. The cuffs are wrapped around the arms and ankles connecting to a plethysmograph sensor that detects the form of volume pulses and an oscillating pressure sensor that determines blood pressure.

The path length from the suprasternal notch to the humerus (Lb) and the suprasternal notch to the ankle joint (La) were determined according to the height of the subject, with the delay time from the ascending point of the brachial waveform to the ascending point of the ankle waveform (DTba) automatically determined. baPWV was assessed with the pulse wave propagation distance (Lb-La) modified with the pulse wave propagation time (DTba) divided into cm/s. [29] The reported inter-observer and inter-observer coefficients of variation were 10% ($r=0.87$, $p<0.01$) and 8.4% ($r=0.98$, $p<0.01$), respectively. The eGFR was evaluated through the formula of the Japanese Society of Nephrology (Equation 1):

$$eGFR=194\times Cr-1.094\times age-0.287 \text{ (mL/min/1.73 m}^2\text{)} \quad (1)$$

for men, and was multiplied by a correction factor of 0.739 for women [30]. The formula for the TyG index was as shown in Equation 2:

$$\ln [\tfrac{1}{2}\text{fasting triglyceride level (mg/dL)} \times \text{fasting plasma glucose (FPG)(mg/dL)}][31]. \quad (2)$$

## Statistical Analysis

Normal and skew distributions of continuous variables are expressed as mean values with standard deviation (SD) and median values with inter-quaternary interval (IQRS), respectively. Classification variables are expressed in terms of frequency and percentage. We used the chi-square test, one-way analysis of variance, or Kruskal-Wallis test to examine the statistical differences between groups stratified by the tertiles of the TyG index. Univariate and multivariate logistic proportional hazard model was used to examine the relationship between the TyG index and the risk of baPWV. Three models were employed: model 1 as a crude model: univariate; model 2 modified with age and gender; and model 3, adjusted for model 2 plus BMI, SBP, DBP, HDL-C, fatty liver, and eGFR. In these models, the median values in each tertile of the TyG index were used for the operation of linear trend tests. The logistic relationship between the TyG and baPWV was estimated using logistic regression with restricted cubic splines. For identification of modifications and interactions, subgroups analyses were developed with stratified linear regression models and the likelihood ratio test (LRT) regarding gender, age (<55 or ≥55 years), BMI (<25 or ≥25 kg/m2), TC (<208 or ≥208 mg/dL), LDL-C (<126 or ≥126 mg/dL), eGFR (<60 or≥ 60 mL/min/1.73 m2), and fatty liver (none, moderate, or severe). All analyses were performed using the statistical software packages in R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.1. Differences with P-values <0.05 were considered statistically significant.

## Results

### Baseline Characteristics of Selected Participants

This cross-sectional study included a total of 912 participants. Table 1 shows the baseline characteristics of the participants according to the tertiles of the TyG index. The mean age of the 912 participants was 51.1 ± 9.6 years and 64.9% were male. Participants in the third group of TyG (Q3) had higher TyG values; were more likely to be male; have higher BMI, SBP, DBP, FBG, uric acid, AST, ALT, γGTP, TC, TG, and LDL-C levels; higher eGFR; were more likely to be current smokers, consume >280 g/week alcohol, exercise <1/week, more likely to have moderate or severe fatty liver, and higher baPWV compared to the other groups (Q1–2). Participants in the third group of TyG (Q3) had lower HDL-C and eGFR values and were more likely to be none or past smokers, consume 0–40 g/week alcohol, exercise ≥1/week, and have no fatty liver compared to the other groups (Q1–2).

Table 1 Baseline characteristics of the study participants sorted by tertiles of TyG.

| | All participants | Q1(<7.96) | Q2(7.96~8.57) | Q3(>8.57) | P value |
|---|---|---|---|---|---|
| Participants(n) | 912 | 304 | 304 | 304 | |
| TyG index | 8.3 ± 0.7 | 7.6 ± 0.3 | 8.3 ± 0.2 | 9.0 ± 0.4 | < 0.001 |
| Sex (n (%)) | | | | | < 0.001 |
| Males | 592 (64.9) | 128 (42.1) | 203 (66.8) | 261 (85.9) | |
| Females | 320 (35.1) | 176 (57.9) | 101 (33.2) | 43 (14.1) | |
| Age(years) | 51.1 ± 9.6 | 50.7 ± 10.1 | 51.6 ± 9.4 | 51.1 ± 9.2 | 0.493 |

| | | | | | |
|---|---|---|---|---|---|
| BMI(($kg/m^2$) | 23.1 ± 3.1 | 21.8 ± 2.5 | 23.1 ± 3.3 | 24.5 ± 3.0 | < 0.001 |
| SBP (mmHg) | 120.2 ± 15.0 | 114.7 ± 13.9 | 120.9 ± 15.4 | 125.1 ± 13.7 | < 0.001 |
| DBP (mmHg) | 76.1 ± 10.0 | 72.0 ± 9.4 | 76.4 ± 10.2 | 80.0 ± 8.7 | < 0.001 |
| FBG (mg/dL) | 98.1 ± 14.1 | 92.2 ± 7.6 | 98.0 ± 10.4 | 104.0 ± 18.9 | < 0.001 |
| Uric acid(mg/dL) | 5.3 ± 1.4 | 4.6 ± 1.3 | 5.2 ± 1.3 | 6.0 ± 1.3 | < 0.001 |
| AST(IU/L) | 19.0 (16.0, 23.0) | 19.0 (16.0, 22.0) | 19.0 (16.0, 23.0) | 21.0 (17.0, 26.0) | < 0.001 |
| ALT(IU/L) | 19.0 (14.0, 26.0) | 16.0 (12.8, 20.0) | 18.0 (14.0, 23.2) | 23.0 (18.0, 34.0) | < 0.001 |
| γGTP(IU/L) | 19.0 (14.0, 28.0) | 14.0 (11.0, 19.0) | 18.5 (14.0, 26.0) | 25.0 (18.0, 43.0) | < 0.001 |
| TC (mg/dL) | 209.8 ± 35.9 | 198.4 ± 33.9 | 208.0 ± 33.7 | 223.1 ± 35.8 | < 0.001 |
| TG (mg/dL) | 99.9 ± 74.9 | 44.2 ± 12.3 | 81.8 ± 14.8 | 173.6 ± 87.3 | < 0.001 |
| HDL-C(mg/dL) | 53.5 ± 14.6 | 62.0 ± 14.0 | 53.4 ± 13.1 | 45.2 ± 11.4 | < 0.001 |
| LDL-C(mg/dL) | 128.1 ± 31.7 | 116.6 ± 29.2 | 130.4 ± 28.7 | 137.1 ± 33.5 | < 0.001 |
| eGFR(mL/min/1.73$m^2$) | 70.4 ± 12.0 | 73.5 ± 13.0 | 70.2 ± 11.4 | 67.6 ± 11.0 | < 0.001 |
| Current smoker (n (%)) | | | | | < 0.001 |
| None or past | 715 (78.4) | 263 (86.5) | 233 (76.6) | 219 (72) | |
| Current | 197 (21.6) | 41 (13.5) | 71 (23.4) | 85 (28) | |
| Alcohol group (n (%)) | | | | | < 0.001 |
| 0-40g/week | 594 (65.1) | 225 (74) | 194 (63.8) | 175 (57.6) | |
| 40-140g/week | 150 (16.4) | 42 (13.8) | 59 (19.4) | 49 (16.1) | |
| 140-280g/week | 88 (9.6) | 23 (7.6) | 33 (10.9) | 32 (10.5) | |
| more than 280g/week | 80 (8.8) | 14 (4.6) | 18 (5.9) | 48 (15.8) | |
| Regular exercise (n (%)) | | | | | 0.008 |
| ＜1/week | 735 (80.6) | 229 (75.3) | 247 (81.2) | 259 (85.2) | |
| ≥1/week | 177 (19.4) | 75 (24.7) | 57 (18.8) | 45 (14.8) | |
| Fatty liver (n (%)) | | | | | < 0.001 |
| None | 647 (70.9) | 274 (90.1) | 229 (75.3) | 144 (47.4) | |
| Moderate or severe | 265 (29.1) | 30 (9.9) | 75 (24.7) | 160 (52.6) | |
| Menopausal state (n (%)) | | | | | 0.071 |
| Menopausal | 138 (43.1) | 86 (48.9) | 36 (35.6) | 16 (37.2) | |
| Postmenopausal | 182 (56.9) | 90 (51.1) | 65 (64.4) | 27 (62.8) | |
| ABI | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.2 ± 0.1 | 0.001 |
| baPWV(cm/s) | 1415.8 ± 246.3 | 1350.7 ± 226.1 | 1424.5 ± 234.6 | 1472.1 ± 262.0 | < 0.001 |

Notes: Values are expressed as mean ± standard deviation or n (%). Abbreviations: TyG index, triglyceride glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, gamma-glutamyl transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; ABI, ankle-brachial index; baPWV, brachial to ankle pulse wave velocity.

**Univariate Analysis for baPWV**

Table 2 presents the univariate analysis results of the relationship between risk factors and baPWV. The univariate logistics model showed that BMI, HDL-C level, current smoker, regular exercise, and ABI were not associated with baPWV. In contrast, gender, age, SBP, DBP, FBG, uric acid, AST, ALT, γGTP, TC, TG, TyG, and LDL-C levels, eGFR, alcohol use, fatty liver, and menopausal state were positively related to baPWV.

Table 2 Univariate analysis of baPWV.

| | OR (95%CI) | P value |
|---|---|---|
| Sex (n (%)) | | 0.035 |
| Males | Ref. | |
| Females | 0.74 (0.56,0.98) | |
| Age(year) | 1.10 (1.09,1.12) | < 0.001 |
| BMI ($kg/m^2$) | 1.04 (1.00,1.08) | 0.069 |
| SBP (mmHg) | 1.07 (1.06,1.09) | < 0.001 |
| DBP (mmHg | 1.10 (1.09,1.12) | < 0.001 |
| FBG (mg/dL) | 1.04 (1.02,1.05) | < 0.001 |
| Uric acid(mg/dL) | 1.14 (1.04,1.26) | 0.007 |
| AST(IU/L) | 1.03 (1.01,1.04) | 0.004 |
| ALT(IU/L) | 1.01 (1.00,1.02) | 0.024 |
| γGTP(IU/L) | 1.01 (1.00,1.02) | 0.001 |
| TC (mg/dL) | 1.01(1.00,1.01) | < 0.001 |
| TG (mg/dL) | 1.00 (1.00,1.01) | < 0.001 |
| TyG index | 1.84 (1.50,2.27) | < 0.001 |
| HDL-C(mg/dL) | 0.99 (0.99,1.00) | 0.249 |
| LDL-C(mg/dL) | 1.01 (1.00,1.01) | 0.012 |
| eGFR($mL/min/1.73m^2$) | 0.96 (0.94,0.97) | < 0.001 |
| Current smoker (n (%)) | | 0.467 |
| None or past | Ref. | |
| Current | 0.89 (0.65,1.22) | |
| Alcohol group (n (%)) | | 0.08 |
| 0-40g/week | Ref. | |
| 40-140g/week | 0.98 (0.68,1.40) | 0.896 |

| | | |
|---|---|---|
| 140-280g/week | 1.35 (0.86,2.11) | 0.192 |
| more than 280g/week | 1.73 (1.08,2.77) | 0.022 |
| Regular exercise (n (%)) | | 0.814 |
| ＜1/week | Ref. | |
| ≥1/week | 1.04 (0.75,1.45) | |
| Fatty liver (n (%)) | | < 0.001 |
| None | Ref. | |
| Moderate or severe | 1.92 (1.44,2.56) | |
| Menopausal state (n (%)) | | < 0.001 |
| Menopausal | Ref. | |
| Postmenopausal | 5.37 (3.20,9.01) | < 0.001 |
| ABI | 3.20 (0.49,20.72) | 0.222 |

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, gamma-glutamyl transferase; TC, total cholesterol; TG, triglyceride; TyG index, triglyceride glucose index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index; baPWV, brachial to ankle pulse wave velocity; CI, confidence interval.

## Unadjusted and Adjusted Logistics Models

Linear logistic models were adopted to evaluate the independent relationship between the TyG index and baPWV (univariate and multivariate logistics models). Table 3 presents the effect sizes (ORs) and 95% confidence intervals (95% CIs). In the crude model (model 1), a one-unit increase in the TyG index was related to an 84% higher risk of incident increased baPWV (OR 1.84, 95% CI 1.50–2.27). In model 2, a one-unit increase in TyG index increased the risk of evolving baPWV by 91% (OR 1.91, 95% CI 1.49–2.44) after adjusting for gender and age. In model 3, each one-unit increase in TyG index was a 55% higher risk of incident increased baPWV (OR 1.57, 95% CI 1.14-2.18). For sensitivity analysis, we transformed the TyG index into a categorical variable (tertile of TyG index). The results showed that the P-value for the trend of TyG index as categorical variables was concomitant with the result of the TyG index as continuous variables in the different models.

Table 3 Relationship between TyG and baPWV in different models.

| | Model1 | P value | Model2 | P value | Model3 | P value |
|---|---|---|---|---|---|---|
| TyG index | 1.84 (1.50,2.27) | < 0.001 | 1.91 (1.49,2.44) | < 0.001 | 1.57 (1.14,2.18) | 0.006 |

| | | | | | | |
|---|---|---|---|---|---|---|
| TyG index | | | | | | |
| Q1(<7.96) | Ref. | | Ref. | | Ref. | |
| Q2(7.96~8.57) | 1.74 (1.25,2.42) | < 0.001 | 1.66 (1.15,2.41) | 0.196 | 1.43 (0.93,2.19) | 0.101 |
| Q3(>8.57) | 2.42 (1.74,3.36) | < 0.001 | 2.50 (1.70,3.71) | < 0.001 | 1.78 (1.08,2.95) | 0.024 |
| P for trend | | < 0.001 | | < 0.001 | | 0.024 |

Model 1 was not adjusted. Model 2 was adjusted for gender and age. Model 3 was adjusted for gender, age, BMI, SBP, DBP, HDL-C, fatty liver, eGFR. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose index; baPWV, brachial to ankle pulse wave velocity; CI, confidence interval.

**Threshold Effect Analysis of the TyG on Incident baPWV**

We used a logistics regression model with cubic spline function to assess the correlation of TyG index and baPWV (Figure 2). After adjusting for gender, age, BMI, SBP, DBP, TC, LDL-C, fatty liver, eGFR, TyG index and baPWV showed positive linear correlation.

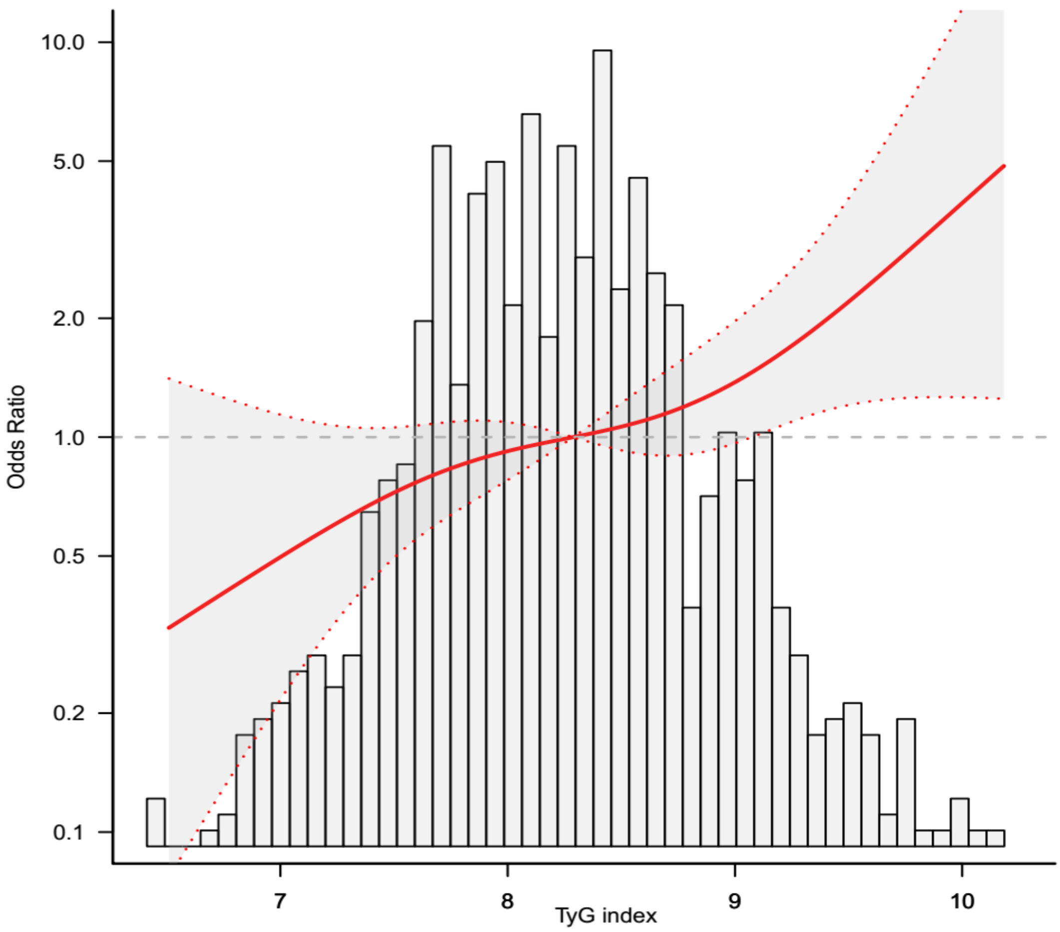


Figure 2 The relations between TyG index and baPWV

The grey histograms represent the distributions between variables. The solid red curve indicates the smoothing curve fit between variables. The grey zone indicates the 95% confidence interval of the curve fit. Data was adjusted for gender, age, BMI, SBP, DBP, HDL-C, fatty liver, eGFR. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose index; baPWV, brachial to ankle pulse wave velocity; CI, confidence interval.

## Subgroup Analyses

The results of subgroup analyses of the association between the TyG index and baPWV are indicated in Figure 3. The participants were split into subgroups and the results indicated that there exists a steady relationship between TyG and incident baPWV in different subgroups.

| | <1400cm/s(n) | ≥1400cm/s(n(%)) | adj OR(95%CI) | *P* value | *P* for interaction |
|---|---|---|---|---|---|
| Sex | | | | | 0.693 |
| Males | 592 | 278 (47.0) | 1.50 (1.07,2.10) | 0.020 | |
| Females | 320 | 127 (39.7) | 1.69 (1.05,2.72) | 0.030 | |
| BMI (kg/m$^2$) | | | | | 0.988 |
| <25 | 690 | 301 (43.6) | 1.62 (1.17,2.24) | 0.004 | |
| ≥25 | 222 | 104 (46.8) | 1.71 (0.99,2.98) | 0.057 | |
| Age (years) | | | | | 0.714 |
| <55 | 552 | 173 (31.3) | 1.56 (1.08,2.24) | 0.017 | |
| ≥ 55 | 360 | 232 (64.4) | 1.59 (0.97,2.59) | 0.065 | |
| TC (mg/dL) | | | | | 0.239 |
| <208 | 451 | 174 (38.6) | 1.53 (1.02,2.30) | 0.039 | |
| ≥208 | 461 | 231 (50.1) | 1.22 (0.81,1.83) | 0.352 | |
| LDL−C (mg/dL) | | | | | 0.489 |
| <126 | 445 | 182 (40.9) | 1.59 (1.11,2.27) | 0.011 | |
| ≥126 | 467 | 223 (47.8) | 1.27 (0.81,1.99) | 0.290 | |
| eGFR (mL/min/1.73m$^2$) | | | | | 0.699 |
| <60 | 172 | 99 (57.6) | 1.37 (0.75,2.50) | 0.310 | |
| ≥60 | 740 | 306 (41.4) | 1.43 (1.05,1.95) | 0.022 | |
| Fatty liver | | | | | 0.443 |
| None | 647 | 257 (39.7) | 1.67 (1.19,2.35) | 0.003 | |
| Moderate or severe | 265 | 148 (55.8) | 1.12 (0.68,1.84) | 0.659 | |

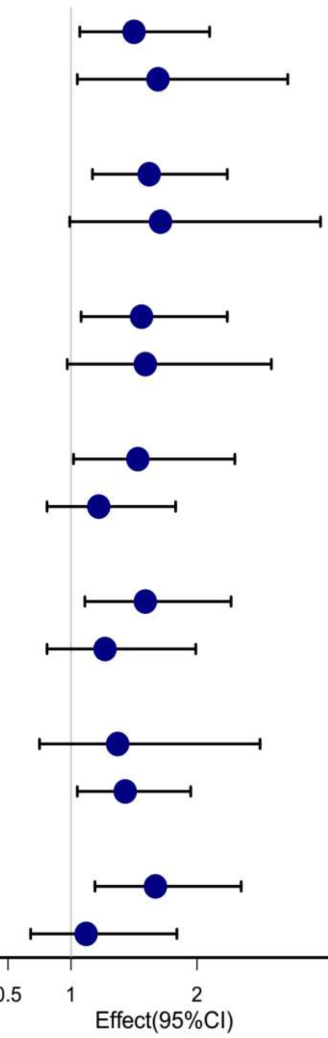


Figure 3 Subgroup analyses of the association between TyG index and baPWV.

Notes: Adjusted for gender, age, BMI, SBP, DBP, HDL-C, fatty liver, and eGFR. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol;

eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose index; baPWV, brachial to ankle pulse wave velocity; CI, confidence interval.

## Discussion

After controlling for covariates, the results of our population-based cross-sectional study showed a positive and linear association between the TyG index and baPWV as a marker of arterial stiffness in a Japanese population. The results were stable in subgroups according to gender, age, BMI, TC, LDLC, eGFR, and fatty liver. Our findings provide evidence of the substantial role of IR in subclinical atherosclerosis in the general population.

Several studies have reported the relationship between the TyG index and baPWV. In a 1-year follow-up study of 366 patients, An et al. reported that IR was an independent predictor of atherosclerotic plaque progression in patients with coronary heart disease [32]. A cross-sectional study in China of 823 participants who underwent echocardiographic examination found that the TyG index was not significantly associated with baPWV [33]. In contrast, we found that the TyG index was significantly positively correlated with subclinical atherosclerosis as measured by baPWV. In another cross-sectional study, Li et al. showed that the TyG index was independently and positively associated with baPWV ($\beta$ = 1.02; 95% confidence interval [CI] 0.83–1.20) in hypertensive patients. The participants in the highest TyG quartile had a higher risk of increased baPWV (OR,2.12; 95% CI,1.80–2.50) after adjusting for age, sex, education, BMI, waist circumference, physical activity, current smoking, current drinking, SBP, DBP, levels of serum uric acid, serum homocysteine, HDL-C, and LDL-C, eGFR, self-reported diabetes, antihypertensive drug use and antiplatelet drug use [34]. Moreover, in a cross-sectional including 2,818 Japanese participants, the TyG index showed a good correlation with HOMA-IR (men: r=0.47, women: r=0 multivariate linear regression analysis (men: $\beta$=0.11, women: $\beta$ =0.14) and especially with increased high baPWV (men: OR 1.27, 95% CI 1.07–1.49; women: OR 1.53, 95% CI 1.16–2.02) in multivariate linear regression analyses. The associations were stronger in women than in men [35]. However, our study results showed no sex differences and the trends did not differ by sex in the subgroup analysis (men: adjusted OR 1.50, 95% CI 1.07–2.10; women: adjusted OR 1.69, 95% CI 1.05–2.72; P for interaction=0.693).In another recent study of 2830 elderly Chinese individuals, Zhao et al. reported that the TyG index was significantly associated with arterial stiffness as measured by carotid-femoral pulse wave velocity (cfPWV; OR 1.86, 95% CI 1.37–2.53), baPWV (OR 1.39, 95% CI 1.05–1.84) for macrovascular arteriosclerosis and CKD (OR 1.67, 95% CI 1.10–1.50) for microvascular arteriosclerosis after adjusting for age, sex, BMI, waist circumference, smoking habit, hypertension, family history of premature CVD, diabetes, HDL-C, LDL-C, insulin therapy, and statin therapy [36]. However, we found no significant interaction effect of eGFR and TyG in the subgroup analysis (eGFR <60 mL/min/1.73 m2, adjusted OR 1.37, 95% CI 0.75–2.50; eGFR ≥60 mL/min/1.73 m2, adjusted OR 1.43, 95% CI 1.05–1.95, P for interaction=0.699). In a study of 3,587 Korean adults, Lee et al. reported that participants in the highest TyG quartile had a higher risk of arterial stiffness as assessed by baPWV (men: OR 2.92; 95% CI 1.92–4.44; women: OR 1.84; 95% CI 1.15–2.96) after adjusting for multiple risk factors [37]. These findings were consistent with the results of our study. In addition, in a study of 2,560 relatively healthy Korean subjects, Won et al. also reported a positive association between TyG index and arterial stiffness ($\beta$= 0.158), consistent with our results. Moreover, our inclusion criteria were more stringent, with an ABI<0.95 to exclude patients with preexisting arteriosclerosis. Furthermore, our stepwise regression analysis showed that TC and LDL-C might influence the correlation between the TyG index and baPWV. Therefore, we divided TC and LDL-C into two parts for subgroup analysis. The results showed that TC, LDL-C, and TyG index had no interaction effect on baPWV (TC <208 mg/dL: adjusted OR 1.53, 95% CI 1.02–2.30; TC ≥208 mg/dL: adjusted OR 1.22, 95% CI 0.81–1.83, P for interaction=0.239; LDL-C <126 mg/dL adjusted OR 1.59, 95% CI 1.11–2.27; LDL-C≥126 mg/dL. adjusted OR 1.27, 95% CI 0.81–1.99; P for interaction=0.489). Therefore, the positive association between TyG index and baPWV was robust.

The strengths of this study include: (1) our study had stricter cohort criteria for inclusion by excluding patients with symptomatic coronary artery disease (CAD) and included a broad age range (24–84 years), not merely older persons, as well as ABI<0.95. (2) This study is the first to report the relationship between the TyG index and baPWV in Japan. (3) We analyse the TyG index as both continuous and categorical variables to reduce the result contingency and increase the result robustness. (4) In subgroup analysis, likelihood ratio tests and hierarchical linear regression model were applied to confirm modifications and interactions. The results were stable in different subgroups.

This study has several additional limitations. First, the cross-sectional design meant that we could not exclude causal relationships based on the findings. Second, the analysis did not include the HOMA-IR index, although this index is the gold standard method for measuring IR. However, previous studies demonstrated a close relationship between HOMA-IR and the

TyG index [39]. In addition, the TyG index is more cost-effective and easier to calculate in routine clinical practice as previous reported[40].

## Conclusions

To summarize, the results of this study showed an independent association between the TyG index and arterial stiffness, as measured by baPWV, in a relatively healthy Japanese population after adjusting for conventional factors. These results suggest that IR plays a substantial role in subclinical atherosclerosis and might be an important target for preventing major CV disease.

## Data Availability

The original data are freely downloaded at http://www.Datadryad.org/.

## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.


## Funding Statement

This work was supported by the Specific Research Foundation of Sport of Guangdong Province [No. GDSS2020N80, GDSS2020M006], the Clinical Research Projects of the First Affiliated Hospital of Guangzhou Pharmaceutical University (No. TZDXZX201909) and the Key Realm R&D Program of Guangdong Province [No.2018B030332001].

## Acknowledgments

The authors are grateful for the suggestions and comments from Jie Liu, PhD (Department of Vascular and Endovascular Surgery, Chinese PLA General Hospital) for reviewing the manuscript, which have been very helpful in improving the manuscript.


## References


[1] Naghavi M., Abajobir AA., Abbafati C., et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global

Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-1210. doi: 10.1016/S0140-6736(17)32152-9.

[2] Wang L, Zhi F, Gao B, et al. Association between lipid profiles and arterial stiffness: A secondary analysis based on a cross-sectional study. J Int Med Res. 2020;48(7):300060520938188. doi: 10.1177/0300060520938188.

[3] Nagasato D., Tabuchi H., Masumoto H., et al. Prediction of age and brachial-ankle pulse-wave velocity using ultra-wide-field pseudo-color images by deep learning. Sci Rep. 2020;10(1):19369. doi: 10.1038/s41598-020-76513-4.

[4] Tsuchikura S., Shoji T., Kimoto E., et al. Brachial-ankle pulse wave velocity as an index of central arterial stiffness. J Atheroscler Thromb. 2010;17(6):658-65. doi: 10.5551/jat.3616.

[5] Zhao S, Yu S, Chi C, et al. Association between macro- and microvascular damage and the triglyceride glucose index in community-dwelling elderly individuals: the Northern Shanghai Study. Cardiovasc Diabetol. 2019;18(1):95. doi: 10.1186/s12933-019-0898-x.

[6] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment—insulin resistance and beta-cell function from fasting plasma-glucose and insulin concentrations in man. Diabetologia.1985;28(7):412-9. doi: 10.1007/BF00280883.

[7] Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care. 2000;23(1):57-63. doi: 10.2337/diacare.23.1.57.

[8] Unger G, Benozzi SF, Perruzza F, et al. Triglycerides, and glucose index: a useful indicator of insulin resistance. Endocrinol Nutr.2014;61(10):533-40. English, Spanish. doi: 10.1016/j.endonu.2014.06.009.

[9] Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008;6(4):299-304. doi: 10.1089/met.2008.0034.

[10] Nor NSM, Lee S, Bacha F, et al. Triglyceride glucose index as a surrogate measure of insulin sensitivity in obese adolescents with normoglycemia, prediabetes, and type 2 diabetes mellitus: comparison with the hyperinsulinemic-euglycemic clamp. Pediatr Diabetes. 2016;17(6):458-65. doi: 10.1111/pedi.12303.

[11] Kang B, Yang Y, Lee EY, et al. Triglycerides/ glucose index is a useful surrogate marker of insulin resistance among adolescents. Int J Obesity. 201;41(5):789-792. doi: 10.1038/ijo.2017.14.

[12] Zhang K, Chen Y, Liu L, et al. The Triglycerides and Glucose Index rather than HOMA-IR is more associated with Hypogonadism in Chinese men. Sci Rep. 2017;7(1):15874. doi: 10.1038/s41598-017-16108-8.

[13] Locateli JC, Lopes WA, Simões CF, et al. Triglyceride/glucose index is a reliable alternative marker for insulin resistance in South American overweight and obese children and adolescents. J Pediatr Endocrinol Metab. 2019;32(10):1163-1170. doi: 10.1515/jpem-2019-0037.

[14] Cho YR, Ann SH, Won KB, et al. Association between insulin resistance, hyperglycemia, and coronary artery disease according to the presence of diabetes. Sci Rep. 2019;9(1):6129. doi: 10.1038/s41598-019-42700-1.

[15] Chiu TH, Tsai HJ, Chiou HC, et al. A high triglyceride-glucose index is associated with left ventricular dysfunction and atherosclerosis. Int J Med Sci. 2021;18(4):1051-1057. doi: 10.7150/ijms.53920.

[16] Alizargar J, Bai CH, Hsieh NC, et al. Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. Cardiovasc Diabetol. 2020;19(1):8. doi: 10.1186/s12933-019-0982-2.

[17] Li M, Zhan A, Huang X, et al. Positive association between triglyceride glucose index and arterial stiffness in hypertensive patients: the China H-type Hypertension Registry Study. Cardiovasc Diabetol. 2020;19(1):139. doi: 10.1186/s12933-020-01124-2.

[18] Nakagomi A, Sunami Y, Kawasaki Y, et al. Sex difference in the association between surrogate markers of insulin resistance and arterial stiffness. J Diabetes Complications. 2020;34(6):107442. doi: 10.1016/j.jdiacomp.2019.107442.

[19] Lambrinoudaki I, Kazani MV, Armeni E, et al. The TyG Index as a Marker of Subclinical Atherosclerosis and Arterial Stiffness in Lean and Overweight Postmenopausal Women. Heart Lung Circ. 2018;27(6):716-724. doi: 10.1016/j.hlc.2017.05.142.

[20] Munakata M. Brachial-ankle pulse wave velocity in the measurement of arterial stiffness: recent evidence and clinical applications. Curr Hypertens Rev. 2014;10(1):49-57. doi: 10.2174/157340211001141111160957.

[21] Huang J, Chen Z, Yuan J, et al. Association Between Body Mass Index (BMI) and Brachial-Ankle Pulse Wave Velocity (baPWV) in Males with Hypertension: A Community-Based Cross-Section Study in North China. Med Sci Monit. 2019; 25:5241-5257. doi: 10.12659/MSM.914881.

[22] Liu Y, Zhao P, Cheng M, et al. AST to ALT ratio and arterial stiffness in non-fatty liver Japanese population: a secondary analysis based on a cross-sectional study. Lipids Health Dis. 2018;17(1):275. doi: 10.1186/s12944-018-0920-4.

[23] Wu S, Jin C, Li S, et al. Aging, Arterial Stiffness, and Blood Pressure Association in Chinese Adults. Hypertension. 2019 Apr;73(4):893-899. doi: 10.1161/HYPERTENSIONAHA.118.12396.

[24] Zheng M, Zhang X, Chen S, et al. Arterial Stiffness Preceding Diabetes: A Longitudinal Study. Circ Res. 2020;127(12):1491-1498. doi: 10.1161/CIRCRESAHA.120.317950.

[25] Fukuda T., Hamaguchi M., Kojima T., et al. Association between serum γ-glutamyl transpeptidase and atherosclerosis: a population-based cross-sectional study. BMJ Open. 2014;4(10): e005413. doi: 10.1136/bmjopen-2014-005413.

[26] Hashimoto Y., Hamaguchi M., Kojima T., et al. Modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. J Gastroenterol Hepatol. 2015 Mar;30(3):546-52. doi: 10.1111/jgh.12786.

[27] Ryu S., Chang Y., Kim DI., et al. gamma-Glutamyl transferase as a predictor of chronic kidney disease in nonhypertensive and nondiabetic Korean men. Clin Chem. 2007;53(1):71-7. doi: 10.1373/clinchem.2006.078980.

[28] Hamaguchi M., Kojima T., Itoh Y., et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol. 2007;102(12):2708-15. doi: 10.1111/j.1572-0241.2007.01526. x.

[29] Yamashina A., Tomiyama H., Takeda K., et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res. 2002;25(3):359-64. doi: 10.1291/hypres.25.359.

[30] Matsuo S., Imai E., Horio M., et al; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982-92. doi: 10.1053/j.ajkd.2008.12.034.

[31] Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008;6(4):299-304. doi: 10.1089/met.2008.0034.

[32] An X, Yu D, Zhang R, et al. Insulin resistance predicts progression of de novo atherosclerotic plaques in patients with coronary heart disease: a one-year follow-up study. Cardiovasc Diabetol. 2012; 11:71. doi: 10.1186/1475-2840-11-71.

[33] Chiu TH, Tsai HJ, Chiou HC, et al. A high triglyceride-glucose index is associated with left ventricular dysfunction and atherosclerosis. Int J Med Sci. 2021;18(4):1051-1057. doi: 10.7150/ijms.53920.

[34] Li M, Zhan A, Huang X, et al. Positive association between triglyceride glucose index and arterial stiffness in hypertensive patients: the China H-type Hypertension Registry Study. Cardiovasc Diabetol. 2020;19(1):139. doi: 10.1186/s12933-020-01124-2.

[35] Nakagomi A., Sunami Y., Kawasaki Y., et al. Sex difference in the association between surrogate markers of insulin resistance and arterial stiffness. J Diabetes Complications. 2020;34(6):107442. doi: 10.1016/j.jdiacomp.2019.107442.

[36] Zhao S, Yu S, Chi C, et al. Association between macro- and microvascular damage and the triglyceride glucose index in community-dwelling elderly individuals: The Northern Shanghai Cardiovasc Diabetol. 2019;18(1):95. doi: 10.1186/s12933-019-0898-x.

[37] Lee SB, Ahn CW, Lee BK, et al. Association between triglyceride glucose index and arterial stiffness in Korean adults. Cardiovasc Diabetol. 2018;17(1):41. doi: 10.1186/s12933-018-0692-1.

[38] Won KB, Park GM, Lee SE, et al. Relationship of insulin resistance estimated by triglyceride glucose index to arterial stiffness. Lipids Health Dis. 2018;17(1):268. doi: 10.1186/s12944-018-0914-2.

[39] Du T, Yuan G, Zhang M, et al. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovasc Diabetol. 2014; 13:146. doi: 10.1186/s12933-014-0146-3.

[40] En-qian Liu, Ya-ping Weng, Ai-ming Zhou, Chun-lai Zeng, "Association between Triglyceride-Glucose Index and Type 2 Diabetes Mellitus in the Japanese Population: A Secondary Analysis of a Retrospective Cohort Study", BioMed Research International, vol. 2020, 2947067. https://doi.org/10.1155/2020/2947067.